Е.Н. ЛАШИНА
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Иностранный язык (английский)

CHEMICAL ENGINEERING

Курс для магистрантов по направлению подготовки «Химическая технология»

Учебное пособие

Санкт-Петербург

2020

МИНИСТЕРСТВО НАУКИ И ОБРАЗОВАНИЯ РОССИЙСКОЙ ФЕДЕРАЦИИ

ФЕДЕРАЛЬНОЕ ГОСУДАРСТВЕННОЕ БЮДЖЕТНОЕ ОБРАЗОВАТЕЛЬНОЕ УЧРЕЖДЕНИЕ ВЫСШЕГО ОБРАЗОВАНИЯ

«САНКТ-ПЕТЕРБУРГСКИЙ ГОСУДАРСТВЕННЫЙ УНИВЕРСИТЕТ ПРОМЫШЛЕННЫХ ТЕХНОЛОГИЙ И ДИЗАЙНА»

ВЫСШАЯ ШКОЛА ТЕХНОЛОГИИ И ЭНЕРГЕТИКИ

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Рецензенты: канд. педагогич. наук, доцент кафедры иностранных языков ВШТЭ СПбГУПТД К. А. Сечина;
канд. филол. наук, доцент кафедры русского языка и литературы Санкт-Петербургского горного университета М. Н. Дмитриева.

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ОГЛАВЛЕНИЕ

ПРЕДИСЛОВИЕ

Данное учебное пособие предлагается студентам магистратуры института технологии по направлению подготовки «Химическая технология» для изучения академического аспекта английского языка.

Основной задачей курса «Английский язык» является обучение практическому владению научной речью в сфере профессионального общения.

Основой построения программы обучения является направление, или аспект, «язык для специальных целей» (Language for Specific Purposes - LSP). Данный аспект предполагает развитие навыков, необходимых для освоения соответствующего регистра речи.

Целью данного курса является подготовка высококлассного специалиста международного уровня, одной из составляющих в будущей профессиональной деятельности которого станет языковая грамотность и культура речи. Задачи, стоящие перед студентом: закрепление навыков правильного английского произношения (Oxford English); знание особенностей построения научно-технических текстов из оригинальных источников и овладение техникой работы с ними; самостоятельный поиск и извлечение информации на иностранном языке и её дальнейшее применение в профессиональной сфере; умение поддержать и вести беседу с зарубежными специалистами на темы широкого спектра, с учётом различных деловых культур.

В аспекте «язык для специальных целей» осуществляется: развитие навыков чтения специальной литературы с целью получения информации; знакомство с основами перевода литературы по специальности. Обучение языку специальности ведется на материале произведений речи на профессиональные темы.

Освоение учащимися фонетики (для правильного чтения учащимися аббревиатур и химических формул), грамматики, синтаксиса, словообразования, сочетаемости слов, а также активное усвоение наиболее употребительной

лексики и фразеологии английского языка происходит не в виде заучивания свода правил, а в процессе работы над связными, законченными в смысловом отношении текстами.

Обучение предусматривает: а) формирование фонематического слуха посредством аудирования; б) формирование практических навыков и умений чтения и перевода; в) развитие устной речи; г) отработку грамматического материала с последующим использованием в разговорной речи; д) формирование навыков самостоятельной работы.

В программу самостоятельной работы студентов входят освоение теоретического и практического материала, разобранного вместе с преподавателем на занятиях, подготовка к практическим занятиям в форме словарной работы со статьей, запоминание произношения и написания новых слов и выражений, построение и разучивание диалогов по учебной программе, формирование умений свободно выражать мысли на изучаемом языке, составлять эссе и делать презентацию по заданной теме.

Часть I. ФОНЕТИКА

Английский алфавит

1.	A a	[eɪ]	14	N n	[en]
2.	B b	[bi:]	15	O o	[əʊ]
3.	C c	[si:]	16	P p	[pi:]
4.	D d	[di:]	17	Q q	[kju:]
5.	E e	[i:]	18	R r	[ɑ:]
6.	F f	[ef]	19	S s	[es]
7.	G g	[dʒi:]	20	T t	[ti:]
8.	H h	[eɪtʃ]	21	U u	[ju:]
9.	I i	[aɪ]	22	V v	[vi:]
10.	J j	[dʒeɪ]	23	W w	['dʌbl'ju:]
11.	K k	[keɪ]	24	X x	[eks]
12.	L l	[el]	25	Y y	[waɪ]
13.	M m	[em]	26	Z z	[zed]

Чтение окончания -s (-es)

-s читается **[z]** после гласных и звонких согласных:

lives, mills, stands, forms, stays, tries, trees, goes, studies, cars

[s] после глухих согласных:

likes, parents, flats, stops, asks, maps

[ɪz] после шипящих и свистящих звуков [s, z, ʃ, ʧ, ʒ, ʤ]:

sizes, boxes, watches, bridges, colleges, washes, wishes, gases, a'ddresses, pages, uses, branches, classes

Примечание: помните, что окончание -s бывает у существительных и глаголов.

Не следует путать:

- у существительных окончание **-s** – признак *множественного* числа: papers (бумаги, документы), books, students, forms (формы), lights (огни);

- у существительных окончание **-'s** – признак *притяжательного* падежа (отвечает на вопрос **чей?**). Сравните:

my friend	мой друг
my friend**s**	мои друзья
my friend**'s** work	работа моего друга
my friend**s'** work	работа моих друзей

- у глаголов окончание **-s** – признак третьего лица *единственного* числа во времени Present Simple: he (she) reads – он (она) читает, he (she) knows – он (она) знает, he (she) goes – он (она) идёт, he (she, it) lights – он (она, оно) освещает, it snows – идёт снег, he (she, it) influences – он (она, оно) влияет.

Задание 1.

Прочтите следующие слова:

advises, matches, prizes, sheets, thinks, works, photos, stories, shows, throws, pulps, cooks, rises, 'services, causes, forces, cities, maps, pages, judges, passes, sciences, tries, answers, presses, places, praises, stops, asks, wishes, takes, papers, fibers, chemicals, inches, roots, de'velops, 'surfaces, pro'duces, makes, wastes, 'furnaces, 'purposes, woods, 'processes, 'influences, bags, 'methods, 'differences, 'differs, 'offers, su'ggests, pro'poses, studies, reaches, runs, scientists.

Чтение окончания -ed

-ed читается **[d]** после звонких согласных и гласных:

formed, dried, tried, closed, played, studied, changed, functioned, contained, used, planned, employed

[t] после глухих согласных:

worked, watched, stopped, helped, liked, stressed, forced, walked, cooked, pulped

[ɪd] после согласных **t** и **d**:

waited, invited, wanted, decided, visited, de'manded, com'pleted, su'pported, acted, di'rected, consisted, 'limited, tested, resulted

Задание 2.

Прочтите следующие слова:

washed, di'vided, de'veloped, burned, im'proved, ab'sorbed, pro'duced, helped, learned, 'regulated, mixed, 'generated, 'operated, pro'vided, liked, in'tended, turned, ex'tracted, com'bined, suited, bleached, 'separated, 'processed, trained, con'verted, solved, missed, di'ssolved, re'mained, in'cluded, heated, produced, po'lluted, 'influenced, manu'factured, con'taminated, changed, looked, littered, a'ttracted, dropped, e'quipped, printed, planted, warmed, lasted.

Часть II. ГРАММАТИКА

ПЕРЕВОД ДВУЧЛЕННЫХ И МНОГОЧЛЕННЫХ АТРИБУТИВНЫХ СЛОВОСОЧЕТАНИЙ, ВЫРАЖЕННЫХ СУЩЕСТВИТЕЛЬНЫМИ ("ЦЕПОЧКИ" СУЩЕСТВИТЕЛЬНЫХ)

Инструкция I. Двучленные или многочленные атрибутивные словосочетания, или "цепочки" существительных, — это словосочетания, состоящие из существительного и определений, расположенных слева от него.

В качестве левого определения могут быть *существительные* (от двух до пяти или шести). Существительным могут предшествовать: прилагательное, причастие, местоимение или числительное, а также сочетания из этих слов, соединенные дефисом.

Необходимо обратить внимание на то, что внутри такого сочетания *слова не отделены друг от друга ни артиклями, ни предлогами, ни запятыми*:

strong acid pump;

white water treatment equipment;

high consistency oxygen bleaching system.

Для перевода "цепочки" существительных важно найти в ней основное слово. Помните, что *основным словом* любой "цепочки" существительных, является *последнее существительное, с которого и следует начинать анализ* такой "цепочки". Все существительные и другие части речи, стоящие слева от основного слова, являются *определениями* к нему (отвечают на вопрос "какой?", "какие?"). Справа от основного слова, указывая на то, что "цепочка" закончилась, может стоять новый артикль, предлог, местоимение, прилагательное, причастие или глагол-сказуемое с предшествующим наречием или без него.

I. Перевод двучленных словосочетаний ("цепочки" состоят из двух существительных).

Инструкция 2. Перевод двучленных словосочетаний *начинаем с последнего существительного*, а существительное, стоящее слева, переводится *существительным в родительном падеже.*

Образец:
1) pulp quality - качество целлюлозы;
2) water level - уровень воды;
3) wood consumption - расход древесины;
4) cooking time -продолжительность варки;

a) stock (волокнистая масса) preparation;
stock temperature;
stock production;
sheet properties;
sheet formation (формование).

Инструкция 3. В "цепочке", состоящей из двух существительных, первое переводится *прилагательным.*

Образец:
1) wood fiber - древесное волокно;
2) gas bleaching - газовая отбелка;
3) cooking acid - варочная кислота;
4) paper stock - бумажная масса;

wood chips; acid digester; wood species (порода); sulphite digestion; oxygen bleaching; stock pump; laboratory tests; spruce chips; bleaching plant (отдел); hand operation; pine chips; water vapor; cooking process; bag paper.

Инструкция 4. Перевод "цепочки" существительных начинаем с последнего существительного, а первое переводим *существительным с предлогом (в, из, на, для и др.).*

Образец: 1) hardwood pulp - целлюлоза *из* лиственной древесины;
2) drying costs - затраты *на* сушку (затраты, связанные *с* сушкой);
3) pollution control - борьба *с* загрязнением;

digester pressure; softwood pulp; acid (кислая среда) hydrolysis; linen (льняное тряпье) paper; board products; evaporator (испаритель) gases; hardwood sulphite pulp.

II. Перевод многочленных словосочетаний ("цепочки" существительных состоят из трех и более существительных и других частей речи).

Инструкция 5. При переводе многочленных словосочетаний рекомендуем:

1) перевести последнее существительное "цепочки";
2) разбить остальную часть словосочетания на *смысловые группы* и перевести их (внутри смысловой группы анализ проводится слева направо);
3) перевести все словосочетание (всю "цепочку"), следуя справа налево.

Образец: 1) stock mixing| *system* – система для смешивания массы;
2) wood fiber| *products* – изделия из древесного волокна;
3) water quality| *results* – результаты по качеству воды;
4) stock preparation| machine *operation* – работа машины по приготовлению массы.

В данных словосочетаниях - по две смысловые группы. Основное слово выделено курсивом.

Переведите, следуя инструкции 5.

a)

chip packing (уплотнение) device;

strong acid pump;

stock preparation machine;

paper machine operation;

fiber suspension flow;

b)

paper formation (формование) time;

chlorine dioxide generation (образование);

pulp preparation operation (процесс);

steam flow rate;

headbox (напорный ящик) control (регулирование) system;

c)

chain (цепь) length distribution (распределение);

fiber length distribution;

chemicals recovery system;

heat transfer (передача) coefficient;

water conservation costs (затраты);

d)

fiber wall thickness;

cooking liquor circulation;

gas diffusion constant;

quality control method;

paperboard test (анализ) result;

e)

plant design changes;

cooking liquor pressure;

stock preparation equipment;

air pollution (загрязнение) problem;

air pollution abatement (уменьшение);
water purity level (степень).

Образец: sodium base| sulfite *pulping*
Sulfite pulping – сульфитная варка;
Sodium base – натриевое основание;
= сульфитная варка на натриевом основании.

Переведите, используя образец:

various cooking liquor composition;
high yield sulfite pulp;
constant vapor phase region;
ammonia base sulfite pulping;
caustic soda recovery (регенерация) system;
white water (оборотная вода) treating equipment;
paper mill steam supply (обеспечение);
particle size distribution determination;
calcium base cooking liquor.

Инструкция 6. Если "цепочка" существительных *начинается с прилагательного,* необходимо обратить внимание на то, *к какому слову оно относится.*

Образец: 1) high yield pulp – целлюлоза с высоким выходом;
2) new sheet structure – новая структура листа;
3) maximum cooking temperature – максимальная температура варки.

Инструкция 7. В состав "цепочки" существительных в качестве определения могут входить числительные, местоимения, причастия, существительные в притяжательном падеже и т.д. Обратите внимание, *к какому слову эти определения относятся.* Помните, что *основное слово словосочетания – последнее существительное.*

Образец: 1) this high pressure steam– этот пар высокого давления;
2) rate determining factor – фактор, определяющий скорость.

Инструкция 8. Иногда одно из слов "цепочки" существительных необходимо перевести *поясняющими словами (группой слов).*

Образец: 1) paperboard machine – машина *для выработки картона;*
2) chipping operation – предприятие, *осуществляющее заготовку щепы;*
3) bark products – продукты *переработки коры.*

СТРАДАТЕЛЬНЫЙ ЗАЛОГ ГЛАГОЛОВ
(THE PASSIVE VOICE)

Инструкция 1. Страдательный залог глагола употребляется в том случае, если само *подлежащее не действует*, действие совершается *над ним*.

Глагол-сказуемое в страдательном залоге можно найти в предложении по вспомогательному глаголу ***"to be"*** в соответствующем времени, лице и числе и ***Past Participle*** (причастию прошедшего времени смыслового глагола).

Примечание 1

Past Participle (Participle II) образуется путем прибавления окончания *-ed* к правильным глаголам. Если глагол неправильный, употребляется его *3-я форма* (built, taken, written…). Рекомендуем повторить 3 формы неправильных глаголов.

Примечание 2

Обратите внимание на то, что Past Participle правильных глаголов совпадает по форме со временем Past Simple (produced, achieved). Определить их можно только в контексте. (Подробнее о Past Participle см. в разделе, посвященном причастиям).

Таблица 1

Страдательный (пассивный) залог

Образуется: глагол to be (в соответствующем времени) + Participle II

Правила и способы перевода	Пример	Перевод
1. Страдательный залог показывает, что действие глагола-сказуемого направлено на лицо или предмет, выраженный подлежащим.	**He** was given a task.	**Ему** дали задание.
В ряде случаев подлежащее переводится прямым или косвенным дополнением и ставится, соответственно, в форме винительного или дательного падежа.	**We** were informed that a new idea had been advanced recently.	**Нас** информировали, что новая идея была выдвинута недавно.
2. Если после глагола в пассиве есть дополнение с предлогом **by** или **with**, то оно указывает, кем или чем производится действие. Предлоги переводятся «путём», «при помощи», «посредством» либо соответствуют творительному падежу и не переводятся.	The calculation is done **by computer programs**.	Подсчёты делаются **компьютерными программами** (**при помощи** компьютерных программ).
	The production line is supplied **with raw material**.	Производственная линия снабжается **сырьём**.

Продолжение табл. 1

Правила и способы перевода	Пример	Перевод
3. Сочетанием глагола «быть» с кратким страдательным причастием с суффиксами -н- или -т-. Глагол «быть» в настоящем времени опускается.	The mill is built by the workers. are built was built were built has been built have been built shall/will be built will be built	Фабрика построена рабочими. построены была построена были построены была построена были построены будет построена будут построены
4. Глаголом на **-ся** в соответствующем времени, лице и числе.	The goods **are being sold** with profit. **were being sold**	Эти товары **продаются** с прибылью. **продавались**
5. Глаголом действительного залога в 3-м лице множественного числа, в неопределённо-личном предложении.	The company's account **is checked**. was checked will be checked	Отчёт компании **проверяют**. проверили будут проверять

Окончание табл. 1

Правила и способы перевода	Пример	Перевод
6. Глаголы с относящимся к ним предлогом, которые переводятся также глаголами с предлогом: to depend on – зависеть от to insist on –настаивать на to look at – смотреть на to rely on – опираться на to speak of (about) – говорить о to refer to – ссылаться на, называть to deal with – иметь дело с и др. переводятся глаголами в неопределённо-личной форме, причём соответствующий русский предлог ставится перед английским подлежащим.	The new plant is much spoken **about**. This article was often referred **to**.	**О** новом заводе много говорят. **На** эту статью часто ссылались.
7. Глаголы без предлогов, которые переводятся глаголами с предлогом: to affect – влиять на to answer – отвечать на to influence – влиять на to follow – следовать за и др. переводятся глаголами в активном залоге или неопределённо-личной форме, причём соответствующий русский предлог ставится перед английским подлежащим.	The conditions of work are greatly affected by the government.	**На** условия работы сильно влияет правительство.

НЕЛИЧНЫЕ ФОРМЫ ГЛАГОЛА
ИНФИНИТИВ (INFINITIVE)

Инфинитив – основная форма глагола, от которой образуются все личные формы глагола во всех группах времен в действительном и страдательном залогах. Инфинитив, или неопределенная форма глагола, сочетает в себе свойства глагола и существительного.

Признаком инфинитива является частица "to". Она иногда опускается:
после модальных и вспомогательных глаголов; must (can) produce; do not produce; Did the mill produce? Will produce и т.д.
после глаголов физического восприятия: see, hear, feel, watch, notice в объектных инфинитивных оборотах и некоторых других случаях.

Инструкция 1

Повторите формы инфинитива:

Время	Active Voice	Passive Voice
Indefinite – выражает действие, одновременное с действием, выраженным глаголом-сказуемым	to produce	to be produced
Perfect – выражает действие, предшествовавшее действию, выраженному глаголом-сказуемым	to have produced	to have been produced
Continuous – длительный характер действия	to be producing	___
Perfect Continuous – действие началось в прошлом и все еще продолжается	to have been producing	___

Функции инфинитива

Инструкция 2

Помните, что инфинитив *в роли подлежащего* всегда стоит *перед сказуемым* (в начале предложения).

Переводится:

1) существительным;

2) неопределенной формой глагола.

Образец: *To know English* is necessary. – Необходимо *знать* английский. *Знание* английского необходимо.

Инструкция 3

Инфинитив в роли обстоятельства цели отвечает на вопрос "для чего?", "с какой целью?". Стоит либо в начале, перед подлежащим, либо в конце предложения. Может вводиться союзами *so as (to) – с тем, чтобы, in order (to) – для того чтобы.*

Переводится:

1) *неопределенной формой глагола с союзом "чтобы", "для того, чтобы";*
2) *существительным с предлогом "для".*

Образец: *To know* English you should work hard. – *Чтобы знать* английский, вы должны много работать.

Инструкция 4

Инфинитив *в роли обстоятельства следствия* отвечает на вопрос "для чего?" и стоит после слов *too* – слишком, *enough, sufficiently* – достаточно, *sufficient* – достаточный, *very* – очень. *Переводится неопределенной формой глагола с*

союзом "(для того) чтобы". Сказуемое при переводе часто имеет *оттенок возможности*.

Образец: 1) I am *too* tired *to go* to the exhibition – Я *слишком* устал, чтобы идти на выставку (чтобы я *мог* пойти…)

2) He is clever *enough to understand* it. – Он *достаточно* умен, чтобы (он *мог*) понять это.

Примечание

В английском языке слово "enough" всегда стоит после прилагательного, но перевод следует *начинать именно с "enough"*, а потом переводить прилагательное: strong enough – достаточно прочный; accurate enough – достаточно точный и т.д.

Инструкция 5

Обратите внимание на *инфинитив в роли определения*. *Он всегда стоит после определяемого существительного* и отвечает на вопрос "какой?". Инфинитив в роли определения чаще всего *имеет форму страдательного залога* и *переводится определительным придаточным предложением*, вводимым союзным словом *"который"*. Сказуемое русского предложения выражает *долженствование*, *будущее время* или *возможность*.

Образец: 1) The method *to be used – метод, который нужно (можно, будут) использовать.*

2) A beater roll breaks up the material *to be pulped*. – Барабан ролла измельчает сырье, *которое нужно* превратить в массу (*которое будет превращено в массу*).

Инструкция 6

Инфинитив – часть сказуемого. Инфинитив может быть частью: а) простого сказуемого; б) составного именного или в) составного модального сказуемого

(=составного глагольного сказуемого) лишь в том случае, если ему предшествуют глаголы *to be, to have, модальный или вспомогательный глагол.*

Образец:

1) The purpose of the system *is to maximize* production. - Цель этой системы – максимально повысить производительность. Цель системы *состоит в том*, чтобы максимально… Целью системы *является* максимальное повышение…
2) The system *is (has) to maximize* production = The system *must (should) maximize* production. – Эта система должна максимально повысить производительность.

Таблица 2

ПРИЧАСТИЕ

Вид причастия	Функция в предложении и перевод		
	часть сказуемого	определение	обстоятельство
1. Participle I Active voice **selling writing**	He **is selling** his goods. Он **продаёт** свои товары. (Для образования времен группы Continuous. Самостоятельно не переводится).	The merchant **selling** his goods pays a profits tax. Торговец, **продающий** свои товары, платит налог с прибыли. The seller examined the letter **containing** an interesting offer. Продавец изучил письмо, **содержавшее** интересное предложение. (Причастие на -щий, -вший).	(When, while) **selling** his goods, the merchant pays a profits tax. **Продавая** свои товары, торговец платит налог с прибыли. (Деепричастие на -а, -я).
2. Participle I Passive voice **being sold being written**	The goods are **being sold**. Товары **продаются.** (Для образования группы времен Continuous пассивного залога. Самостоятельно не переводится).	The goods **being sold** were foreign made. **Продаваемые** товары были произведены за границей. (Причастие на -емый, -имый).	(**While**) **being moved** the goods are insured against all risks. **Когда** их **перевозят** (**во время перевозки**) товары страхуются против всех рисков. (Придаточное обстоятельственное предложение; существительное с предлогом).

Окончание табл. 2

Вид причастия	Функция в предложении и перевод		
	часть сказуемого	определение	обстоятельство
3. Participle II Passive voice **sold** **written**	1) He **has sold** his goods. Он продал свои товары. (Для образования времен Perfect. Самостоятельно не переводится). 2) The goods **are sold**. Товары проданы. (Для образования пассивного залога. Самостоятельно не переводится).	The goods **sold** gave substantial profit. **Проданные** товары принесли существенную прибыль. The problem **discussed** yesterday is very important. Проблема, **обсуждавшаяся** вчера, очень важна. (Причастие на -щийся, -мый, -ный, -тый, -вшийся).	**If sold**, the goods will give substantial profit. **Если их продать**, товары принесут существенную прибыль. (Обстоятельственное придаточное предложение).
4. Perfect Participle active voice **having sold** **having written**	–	–	**Having sold** his goods he got substantial profits. **Продав** свои товары, он получил существенную прибыль. (Деепричастие на -ив, -ав).
5. Perfect Participle Passive voice **having been sold** **having been written**	–	–	**Having been sold**, the goods gave substantial profit. **После того как товары были проданы**, они принесли существенную прибыль. (Придаточное обстоятельственное предложение).

Таблица 3

ГЕРУНДИЙ

Функция в предложении	Примеры	Перевод
1. Подлежащее	**Chartering** of ships is very important for shipments of goods.	**Фрахтование** кораблей (**фрахтовать** корабли) очень важно для перевозки товаров. (Инфинитив, существительное).
2. Часть сказуемого	The main task is **keeping** customer's accounts.	Главная задача – **хранение** счетов клиентов (**хранить** счета клиентов). (Существительное, инфинитив).
3. Прямое дополнение	The situation requires **controlling** the supply.	Ситуация требует **управлять** (**управления**) поставками. (Инфинитив, существительное).
4. Определение (обычно с предлогом **of, for** после существительного)	The ability **of influencing** the commerce is studied attentively.	Способность **влиять** (**влияния**) на торговлю изучается внимательно. (Существительное, инфинитив).
5. Обстоятельство (обычно с предлогами: **in – при, в то время как,** **on (upon) – по, после,** **after – после,** **before – перед,** **by – творит. падеж,** **instead of – вместо того чтобы,** **for – для** и т.д.	He is able to discuss the terms of an order **without receiving** our special authorization.	Он может обсуждать условия заказа **без получения** (**не получая**) нашего специального разрешения на это. (Существительное с предлогом, деепричастие с отрицанием).

Часть III. ЧТЕНИЕ НАУЧНЫХ СТАТЕЙ

ARTICLE 1

Task 1. Read the text below.

Macrocycles: lessons from the distant past, recent developments, and future directions

(by Andrei K. Yudin)

Abstract

A noticeable increase in molecular complexity of drug targets has created an unmet need in the therapeutic agents that are larger than traditional small molecules. Macrocycles, which are cyclic compounds comprising 12 atoms or more, are now recognized as molecules that "are up to the task" to interrogate extended protein interfaces. However, because macrocycles (particularly the ones based on peptides) are equipped with large polar surface areas, achieving cellular permeability and bioavailability is anything but straightforward. While one might consider this to be the Achilles' heel of this class of compounds, the synthetic community continues to develop creative approaches toward the synthesis of macrocycles and their site-selective modification. This perspective provides an overview of both mechanistic and structural issues that bear on macrocycles as a unique class of molecules. The reader is offered a historical foray into some of the classic studies that have resulted in the current renaissance of macrocycles. In addition, an attempt is made to overview the more recent developments that give hope that macrocycles might indeed turn into a useful therapeutic modality.

1. Introduction

A macrocycle is a molecule that contains a cyclic framework of at least twelve atoms. Although the size of naturally occurring macrocycles can reach 50+ atoms in the largest ring, a recent analysis of natural products suggested that 14-, 16-, and 18-membered frameworks are the most common naturally occurring macrocyclic scaffolds. Over the years, many different classes of macrocyclic compounds have been synthesized and/or isolated from natural sources Fig. 1 depicts a selection of just three molecules of this class of compounds. In the history of organic chemistry, crown ethers emerged as the first subclass of synthetic macrocycles that offered a clear relationship between structure and function. Shown in Fig. 1 is 18-crown-6, which possesses micromolar affinity for potassium ions in methanol (Fig. 1A). To date, crown ethers exemplify an intuitively clear consequence of molecular-level organization of electron-donating oxygen atoms on a useful property – metal ion recognition. Also included in Fig. 1 are octreotide, a cyclic octapeptide that mimics the natural hormone somatostatin

and is used for the treatment of growth hormone producing tumors, and erythromycin, a macrolide that is widely used as an antibiotic to treat bacterial infections. Similar to crown ethers, octreotide and erythromycin benefit from the organization of their function-defining elements.

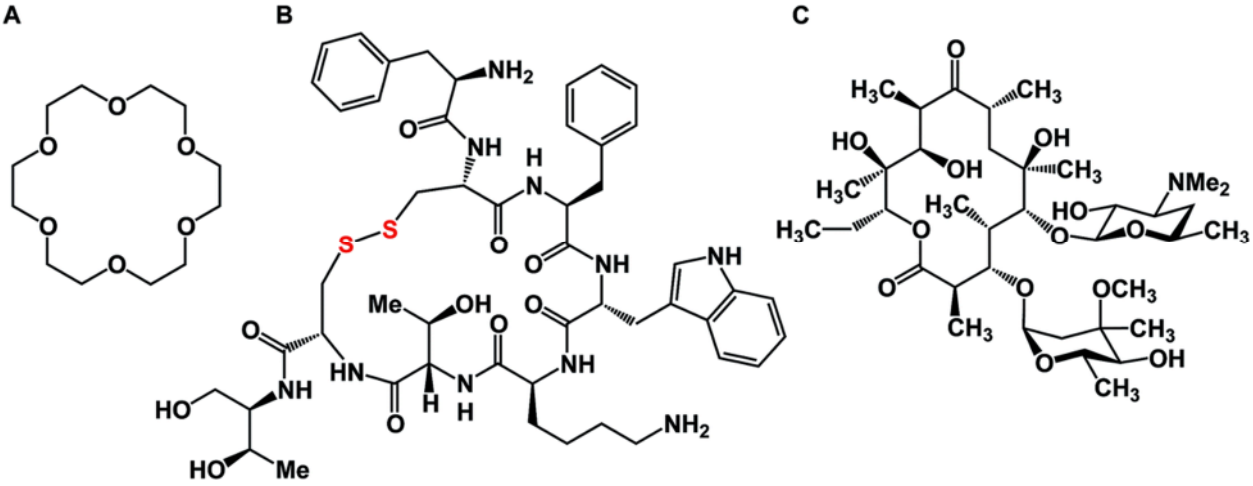


Fig. 1. Representative macrocycles. (A): [18]-Crown-6; (B): octreotide; and (C): erythromycin

While macrocycles have found use in many different areas of chemical science, it is the preorganization of binding elements in the course of a biologically relevant protein/ligand interaction that has been the topic of particularly intense efforts over the past decade. The sustained interest in macrocycles has coincided with a noticeable increase in molecular complexity of therapeutic targets. A growing appreciation of complex protein–protein interactions, which are not easily addressed using small molecules, calls for the development of inhibitors that are more sophisticated than traditional small molecules. In this regard, one might contemplate a difference in how researchers intuit about small molecules in comparison to macrocycles. The small molecule "frame of mind" is about maximizing enthalpic interactions such as hydrogen bonds and salt bridges. On the other hand, bioactive macrocycles are commonly designed with the goal of preorganizing an unstructured linear fragment into a well-defined conformation. The underlying reasoning is to diminish entropic penalties in the course of a protein/ligand interaction. This is not to say that small molecules are somehow exclusively geared to address the enthalpic term of the free energy of binding, whereas macrocycles – its entropy component. In reality, these two energy contributions are exquisitely intertwined.

Among different classes of macrocycles, cyclic peptides and peptidomimetics have received the major share of attention in drug discovery, which is easily explained by the existence of powerful synthetic and biological methods to rapidly put together the amino acid building blocks these molecules consist of. Chemical synthesis of cyclic peptides benefits from the availability of relatively inexpensive orthogonally protected amino acids. In the realm of biological synthesis, DNA and RNA-templated

approaches provide a mechanism for translation of nucleotide codons into amino acid-containing oligomers. Besides a straightforward relationship with amino acid building blocks, there is another reason that peptide-based molecules have received a disproportional amount of attention: cyclic amino acid-containing molecules offer a measurable correlation with the behavior of their linear counterparts. This relationship can serve as a validation tool to establish the merits of converting a linear amino acid sequence into its cyclized form. Beyond preorganization, there is a significant practical consequence of constraining a peptide sequence into a macrocycle, namely an opportunity to address the central liability of linear peptides – their propensity to undergo rapid proteolytic degradation in cells. Indeed, the main reason cyclic peptides resist proteolysis is that their structures do not fit into endopeptidase active sites. Endopeptidases (both intracellular and the ones in the plasma compartment) are known for their propensity to recognize β-sheets in segments that typically involve 4–5 amino acid residues (Fig. 2). This is not easily achievable with medium-sized macrocycles, which is why they are characterized by reduced rates of proteolysis.

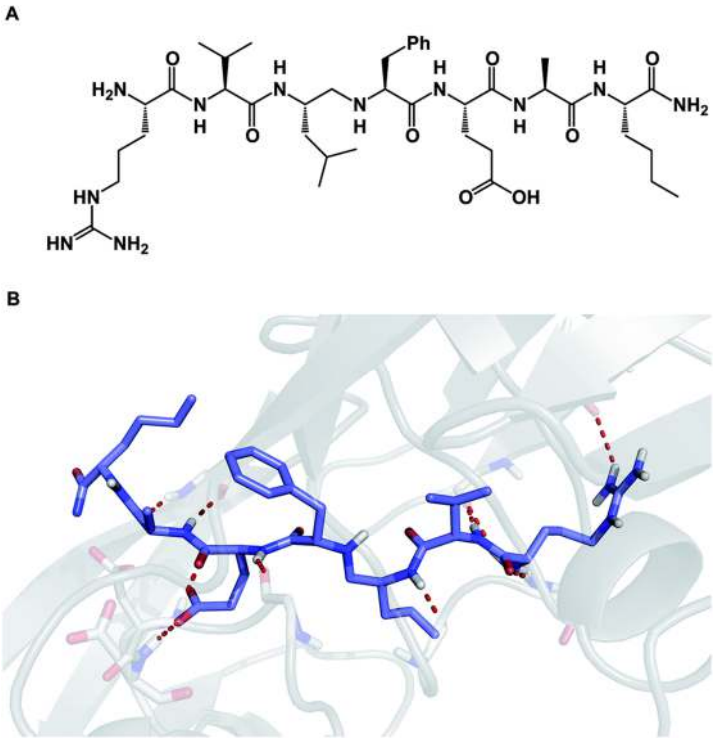


Fig. 2. Peptidases prefer extended conformations: a substrate-derived aminomethylene inhibitor (A) and its complex with the Rous sarcoma virus (RSV) protease S9 (B) (pdb id: 1a94)

The aforementioned properties might paint an erroneous picture that cyclic peptides and other macrocycles in and of themselves belong to some “privileged” class of molecules for therapeutic intervention, the kind that holds clear answers to the challenges facing modern drug discovery, which is inundated with complex protein targets. Unfortunately, this is far from the truth because the large polar surface areas that accompany high amide content come typically at the expense of cellular

permeability, which significantly limits the bioavailability of peptide macrocycles. Indeed, one can consider this to be the Achilles' heel of all large therapeutics designed for intracellular targets. P-glycoprotein (P-gp), a membrane protein, whose job is to remove foreign molecules from cells, presents an additional obstacle to macrocycles. As a result, the greatest conceptual challenge that faces this area of inquiry is how to devise effective synthetic tools that simultaneously bear on the favorable drug-like properties of macrocycles and ensure their target engagement. These two properties are not correlated in drug discovery, which is less of an issue when it comes to small molecules, but can turn into a major consideration in the case of macrocycles. Fig. 3 illustrates this conundrum using the example of cyclosporine A. This molecule is known for its relatively good passive membrane permeability that arises from the network of intramolecular hydrogen bonds that are presumed to form while cyclosporine enters and passes through the lipid bilayer. A molecular-level analysis of the interaction between cyclosporine A and its cellular target cyclophilin paints a different conformational picture, in which the amide groups are involved in target recognition and thus relinquish the intramolecular interactions that contributed to cyclosporine A's entry into the cell. Many researchers have been taking notes from this "cyclosporine lesson" on cellular permeability of large therapeutic agents. The goal of these endeavors has been to design molecules with favorable drug-like properties, such as enhanced cellular permeability, by minimizing their effective polar surface areas. Unfortunately, this quest is not likely to simultaneously deliver optimal target engagement that operates on principles which are related, but seek to align hydrogen bonds donors and acceptors in an "outward" orientation. Without a doubt, this dichotomy of properties is the biggest challenge in this vibrant research area, and successful molecules are most likely going to be outliers, rather than a group that obeys certain rules.

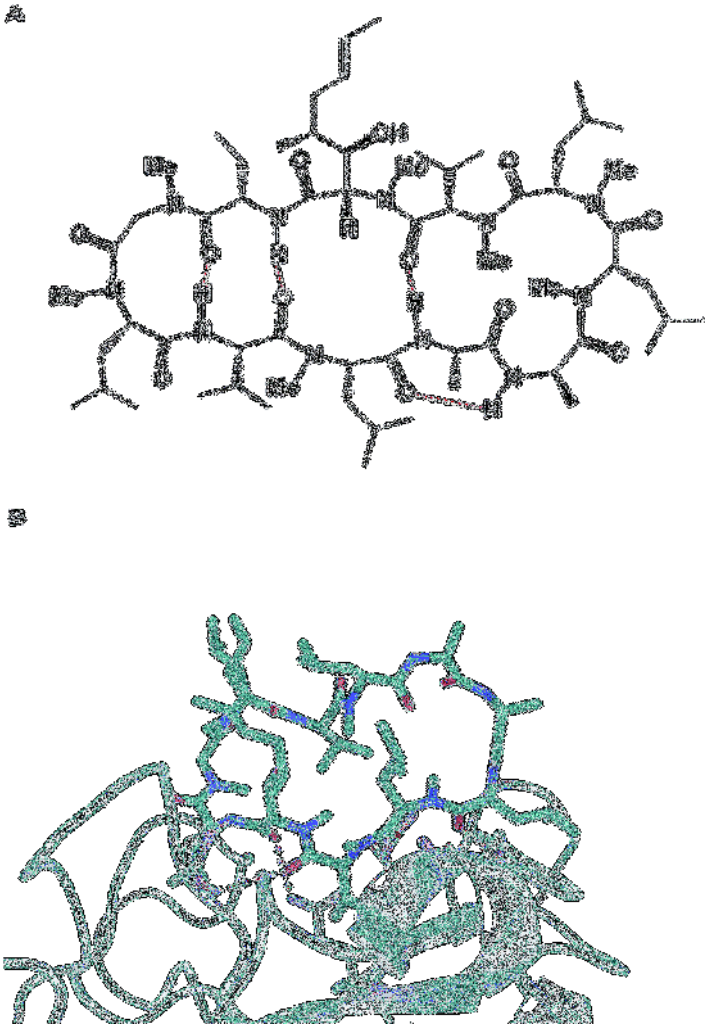


Fig. 3. Cyclosporine A: membrane conformation (A) and conformation during target engagement (B, pdb id: 2z6w)

2. Synthesis of macrocycles

At its core, the challenge of macrocycle construction is about solving the dreaded "ring/chain" equilibrium, well familiar to polymer chemists. A reasonable strategy to minimize the probability of oligomerization and improve cyclization efficiency is to use high dilution or resort to solid-phase synthesis, which affords pseudo-high-dilution conditions. A clever solution that bypasses the need for slow-addition/high-dilution involves phase separation of the macrocyclization catalyst from its substrate. An exhaustive treatment of the known methods of cyclization is not the goal of this perspective as it will be almost impossible to deliver an adequate discussion of all available methodologies. Most of these methods are merely performed with the goal of inducing intramolecular reactivity and are not conceptually different from linear molecule synthesis. However, there are technologies that tackle the challenge of ring-chain equilibrium, and bias reactions away from generating oligomers and polymers without relying on high-dilution.

The differentiation between cyclization and polymerization modes of reactivity is formally captured in the concept of effective molarity, which allows one to parameterize the entropic consequences of ring/chain equilibrium. A recent paper by James and co-workers introduced another useful parameter – the so-called Emac (Efficiency of macrocyclization), which is derived from experimentally determined reaction yield and concentration and is useful in comparing macrocyclization technologies. Synthetic methods that provide good isolated yields of cyclic products often capitalize on the inherent propensity of linear precursors to fold into conformations that are conducive to cyclization. This section discusses the effects of preorganization on reaction efficiency, with a focus on macrocycle modification as a means to produce analogs, and touches upon ways to increase the accessible diversity of structures through the use of biological methods.

2.1. Preorganization of linear precursors for cyclization

Effective preorganization of linear precursors is the function of non-covalent interactions that may operate prior to or during the cyclization. In this regard, peptide preorganization through hydrogen bonding and ion pairing bears resemblance to protein folding. It is well known that about one half of the single domain proteins in the Protein Data Bank have their N- and C-terminal residues in close proximity. This amount is significantly higher than expected on a random probability basis. While the exact reasons for this phenomenon are still debated, similar trends were observed in substantially shorter molecules. In their study of end-to-end loop closure kinetics in polypeptide chains, Daidone and Smith concluded that the loop-closure kinetics in longer peptides are determined by the formation of intra-peptide hydrogen bonds and transient β-sheet structure, which accelerates the search for contacts among residues distant in sequence. Significantly, intramolecular hydrogen bonds were found to lower the free energy of loop closure for longer peptides. The observation of a rollover to slower kinetics and the absence of intra-peptide hydrogen bonds for shorter peptides provided evidence of intrinsic stiffness of the polypeptide chains. Ion-pair interactions, which are inversely proportional to the square of the distance between the charges, were shown by Daidone and Smith to be effective in bringing the ends of linear chains together in fairly short sequences. A kinetic study of this process in solvents of low dielectric constants revealed that pre-cyclization architectures are maintained with two chain ends in close contact through Coulombic interactions. Imaginative approaches to study this kind of behavior are found in the work of Schmuck and co-workers. These authors evaluated the effect of electrostatic attraction between peptide chain termini on the formation of zwitterionic peptide cyclodimers (Fig. 4A). This study further stresses the significance of hydrogen bond-enforced ion pair formation and its effect on peptide conformation.

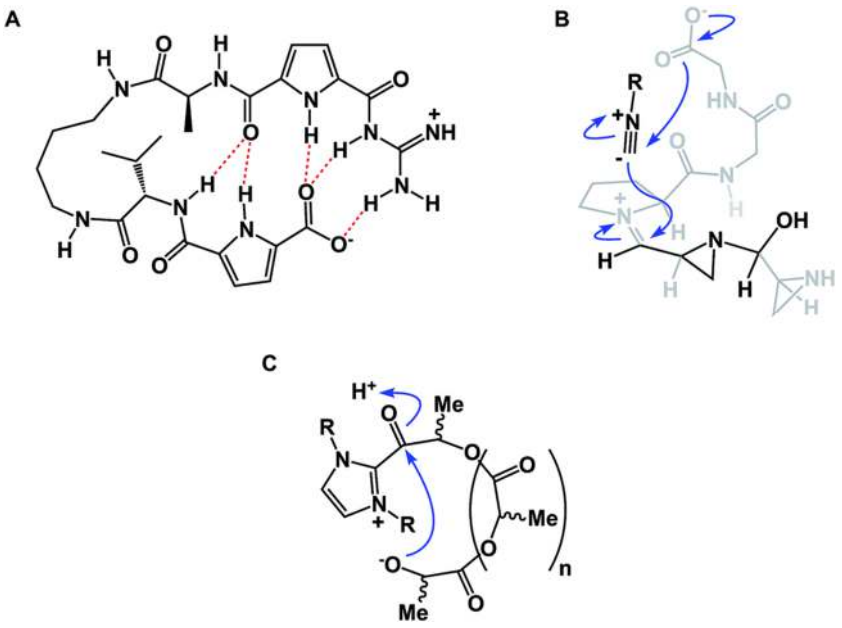


Fig. 4. Zwitterionic control over conformation of linear peptide precursors. (A): Zwitterion-driven formation of circular conformations in solution; (B): zwitterionic control of multicomponent peptide cyclization; and (C): zwitterion-driven formation of cyclic polymers

Our lab's work in the area of aziridine aldehyde-driven macrocyclization of linear peptides has identified electrostatic attraction between the chain termini as one of the decisive factors responsible for the attainment of favorable pre-cyclization conformations and the absence of cyclodimerization and oligomerization by-products at relatively high concentrations. Aziridine aldehydes, which readily dimerize to a fused oxazolidine-containing ring system in N-unprotected form, were central to the success of this chemistry. These molecules show solvent-dependent dissociation into an open dimer form that controls the facial selectivity of isocyanide attack at the incipient iminium ion (Fig. 4B). This process is believed to guide the peptide chain toward formation of an intermediate mixed anhydride. The resulting macrocycles are equipped with N-acyl aziridine rings that allow for site-selective structural modification. Building on the idea of zwitterionic control over pre-cyclization conformation, Londregan and colleagues at Pfizer have developed a pyridine N-oxide-driven macrocyclization. The electrostatic factors involved in this work also echo Waymouth's studies in the area of cyclic polymer synthesis, where zwitterionic control assisted in attaining cyclic conformations prior to ring closure (Fig. 4C). In another thought-provoking study that benefits from zwitterionic control over conformation, Zheng and co-workers explored N-heterocyclic carbene-mediated zwitterionic polymerization toward the synthesis of cyclic peptoids.

2.2. Post-cyclization reactions and side chain reactivity

A substantial proportion of effort expended in the area of bioactive macrocycles is aimed at making structural analogs. Late stage modification of macrocycles is a promising area of research because, once a scaffold with favorable properties has been identified, its folding pattern is likely to be retained in close analogs. Kessler and co-workers found that the presentation of pharmacophoric groups in sterically restricted peptides is predominantly controlled by the amino acid chirality and is less related to the cycle size. The χ1 angle, which defines the conformation about the C(α)–C(β) bond, is the main determinant of the side chain presentation. Kessler's "spatial screening" method allows for systematic interrogation of the geometric parameters of cyclic peptides.

Due to the decisive role of backbone chirality on the macrocycle conformation, methods that allow one to site-selectively modify a macrocyclic compound are expected to be particularly useful in efforts to generate analogs. In their classic work, Seebach and colleagues demonstrated that C-alkylation of sarcosine residues in cyclic tetrapeptides occurs with remarkably high levels of site-selectivity (Fig. 5). Curiously, even a molecule as complex as cyclosporine A could be selectively modified by deprotonation/electrophile trapping. The nucleophilic substitution reaction with alkyl halides at low temperature was shown to result in the introduction of side chains at the sarcosine's methylene moiety of cyclosporine A, whereas N-alkylation became a competing process only at elevated temperature.

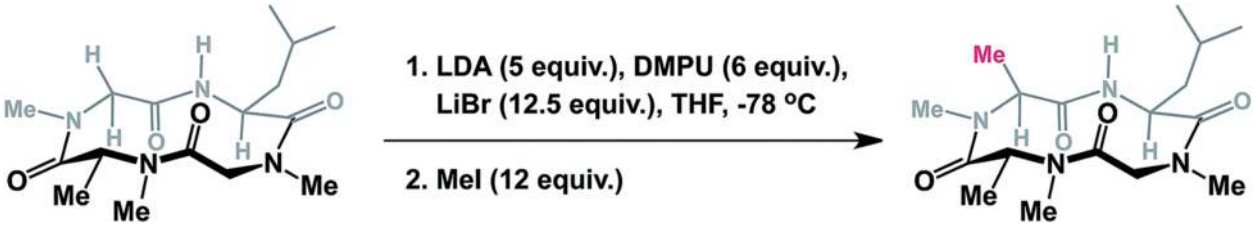


Fig. 5. Seebach's C-selective alkylation of cyclic peptides

While some macrocycles demonstrate substantial rigidity of structure, many of them are rather flexible, inviting a possibility for transannular interactions. These interactions can play an important organizational role. However, unwanted and irreversible transannular reactivity can also take place, particularly in smaller rings. The origins of this effect in cyclic peptides can be traced back to the environment-sensitive amide nucleophilicity. In this regard, an interesting historical analogy to cyclol hypothesis of protein folding might be drawn. A misguided foray into explaining protein folding by D. Winch was based on cyclol formation between adjacent amides. While Pauling quickly showed this proposal to be fundamentally incorrect as the driving force in protein folding, cyclol formation is a well-recognized process that is behind green fluorescent protein (GFP)'s chromophore maturation (Fig. 6A). Due to the proximity of functional groups, similar types of reactions can be expected to operate

within the structures of cyclic peptides. Intramolecular collapse has indeed been observed even in relatively simple cyclic amide-containing molecules. This process is also responsible for the formation of cyclols in the course of spontaneous cyclization of tripeptide sequences. Cyclol-mediated transannular ring closure and condensation in cyclic peptides was also documented by Heimgartner and colleagues (Fig. 6B).

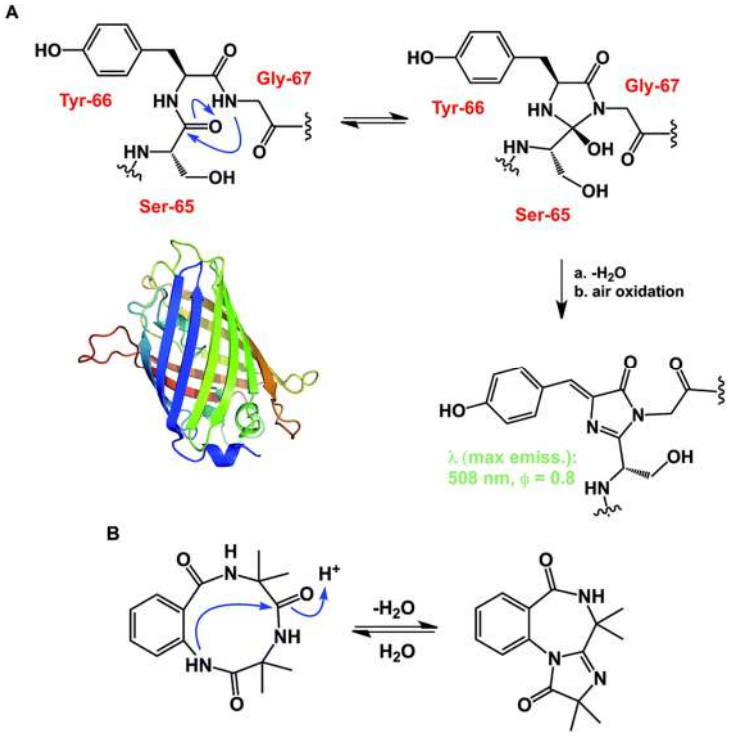


Fig. 6 (A): Cyclol-driven formation of the GFP chromophore; and (B): transannular collapse in cyclic peptides

An interesting case showing intramolecular collapse in medium-sized rings served as the key step in Baran's palau'amine synthesis (Fig. 7A). In this example, the desired transannular cyclization proceeded through the guanidine tautomer, delivering the hallmark trans-5,5 ring system of the natural product. Impressive levels of control over transannular reactivity can be exercised through the use of enantioselective catalysis, which can be seen in Jacobsen's asymmetric transannular Diels–Alder reactions (Fig. 7B). Interesting transannular reactions in peptide macrocycles have been documented by Porco and colleagues (Fig. 7C). In this work, base-mediated transannular cyclizations of macrocyclic bis-lactams driven by olefin isomerization/intramolecular conjugate addition have allowed the authors to access both bicyclic and tricyclic frameworks. While these cases exemplify targeted transannular reactions, they also suggest that caution needs to be exercised when macrocyclic molecules are being synthesized and stored for prolonged periods of time. It is particularly significant in the library mode of synthesis, where LC/MS is routinely used as the main element of quality control, making it difficult to elucidate any rearranged products that may have the same mass as the target molecule.

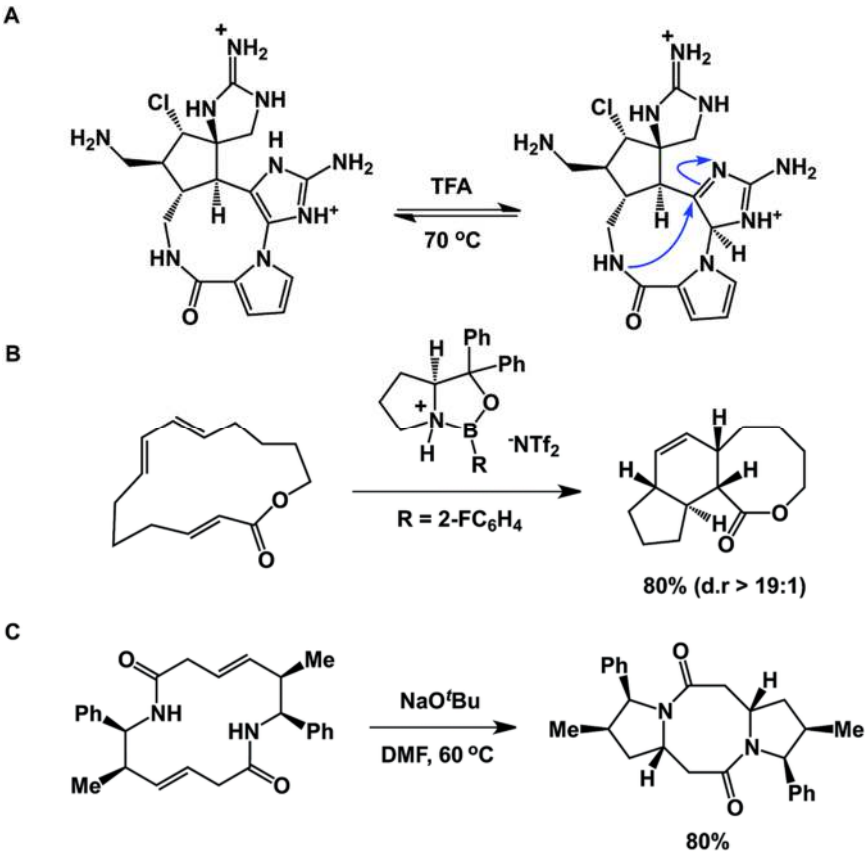


Fig. 7 (A): Transannular attack during palau'amine synthesis; (B): asymmetric control over transannular Diels–Alder cycloaddition; and (C): transannular collapse driven by olefin isomerization-conjugate addition

While amide collapse in large rings is rather rare, the formation of disulfide bonds is not only well-documented, but also serves a significant organizational role in a number of functionally important molecules, including natural products such as romidepsin (Fig. 8A). Romidepsin is a histone deacetylase (HDAC) inhibitor, whose three-dimensional structure is maintained through a single disulfide unit. Defensins constitute much larger ring macrocycles whose structures are “stitched together” by way of a network of disulfide bonds. Molecules such as θ-defensin (Fig. 8B) form the basis of human innate immunity. They are believed to disable susceptible organisms through disruption of the target cell membrane's structural elements. Disulfide bonds in macrocycles serve other important functional roles. Alewood and colleagues demonstrated the pivotal role of vicinal disulfides in affording rigidification of cyclized amino acid sequences. Some peptide macrocycles contain knotted arrangements of multiple disulfide linkages. Given the reversibility of disulfide formation, disulfide scrambling might present an intractable refolding problem. However, complex disulfide-rich molecules often display remarkable fidelity with regard to “returning” to the original state under redox cycling.

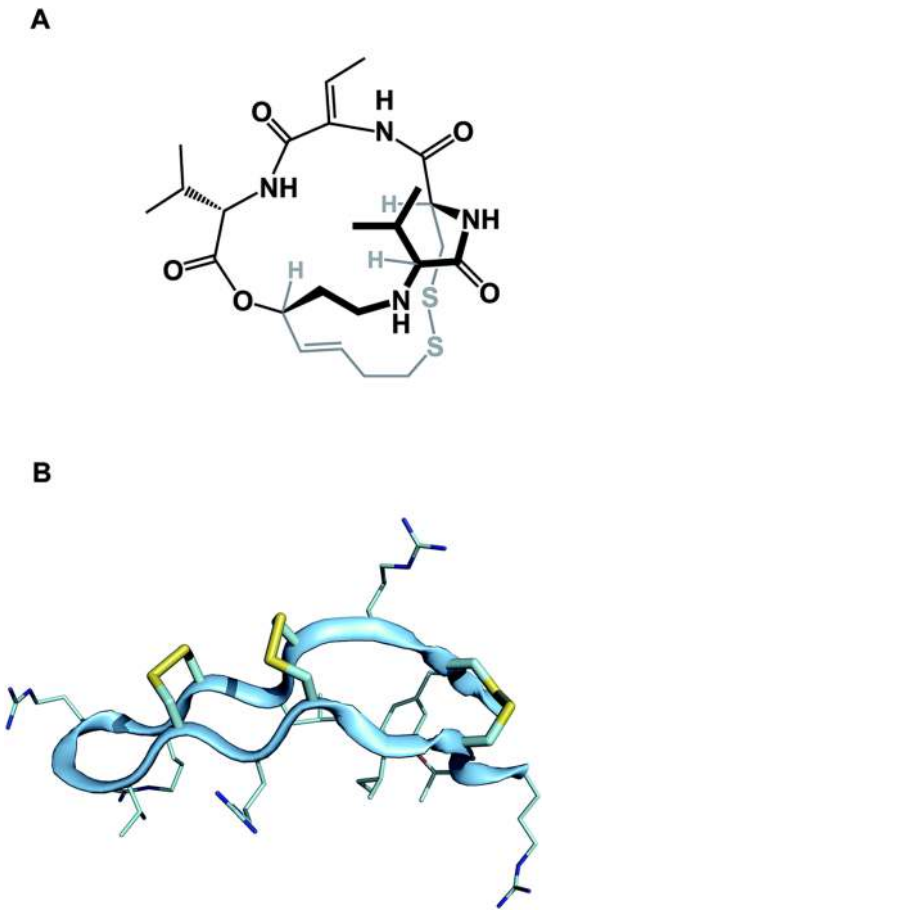


Fig. 8 (A): Romidepsin – disulfide-containing natural product; and (B): θ-defensin and its network of disulfide bonds (shown in yellow)

The idea of using side chain-to-side chain reactivity to enhance the desired presentation of a particular secondary structure has been around for some time. Early efforts by Schultz and co-workers centered around the use of intramolecular disulfide bonds between cysteines in order to increase the helical character of small peptides. Grubbs later employed ring-closing metathesis (RCM) to address this challenge. However, it was not until Schafmeister and Verdine's insight that α-aminoisobutyric acid increases the relative amount of the α-helical form in peptides, that significant improvement in the relative proportion of α-helicity became possible (Fig. 9). The combination of alpha, alpha-disubstituted amino acids and RCM furnished “stapled” peptides that have since been applied in a variety of disciplines. Interestingly, alkane-based linkers that hold these molecules in their α-helical forms are not innocent by-standers: crystallographic evidence suggests that they can engage in stabilizing hydrophobic interactions at the stapled peptide/MCL-1 binding interface.

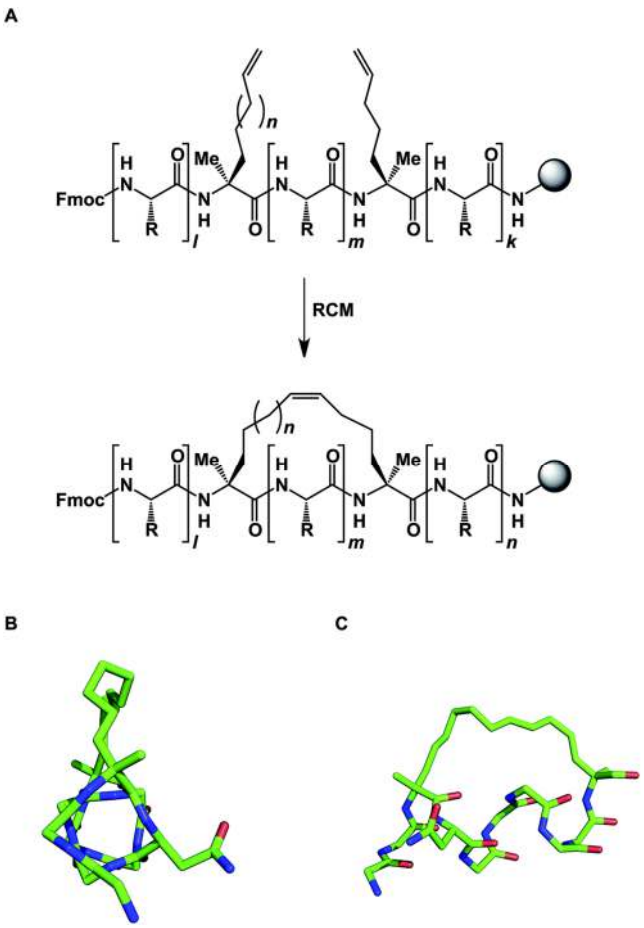


Fig. 9 (A): Stapled peptide synthesis; (B and C): two views of the stapled peptide bound to MDM2 (side chains are omitted for clarity, pdb id: 3v3b)

The proximity of functional groups in the molecules of macrocycles can give rise to interesting structural rearrangements. Building on their earlier studies, Takeya and co-workers discovered a thioamide-driven, site-selective epimerization that takes place in the structures of certain bicyclic peptide natural products. In a similar vein, researchers at Novartis showed that site-selective epimerization of the unmethylated leucine residue of a fungal cyclodepsipeptide is possible by way of O-alkylation followed by oxazole formation and hydrolysis (Fig. 10A). This example further teaches that local environments can exert profound influence over site-selective reactivity in macrocycles. Interestingly, the crystal structure reported for this molecule explains why the non-methylated leucine residue is the most nucleophilic one. This finding also echoes earlier teachings of Seebach and co-workers, who developed conditions for site-selective deprotonation of macrocycles. Yet another intriguing manifestation of intramolecular reactivity comes courtesy of Smythe and Meutermans, who demonstrated that challenging macrocycles can be accessed through the use of a benzylamine-derived auxiliary via a ring-contraction strategy (shown in red in Fig. 10B). In this example, the intramolecular collapse is driven by the relative strength of the product amide bond.

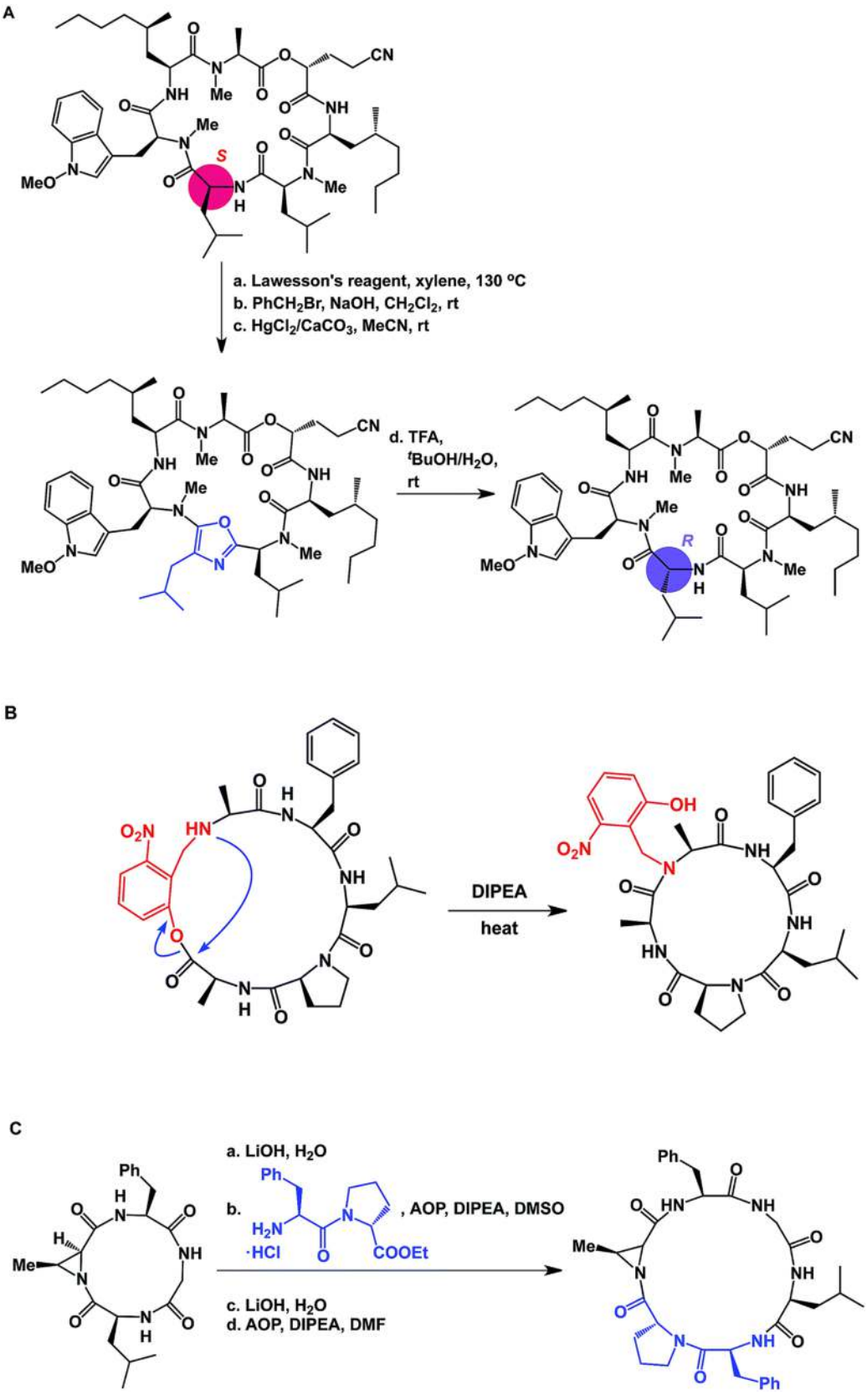


Fig. 10 (A): Site-selective epimerization of a cyclic peptide; (B): ring contraction strategy for macrocycle synthesis; and (C): integrative approach to macrocycles

While the cases discussed above illustrate rearrangements of cyclic peptides or their side chain reactivity, until recently there have been no examples wherein site-

selective ring scission of macrocycles was shown to be synthetically useful. By focusing on the relative weakness of aziridine amides compared to the regular amides, our lab has advanced the concept of site-specific integration of amino acid fragments into the structures of cyclic peptides using a synthetic sequence of hydrolysis/ligation/re-cyclization (Fig. 10C).

Reagent- and catalyst-controlled modification of macrocycles is another vibrant area of research. Miller and co-workers reported on their use of peptide-based catalysts toward site-selective modification of erythromycin A (shown in Fig. 1C). Burke and colleagues resorted to fundamental principles of physical organic chemistry in order to electronically tune reagents toward useful site-selective functionalization reactions and applied this method to the chemoselective functionalization of the complex natural product amphotericin B.

It is appropriate to mention the way in which many cyclic peptides and other macrocycles are biosynthesized because the logic of this chemistry is mirrored in some solid-phase synthesis approaches. A number of naturally occurring macrocyclic peptides are the products of non-ribosomal biosynthesis, during which synthetases tether activated linear intermediates through thioester linkages. Interestingly, isolated thioesterases were shown to promote macrocyclization of linear peptides immobilized on synthetic solid supports. This reaction involves transacylation to the active-site serine followed by deacylation upon intramolecular attack by the amino-terminal nucleophile. A practical example that cleverly emulates the biosynthetic assembly of cyclic peptides has emerged from Tranzyme. Over the years, this company amassed a large library of macrocycles using a solid-phase procedure in which the linear precursor had been connected to the solid support through a thioester linkage. In this chemistry, the macrocyclization event coincides with the N-terminus of the linear chain attacking the thioester group, resulting in traceless product release. Cyclative cleavage to generate macrocycles was also cleverly employed by Rademann and co-workers in their triazole ligation studies.

2.3. Molecular diversity via biosynthetic approaches

One of the long-standing goals of drug discovery is to increase the diversity of accessible structures to allow for broader sampling of the structural space. Combinatorial biochemical methods such as phage display, aptamer SELEX, and mRNA display discussed in this section have shown tremendous promise for the discovery of biopolymer-derived ligands to biological targets. These methods utilize large populations of species such as bacteriophage, and then apply environmental pressure in order to focus the populations by selection. Binding to a biological target of interest is the most commonly used selection pressure. In phage display, each species carries an oligonucleotide tag that not only serves to encode chemical structure, but also provides a template for amplification. Libraries of up to 1013 members have been

successfully generated and used in efforts to discover disulfide-based macrocyclic ligands to protein targets. Incidentally, the RGD (arginine–glycine–aspartic acid) sequence, widely used in cell adhesion studies, emerged from this effort.

Several innovative approaches at the intersection of biology and synthetic chemistry have appeared in recent years. The presence of nucleophilic thiol functional groups in peptides has been explored in imaginative methods that target constrained macrocyclic scaffolds. Fast and quantitative cyclization of linear peptides with unprotected side chains and multiple free cysteines is possible through the use of simple bromomethyl-functionalized aromatic scaffolds. This chemistry, developed by Timmerman and colleagues, runs fast and clean with linear peptides that are 2–30 amino acids long and provides a means to immobilize multiple peptide loops onto a synthetic scaffold. Using mesitylene scaffolds reported by Timmerman, Heinis and colleagues developed a phage display strategy for the selection of bicyclic peptides (Fig. 11). The linear precursors were designed as repertoires with three reactive cysteines that were separated in sequence by several random amino acid residues. The resulting constructs were then fused to the phage gene-3-protein. Subsequent conjugation with tris-(bromomethyl)benzene generated phage-based peptide conjugates and affinity selections led to the discovery of a specific human plasma kallikrein inhibitor, among other applications.

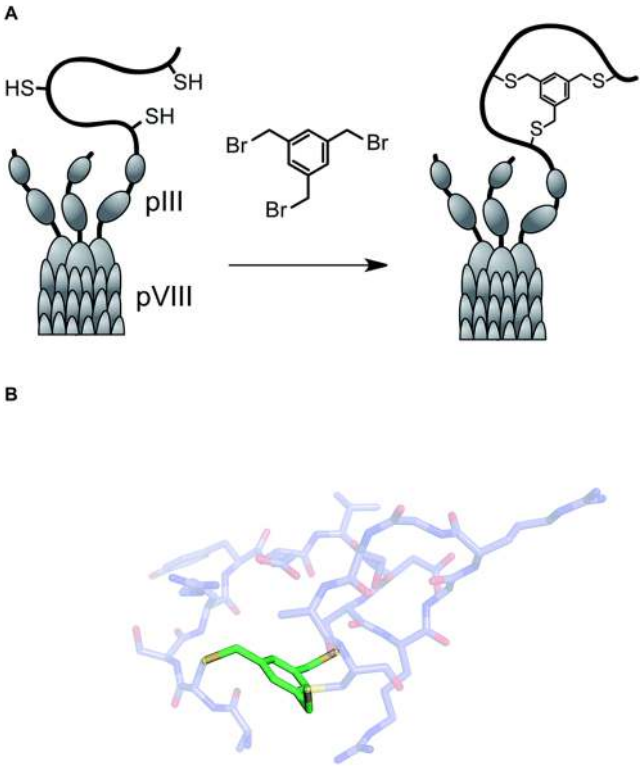


Fig. 11 (A): Integration of tris(bromomethyl)xylene into the phage display workflow; and (B): a pose of a crystallographically characterized xylene-constrained inhibitor of human urokinase-type plasminogen activator (pdb id: 3qn7)

Liu and colleagues used multistep DNA-templated organic synthesis to translate libraries of DNA sequences into libraries of sequence-programmed macrocycles and subjected the resulting DNA-macrocycle conjugates to in vitro selections for protein target affinity. The sequence of the amplified DNA template allowed the authors to de-convolute the results of their binding experiments. Meanwhile, using wPURE and flexizyme-mediated in vitro translation systems, Suga and co-workers genetically reprogrammed the initiation event during translation. It was shown that the translation apparatus tolerated not only proteinogenic amino acids, but also accepted N-acyl groups equipped with various functionalities. This list included electrophilic chloromethyl group on the N-terminus or a lysine side chain, which led to the ribosomal synthesis of cyclic peptides containing thioether bonds. This genetic reprogramming approach, in conjunction with mRNA display, has resulted in the discovery of high affinity binders for a number of relevant targets.

Szostak and colleagues have developed cysteine-mediated approaches for macrocyclization via lanthionine bridge formation or alkylation with dibromo xylene linkers. These approaches have been combined with mRNA display to rapidly prepare and screen macrocyclic peptide libraries. In another approach, Fasan and co-workers explored a clever chemo-biosynthetic strategy toward the generation of macrocyclic organo-peptide hybrids (MOrPHs). This feat was accomplished using a catalyst-free dual oxime-/intein-mediated ligation between ribosomally synthetized precursor proteins containing two orthogonal ligation points and a panel of bifunctional small molecules.

Most of the biological methods of synthesis mentioned above enable the preparation of astounding numbers of diverse macrocycles that are accessible for biological screens. In addition, a direct link between genotype and phenotype allows for the rapid screening and deconvolution of these large and diverse libraries. However, the disadvantage of these methods is that they deliver relatively high molecular weight compounds with large polar surface areas, which are unlikely to be cell-permeable. A certain analogy with the state of the art in combinatorial chemistry of the 1990's might be appropriate. This comparison suggests that emphasis on the numbers is not related to the real bottleneck of drug discovery. History has shown that it is the molecular properties such as microsomal stability and cellular permeability, rather than target engagement, that are the most challenging steps in drug discovery. A synergistic relationship between biology and chemical synthesis undoubtedly needs to be nurtured if macrocycles are to become a useful modality in drug discovery.

3. Properties of macrocycles

When compared to small molecules, a macrocycle/protein interaction is inherently more complex. In some cases, the induced fit model was shown to adequately describe this interaction. Akin to the structural biologists' regard for

induced fit, synthetic chemists view the Curtin–Hammett principle as one of the pillars of not only chemical reactivity, but many other molecular properties. By stressing the importance of kinetics, the Curtin–Hammett principle reveals an interesting analogy to macrocycle/protein target interaction. This principle states that the ground state conformation is not necessarily the reactive (or relevant) one. Significantly, this dictum applies only to systems in which a rapid inter-conversion between two or more accessible conformations can be established. The possibility shown in Fig. 12A describes two accessible macrocycle conformations that can interconvert. If the barrier to interconversion is low and the active conformation is readily sampled, it is immaterial to be concerned about conformational analysis of macrocycles because the system is unlikely to "miss" the desired state. On the other hand, if the barrier is high, the free energy of binding may not be sufficient to induce the desired conformation. This is analogous to the so-called "non-Curtin–Hammett" scenario that exists in chemical reactivity. While this is a rare phenomenon, some macrocycles with complex conformational energy landscapes are likely to undergo slow conformational interconversion, which is expected to influence their properties. For instance, the crystallographically characterized binding conformation of an SH2 domain inhibitor shown in Fig. 12B was readily attained after incubating the macrocycle in the presence of the SH2 protein at 50 °C for 10 minutes before allowing the system to crystallize at room temperature. The results of crystallization experiments at room temperature alone were inferior to those obtained by heating at 50 °C first, followed by crystallization. The challenges inherent to understanding macrocycle conformations are further mirrored in the difficulties that exist during computational docking of macrocycle ligands.

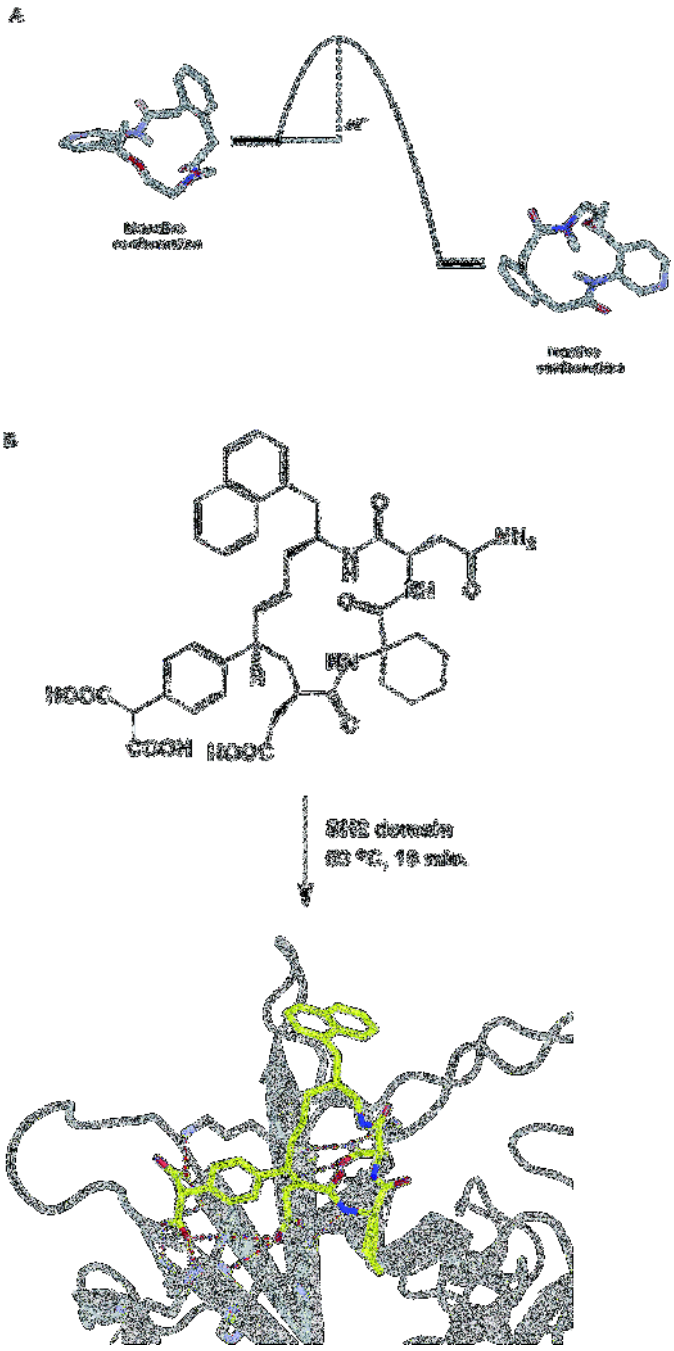


Fig. 12 (A): A hypothetical potential energy diagram linking two macrocycle conformations; and (B): co-crystallization with macrocycles may require energy to overcome the conformational barrier between different states (pdb id: 3aob)

It follows that, while the induced fit is a well-recognized phenomenon, attention must be paid to the inherent capacity of a given macrocycle scaffold to be amenable to the reorganization that is needed in such a process. Given the established correlation between cellular permeability and intramolecular hydrogen bonds (vide infra), one can easily appreciate the challenge: either target engagement or cellular permeability may correspond to a conformation that is not readily accessible. One of the main challenges that faces the field of macrocycles lies in having to simultaneously address these two disparate goals.

To further complicate matters, there are some thought-provoking studies that challenge the dogma that constrained molecule/target interactions are primarily entropy-driven. In a series of elegant experiments, Martin and co-workers questioned the prevailing view that preorganization must have a favorable entropic component (Fig. 13A). The authors demonstrated that entropies of binding of preorganized ligands to their targets could be disfavored when compared to the less potent, yet flexible, controls. It was shown that the enhanced enthalpy of binding could arise from an unexpected involvement of protein/ligand polar contacts. Using PDZ domains as model biological receptors, Spaller and co-workers came up with similar conclusions during their evaluation of macrocycles and stressed the significance of proper linear controls when analyzing a series of macrocycle binders (Fig. 13B).

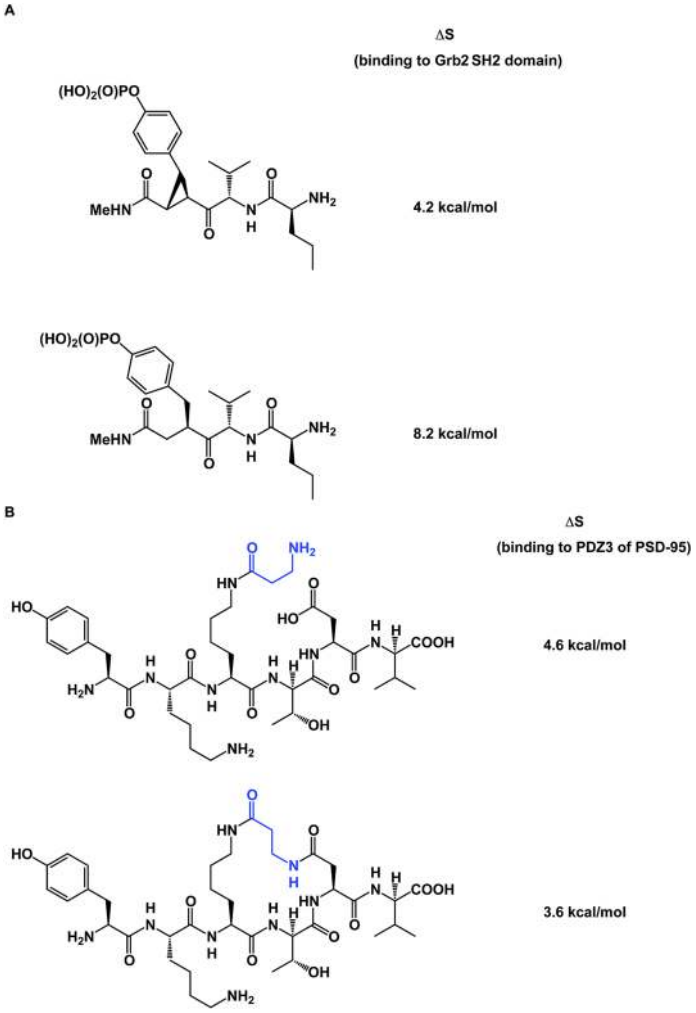


Fig. 13 (A): Constrained small molecules do not always result in more favorable entropy of binding; and (B): macrocycles can show unfavorable binding entropy compared to linear controls

3.1. Conformational analysis

The discussion above leads to the conclusion that it is important to study and understand the conformational preferences in a given macrocycle series. Fig. 14 presents a condensed version of some powerful methods that are now routinely

available to chemists interested in studying cyclic peptides and other types of macrocycles. For instance, recording the 1H NMR chemical shift changes of NH groups as a function of temperature helps identify the slowly exchanging protons that are likely to be tied up in intramolecular hydrogen bonds. In the course of their study of cyclophane macrocycles, which represent a particularly under-populated region of chemical space, James and co-workers resorted to EXSY spectroscopy in order to elucidate chemical exchange between conformations sampled by the macrocycles under scrutiny. The presence of cross-peaks in the EXSY spectra suggested an exchange between different conformations, which were found to slowly interconvert. The exchange rates for the transformation of detected conformations can be established from the experimentally determined parameters during EXSY experiments. X-ray crystallography is another valuable tool in the conformational analysis of macrocycles, although caution is advised with regard to the relevance of this analysis as solvent-dependent behavior in solution can lead to completely different conclusions. Circular dichroism can be indispensable in the studies of protein secondary structure fragments embedded in macrocycles. Here too, one has to be aware of the danger to over-interpret the data. For instance, in an intriguing case, Fairlie demonstrated how a macrocycle with α-helical sub-structure displays β-sheet-like spectrum. The computational prediction of macrocyclic conformations in both free and bound states is significantly more challenging compared to small molecules. In contrast to small molecules, the degrees of freedom in macrocycles are not mutually exclusive and perturbations are "coupled" in such a way that changing one dihedral angle in the backbone affects other dihedral angles, which causes computational conversion to take significantly longer.

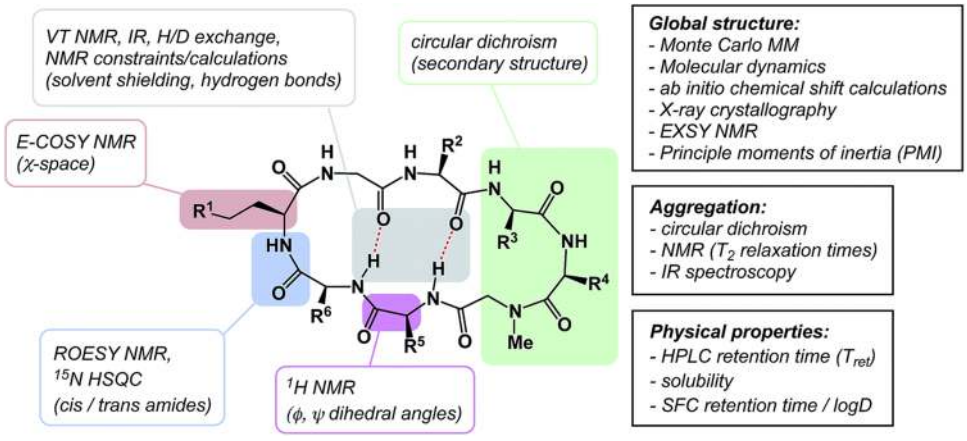


Fig. 14. From measurement to computation: assessing the properties of macrocycles

NMR can be a useful tool for the rational design of conformationally rigidified macrocyclic scaffolds. Fairlie and colleagues were able to show that the 13-membered rings obtained by homologation of a cyclic tetrapeptide are characterized by a marked improvement in the conformational rigidity of the ring. Due to their rigidity, the resulting α3β architectures of cyclic tetrapeptides are especially well-suited for the interrogation of HDAC enzymes. While main-chain chirality is believed to be the

major factor influencing macrocycle conformation, a recent report by Hunter and colleagues provides a rare and exciting possibility that diastereotopically-dependent structural modification of the cyclic peptide core with fluorine atoms can play an important role in structural rigidification (Fig. 15A).

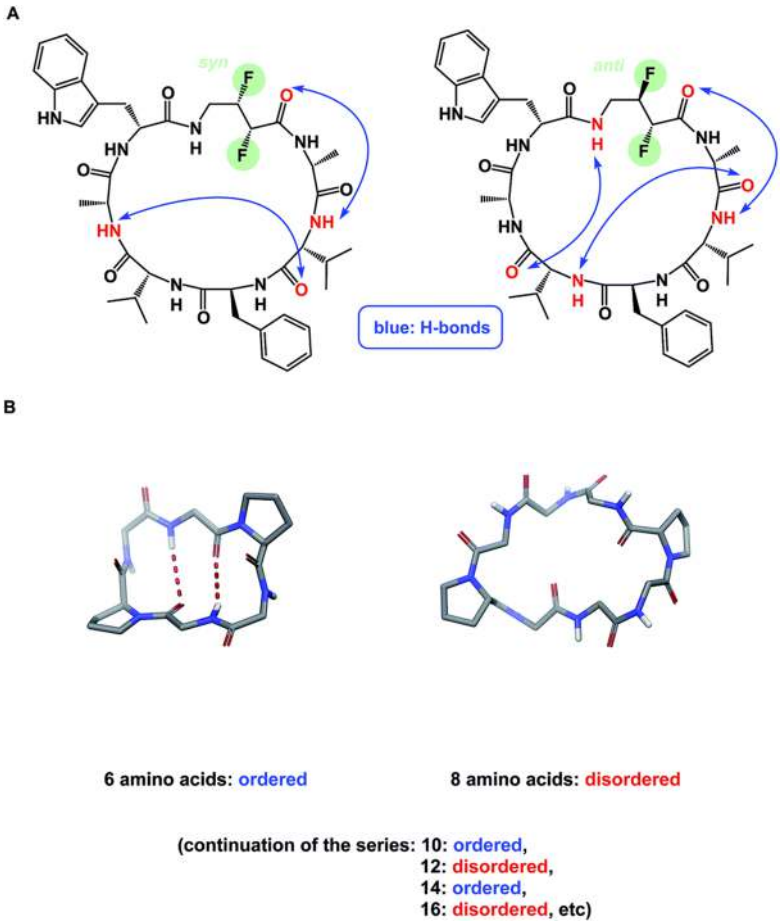


Fig. 15 (A): Control over macrocycle conformation using fluorination; and (B): periodicity of β-sheet formation in cyclic peptides

The solution conformation deduced by NMR can also afford insights needed for the rational design of therapeutic lead structures. In an earlier study, Dinsmore and colleagues at Merck showed how the solution structure of a conformationally flexible inhibitor of FTase suggested a macrocyclic analogue with a substantially improved inhibition profile. Recently, a hybrid sequential molecular mechanics/quantum mechanical approach to modeling cyclic peptides has resulted in an effective method for predicting their 1H and 13C NMR chemical shift values. The utility of this method was tested in a blind fashion and excellent agreement with the experimental NMR chemical shifts was observed.

α-Helix, β-sheet, and β-turn are the most common types of protein secondary structure. These structural types are prevalent in both solution- and solid-phase structures of proteins and are known to mediate the vast majority of protein–protein interactions. Unfortunately, these secondary structures are rarely observed in small linear peptides. Cyclization provides an opportunity to “freeze” these motifs, making

them amenable to conformational analysis and structure/function studies. An interesting consequence of constraining amino acid motifs was noted by Wishart and co-workers, who observed size-dependent periodicity of β-sheet content in cyclic peptides (Fig. 15B). This study proved the long-standing hypothesis that cyclic peptides containing 6, 10, and 14 α-amino acid residues in length exhibit high β-sheet content, whereas macrocycles of 8, 12, and 16 residues exist as random coils. Robinson and colleagues further established (D)-Pro–(L)-Pro linker as an effective means of creating turn structures with high β-sheet content,while Nowick introduced ornithine-derived turn elements as a means to generate and stabilize modular β-sheet motifs.

α-Helices are known to dominate protein–protein interfaces, which is why stapled peptides (macrocyclic peptides covalently constrained with hydrocarbon linkers that stabilize α-helices), have found a range of applications in chemical biology and drug discovery. Recently, Pentelute and co-workers resorted to cysteine-mediated SNAr reactions between peptides and perfluorinated aromatics in order to force linear peptides into stapled versions with constrained presentation of α-helical motifs. Unnatural amino acid turn elements can induce unusual turn structures in the molecules of well-known natural products. Thus, Overhand and co-workers resorted to rigid furanoid sugar amino acids to interrogate the β-hairpin structural elements of gramicidin S. Our lab recently resorted to strategically placed exocyclic amides to ensure conformational homogeneity of macrocycles.60 Ulrich and Komarov employed UV light to control the conformation of cyclic peptides equipped with photochemically sensitive groups (Fig. 16A).

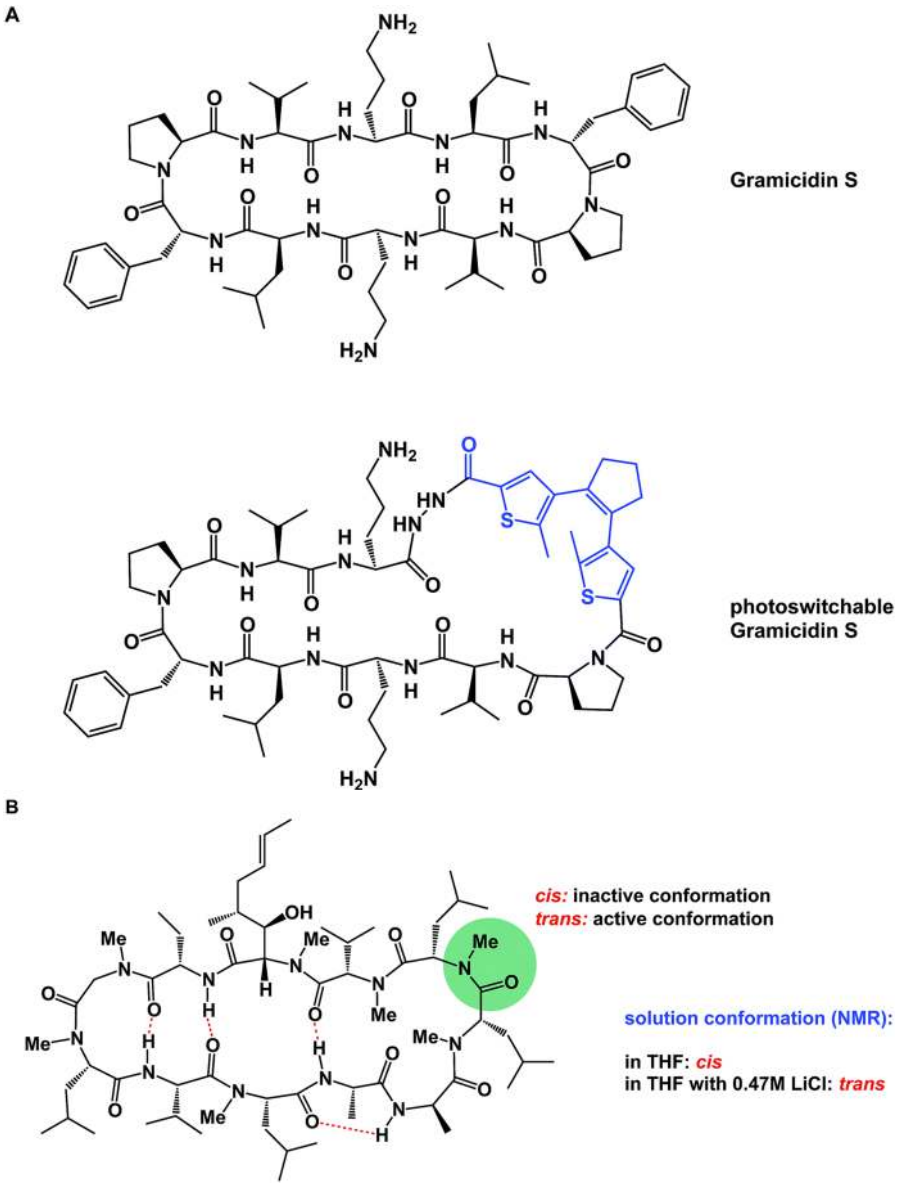


Fig. 16 (A): Light-induced control of gramicidin S; and (B): inducing conformational changes in cyclosporine A

Various additives can exert a profound influence on the solution conformation of macrocycles. In their classic study, Rich and co-workers demonstrated that the addition of lithium chloride to the solution of cyclosporine A in THF influences the geometry of the Leu–Leu bond. It was established that if the Leu–Leu amide linkage in cyclosporine A is in its cis state, the molecule is biologically inactive against its cyclophilin target. Rich and co-workers further demonstrated that the addition of LiCl to cyclosporine A in THF shifts the cis/trans equilibrium toward the bioactive trans form (Fig. 16B). Remarkably, the authors were able to show that the LiCl perturbation method works to alter even the biological properties of cyclosporine A. It was found that a significantly more potent inhibition of cyclophilin takes place in the presence of LiCl.

The conformational properties of macrocycles can have a direct influence on their chemical reactivity. Our lab recently demonstrated macrocycle-dependent regioselectivity during site-selective modification of macrocyclic electrophiles containing N-acyl aziridines. In this chemistry, the peptide structure dictated the adoption of different reactive conformations of the N-acyl aziridine embedded in the ring (Fig. 17). When the aziridine amide adopts a cis conformation, azide anion attacks the α-carbon of Azy (aziridine carboxylic acid) exclusively, leading to the formation of a trans amide-like transition state, wherein allylic strain is minimized. Alternatively, attack at the β-carbon of the Azy residue leads to the development of a less favorable cis-like amide bond. The fact that this regiochemistry is different from that observed in the case of linear Azy-containing peptides attests to the influence of macrocycle conformation over chemical reactivity. This idea is substantiated by the fact that attack at the α-carbon of the Azy residue is preferred in linear peptides.

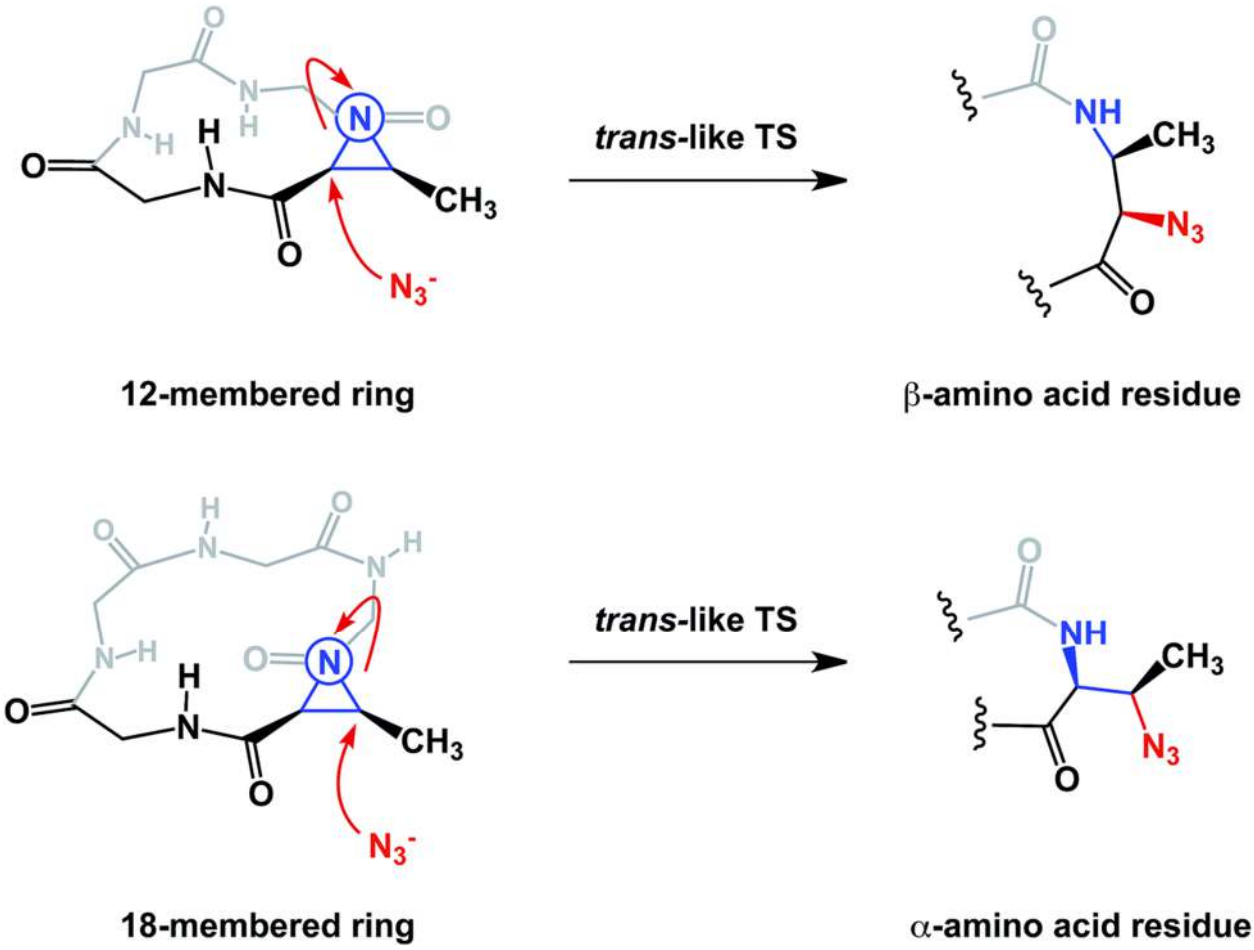


Fig. 17. Kinetic control over cis- and trans- like transition states in macrocycles (amino acid side chains are omitted for clarity)

The knowledge of the three-dimensional properties of constrained amino acid sequences can lead to impressive levels of control over macrocycle self-assembly in solution. Hydrogen bond-driven formation of peptide nanotubes is perhaps the best-known example of this sort of control. Ghadiri and co-workers demonstrated that, when

constrained in macrocycles, alternating D- and L-amino acid sequences give rise to the formation of well-defined nanotubes that have found application as antibacterial agents. This example demonstrates the possibility of controlling aggregation of cyclic peptides in solution using relative stereochemistry of amino acid residues (Fig. 18).

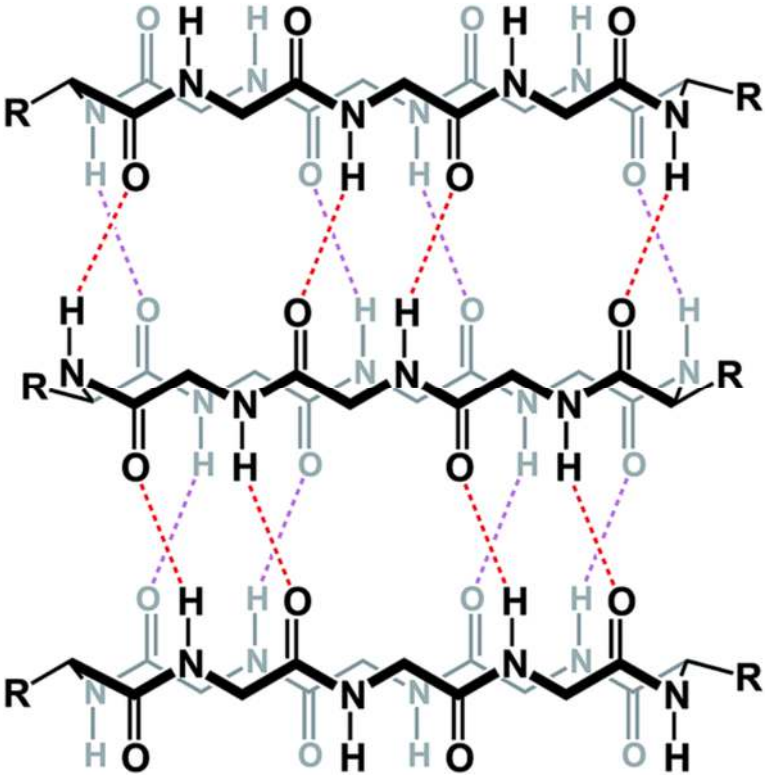


Fig. 18. Formation of nanotubes from cyclic peptides (alternating stereochemistry not included for clarity)

Lastly, the possibility of attaining well-defined conformations in cyclic peptides can have a direct link to their performance in catalysis. Herrmann and co-workers recently introduced a metallopeptide design based on a stable cyclic peptide scaffold that was maintained by an intramolecular disulfide linkage. The authors applied an alanine scanning technique to optimize the catalytic performance of their cyclic peptide catalyst system in Friedel–Crafts and Diels–Alder reactions.

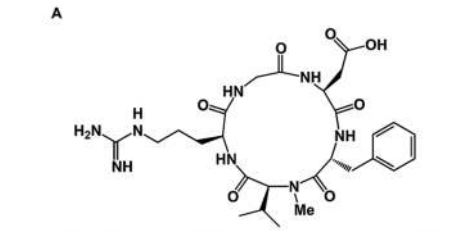
3.2. Structural biology of macrocycles

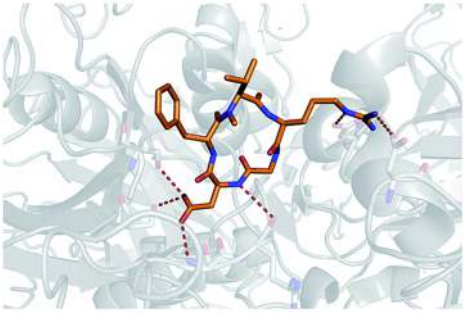
Due to their relatively large size, macrocycles display unique features upon interaction with their protein targets. Topology of the protein surface may dictate if a macrocycle adopts an “edge-on” or a “face-on” binding mode. This analysis by Whitty and co-workers further suggests that a preferred collection of macrocycles aimed at general-purpose drug discovery would benefit from molecules equipped with large and small substituents distributed around the ring. This is expected to increase the chances of finding useful compounds that can interrogate a wide range of protein binding site topologies. Whitty's analysis also suggests that at least five strong binding energy “hot spots” need to be present in a macrocycle, which is more than what is required for the

binding a conventional small molecule drug. Interestingly, the hot spots can be set further apart from what is acceptable for conventional binding sites that are considered druggable. A recent report on the comprehensive analysis of protein surface loops suggests a mechanism by which “hot loops” can be identified and turned into constrained peptide inhibitors.

In cyclic peptides, the correct conformational recapitulation of the amino acid sequence involved in a biological interaction is required for effective agonism or antagonism of a protein target. Incorrect positioning of the binding determinants can easily lead to the wrong conformation. Even a fairly small deviation from the optimal geometry can bring about dramatic consequences. For example, the RGD sequence of amino acids is known to mediate interactions between cell surface integrin receptors and matrix proteins such as vitronectin, laminin, fibrinogen, and fibronectin. That this tripeptide sequence mediates multiple protein-dependent pathways implies distinct conformations of the RGD sequence in different matrix proteins. Kessler and colleagues showed that, when placed into the framework of a 15-membered ring, RGD correctly represents the binding epitope of fibronectin. This study illuminates the importance of choosing the geometrically correct turn motif. Even a minor deviation from the optimal arrangement of dihedral angles was found to result in a significant decline of potency. A constrained RGD/integrin complex was later crystallographically characterized, revealing that the RGD motif inserts into the crevice between the propeller and βA domains and makes contacts with both (Fig. 19A).

A





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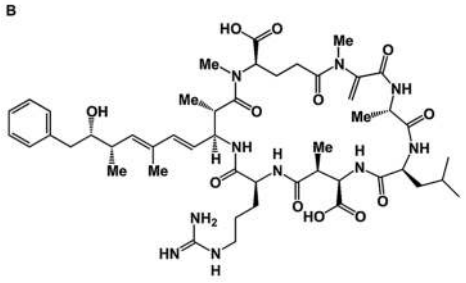

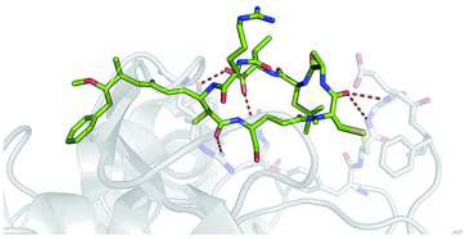

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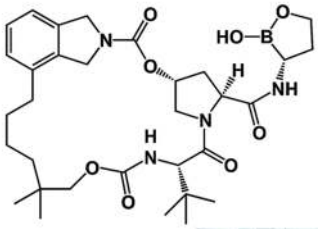

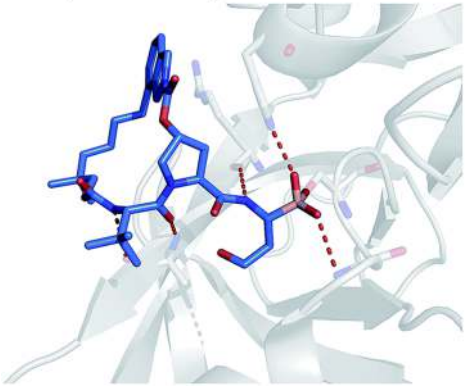

Fig. 19. Selected crystal structures of macrocycles and their targets. (A): An RGD-based macrocycle complexed with the extracellular segment of integrin α5β3 (pdb id: 1lfg); (B): microcystin – a covalent phosphatase inhibitor (pdb id: 1fjm); and (C): Anacor's boron-containing macrocyclic HCV inhibitor (pdb id: 2xni)

Macrocycles are also capable of covalent inhibition of their protein targets, which is notable given how much attention has been devoted to the development of covalent inhibitors. It is quite possible that combining the benefits that accrue as a result of increasing an inhibitor's polar surface with covalent bond formation can result in significant gains in potency. Given the possibility of rapid target ID, synthetic cyclic peptide electrophiles are likely to emerge as important tool compounds, particularly in phenotypic screens. In this regard, cyclic peptide natural products such as microcystin provide an inspiration. Thus, microcystin forms a covalent bond with the surface-exposed nucleophilic Cys-273 residue of PP1 phosphatase through Michael addition to the dehydroalanine moiety (Fig. 19B). Synthetic macrocycles that interact with oxygen-based active site residues include boron-containing molecules that were designed at Anacor. In this study, a new series of HCV NS3 serine protease inhibitors equipped with a cyclic boronate moiety at the P1 position of an HCV inhibitor scaffold, were developed and characterized by X-ray crystallography (Fig. 19C).

3.3. Cellular permeability and oral bioavailability

While the aforementioned structural features of macrocycles are significant from the standpoint of target engagement, they are unfortunately not related to properties that ensure bioavailability and other therapeutically relevant characteristics. Large polar surface area is the biggest obstacle preventing cyclic peptides and other macrocycles from being taken up by cells. The lion's share of current efforts goes into identifying macrocycles with drug-like properties.

There are two main ways in which chemicals are thought to permeate cellular membranes: passive and active transport. The passive type of cellular entry is characterized by molecular diffusion driven by a concentration gradient, whereas the active entry type is energy-driven and involves molecular transporters. The most common assays that are used in comparative studies of a macrocycle's capacity to traverse cells are PAMPA (Parallel Artificial Membrane Permeability Assay) and Caco-2 cellular permeability assays. In this regard, it is exciting to note some surprisingly simple permeability surrogates that have appeared in the literature. One of them is based on supercritical fluid chromatography, which has enabled improved permeability design.

The correlation between three-dimensional structure and cellular permeability is a fascinating area of contemporary research. Fernandez introduced the concept of

under-wrapped hydrogen bonds (under-wrap = expose to solvent) and applied a variety of metrics to rank peptide ligands in terms of their cellular permeability, arguing that manipulation of intramolecularly under-wrapped electrostatic interactions in proteins can be exploited as a strategy to create molecules with enhanced ability to penetrate biological membranes. Lokey's group carried out a detailed study aimed at further examining the hypothesis that intramolecular hydrogen bonds improve passive membrane permeability of cyclic peptides. This investigation confirmed that membrane permeability of cyclic peptides is likely governed by a combination of intramolecular hydrogen bonding along with the protection of amide NH groups from solvation. Subtle differences in structure can play a decisive role in this process. For example, diastereomeric macrocycles can display notable differences in their ability to penetrate cells, which speaks to the adoption of different patterns of hydrogen bonds in structurally similar compounds. In the case of cyclic peptides, many efforts are aimed at improving cellular permeability by selective N-methylation of backbone amides. This strategy brings about a reduction of the polar surface area of a given cyclic peptide and increases the probability of intramolecular hydrogen bonds between the remaining NH amides and carbonyl oxygens. Using a library of 54 cyclic peptides with different N-methylation patterns, Kessler's lab designed structures that represent highly Caco-2 permeable templates amenable for grafting applications. This has become possible due to the defining role of the macrocycle core elements, and not the side chains, on the overall conformation. Interestingly, complete N-methylation can be detrimental to cellular permeability, highlighting a delicate balance that exists between a given molecule's permeability and lipophilicity. Thus, Lokey and co-workers showed that a partially N-methylated derivative shown in Fig. 20A was significantly more permeable in PAMPA assays than the corresponding per-methylated version. This was attributed to the more solvent-exposed nature of amide carbonyl oxygens in the per-methylated molecule's conformation, hinting at its higher effective polar surface area and, hence, diminished lipophilicity. Such findings are not intuitively clear by a visual examination of structures alone. Thankfully, computational tools can be effective in efforts to rationalize and predict the pattern of hydrogen bonds that is optimal for cellular permeability.

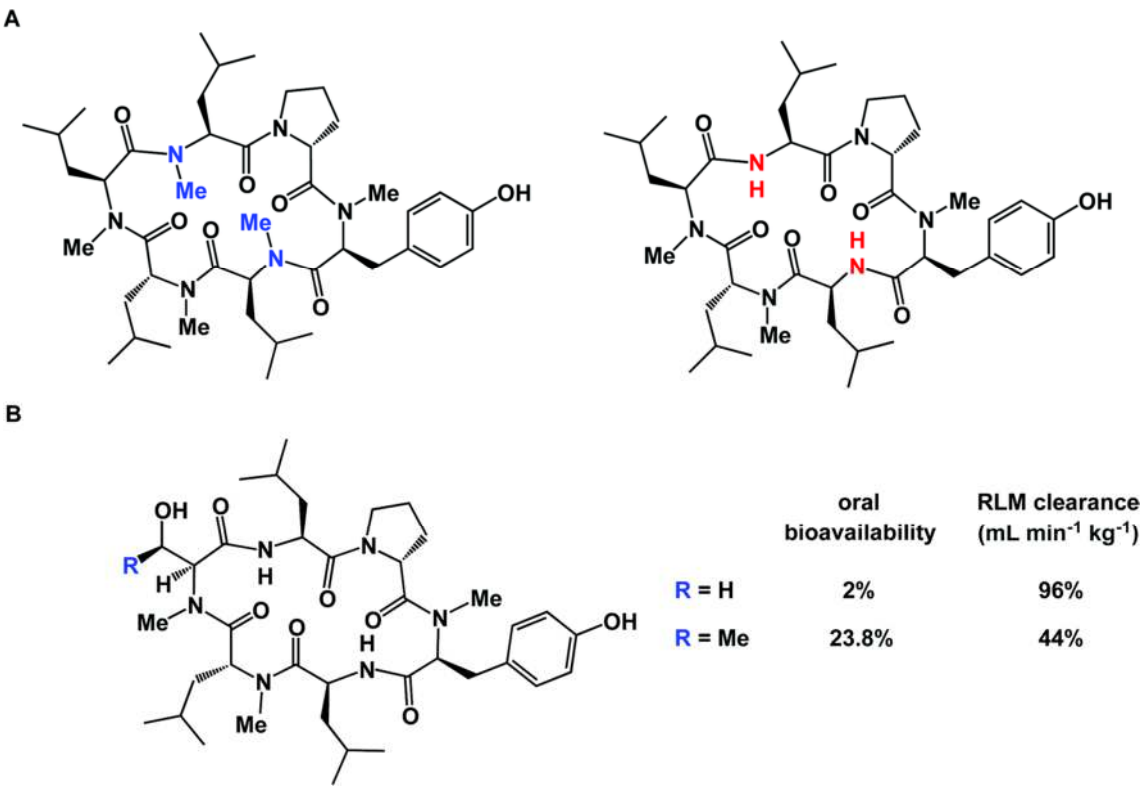

Fig. 20. Subtle structure/properties effects in macrocycles. (A): Excessive N-methylation can be a detriment to cellular permeability; and (B): a dramatic effect of serine for threonine substitution on intrinsic clearance in rat liver microsome

It should be noted that one important factor that needs to be taken into account when considering N-methylation is the potential for chemical instability, which has been reported for excessively N-methylated peptides. In this regard, it is encouraging to see studies which suggest that macrocycles without N-methylation can be orally bioavailable. At present, this comes at the expense of relying on excessively hydrophobic side chains to shield polar amide groups from solvent exposure. It will be important to see follow-up cases where a greater variety of side chains can be accommodated in this approach.

When it comes to active membrane transport, the situation is substantially more complicated. Although parsing out the involvement of protein transporters at an early stage of lead generation could be extremely challenging, it is advisable to understand whether or not a given macrocycle series is subject to P-gp efflux. Structural data, pointing at the mechanisms by which P-gp can interact with macrocycles, has appeared in recent years. For instance, in an intriguing paper, Chang and colleagues showcased how the “dreaded” P-gp protein accommodated both enantiomers of a cyclic peptide molecule in its cavity (Fig. 21A).5 Nureki and co-workers reported on their structural characterization of a key multidrug and toxic compound extrusion (MATE) family transporter in complex with an in vitro selected thioether-based macrocyclic peptide (Fig. 21B). These studies suggest yet another parameter that awaits understanding in this area of research: how to modulate transporter-mediated removal of macrocycles

from cells. This relates to both diminishing efflux in order to ensure adequate target engagement and enhancing efflux to avoid cytotoxicity due to accumulation.

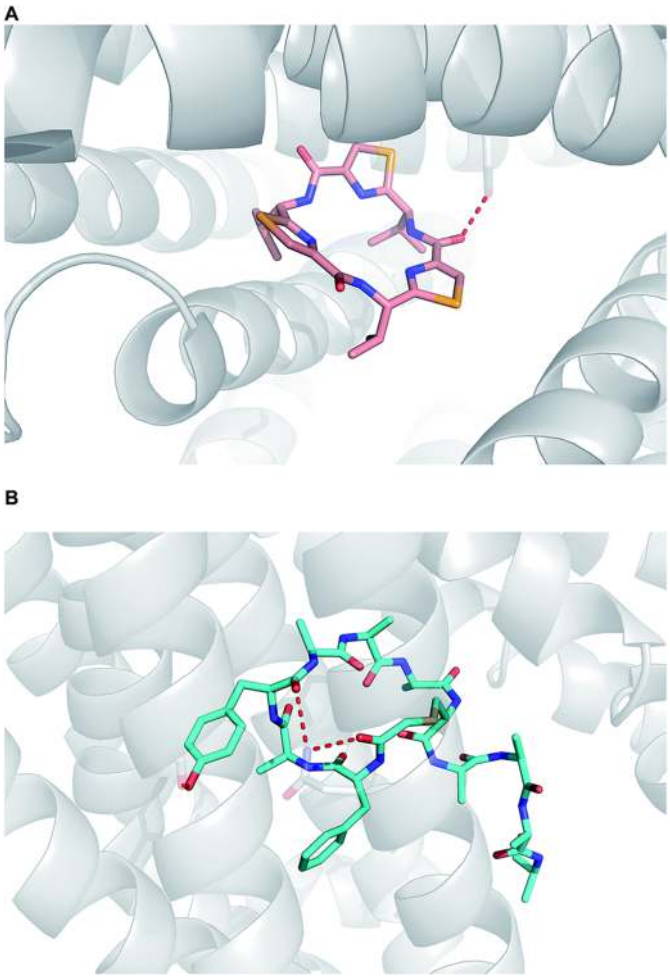

Fig. 21. Macrocycles complexed with transporters. (A): P-gp complexed with a selenium-containing cyclic peptide (pdb id: 3g61); and (B): multidrug and toxic compound extrusion transporter complexed with a cyclic peptide (pdb id:3vvr)

Oral bioavailability adds another layer of complexity to evaluating the potential of macrocycles as promising drug candidates. Orally active and/or bioavailable peptide macrocycles that are currently on the market include cyclosporine A, linaclotide, and some somatostatin analogs, such as octreotide. Clearly, all of these compounds violate the “rule of 5”, further reinforcing the significance of understanding oral bioavailability of molecules that belong to the “Beyond the rule of 5” (Bro5) class.

Microsomal stability is typically evaluated by subjecting a compound to rat liver microsomes (RLM). This kind of study can be exceptionally useful as concrete steps aimed at improving molecular profiles can be identified. Unfortunately, full metabolite identification (MetID) profiles of macrocycles can be very expensive and are not performed routinely, at least in the academic setting. Streamlining of these assays is expected to be enabling and will result in innovative chemical approaches to site-selective macrocycle modification. The poorly-understood balance between the three-

dimensional structure and microsomal stability of macrocycles is further illuminated by comparing the dramatic difference observed when structurally similar molecules are exposed to RLM analysis (Fig. 20B). The serine derivative was shown to have 96 mL min−1 kg−1 RLM clearance, whereas the threonine-containing congener was substantially less stable (44 mL min−1 kg−1 RLM clearance). Oddly enough, the serine-containing peptide actually had an oral bioavailability of only 2% compared to the threonine-containing peptide which was 23.8% orally bioavailable. This example underscores the highly empirical nature of efforts to identify orally bioavailable macrocycles and suggests that finding a correlation between oral bioavailability and scaffold design is likely to be challenging. Yet, the discovery of orally bioavailable peptides continues to be the subject of intense investigations and oral bioavailability can be established even for fairly large molecules. It should also be acknowledged that, while striving for oral bioavailability is a worthy goal, peptides provide an opportunity to develop exquisitely potent compounds, which can offset their poor drug-like properties. Ultimately, reaching the desired therapeutic profile can be realized using special additives. A case in point is octreotide: in a well-known study, its oral bioavailability was reported to be only 0.3%, yet it could be dramatically improved by formulation. In this regard, the advent of nanotechnology and new drug delivery modalities is expected to play a pivotal role in ensuring that macrocycles reach their therapeutic targets and remain reasonably bioavailable.

4. Conclusions

Macrocycles constitute an exciting class of molecules with a tremendous upside in drug discovery and other fields of inquiry. Their complex structures invite the development of novel cyclization technologies with improved efficiency. It is equally important to have the modern tools of synthesis bear on site-selective structural modification of existing macrocycle cores. In efforts to come up with new synthetic tools aimed at macrocycles, chemists need to be aware of the propensity of macrocycles to be susceptible to transannular interactions. These interactions can deliver dividends in areas that require conformational constraint, but attention must be paid to the potentially detrimental consequences of particularly strong transannular interactions that can lead to unanticipated intramolecular reactivity and “collapse”. The availability of broadly applicable methods that address these long-standing goals will further facilitate synthesis-driven improvement of macrocyclic lead molecules in drug discovery. At the same time, detailed knowledge of the three-dimensional preferences of macrocycles, complicated by the presence of partially rotatable bonds, will serve areas in which functional outcomes are rooted in one's ability to modulate intermolecular interactions. Control over the so-called χ-space, that defines conformational movement of side chains, is one of the most difficult areas to address. In this regard, there is a certain irony in overemphasizing the significance of new ways to form macrocyclic ring structures: these studies offer constraints over ϕ and ψ

dihedral angles, but they provide little towards control in the "χ-space" which defines the side chain orientation (Fig. 22).

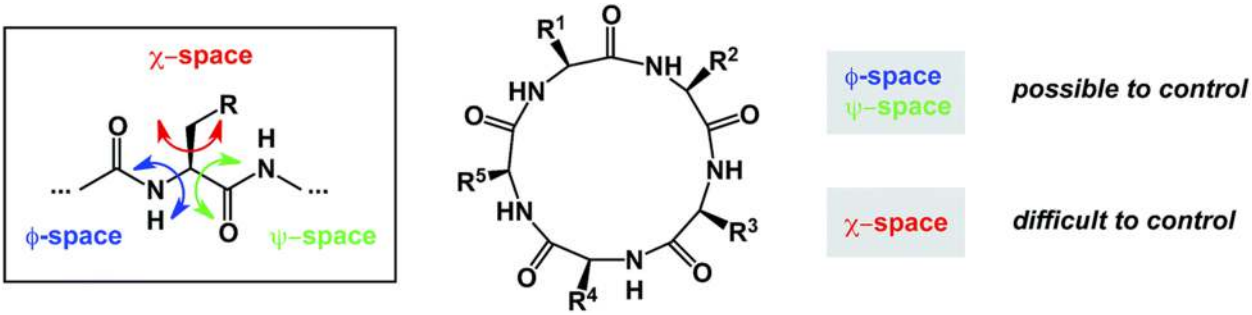

Fig. 22. Peptide macrocycles and the challenge of conformational control in all areas of accessible space

When it comes to cyclic peptides, it would be useful to see a greater variability with regard to accessible synthetic building blocks. Indeed, approaches to macrocycles based on improving compound profiles using amino acid modifications tend to underemphasize the relative significance of non-amino acid building blocks – the ones that do not suffer from the limitations of peptide linkages. Chemists need to keep in mind that, just because amino acids are readily available in their protected forms and are suited for streamlined synthesis of linear precursors to cyclization, it does not mean that there is anything inherently special to them (an exception is when the goal is to rationally constrain a particular protein secondary structure motif). As a result, overemphasizing the attempts to render amino acid-derived materials "more palatable" might result in approaches that detract from rapid optimization of the function-defining characteristics of molecules. In this regard, structure-driven efforts aimed at peptidomimetic macrocycles should be encouraged.

The most difficult questions in the area of biologically active macrocycles will likely relate to reconciling the synthetic and biological approaches to synthesis. The domain of chemical synthesis is fertile with methods that enable the development of molecules with optimal pharmacological profiles. Unfortunately, the accessible molecular diversity is still a challenging proposition. In contrast, biological synthesis appears to readily provide enormous molecular diversity, albeit at the expense of offering only a limited palette of useful building blocks. In addition, the molecules that are accessible with biological methods are rarely attractive drug candidates, particularly when it comes to intracellular targets. The inherent friction between the synthetic and biological domains of synthesis is likely to result in exciting innovations in the years to come.

Acknowledgements

I would like to thank the past and present members of my research group at the University of Toronto. I would like to particularly acknowledge the efforts of Dr Conor Scully, Dr Jen Hickey, Dr Chris White, Benjamin Chung, Dr Ryan Hili, Dr Vishal Rai,

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Words and word combinations:

- drug target – мишень для лекарства (цель лечения);
- unmet [ˌənˈmet] – неудовлетворенный;
- to be up to the task – быть готовым к задаче;
- cellular [ˈselyələr] – клеточный;
- straightforward [ˌstrātˈfôrwərd] – простой;
- heel [hēl] – пятка (пята);
- overview [ˈōvərˌvyo͞o] – обзор;
- foray [ˈfôrˌā] – набег;
- framework [ˈfrāmˌwərk] – рамка, структура;
- subclass [ˈsəbklas] – подкласс;
- consequence [ˈkänsikwəns] – следствие;
- sustained [səˈstānd] – устойчивый;
- to coincide [ˌkōənˈsīd] – совпадать;
- frame of mind – граница разума;
- hydrogen bonds – водородные связи;
- salt bridges – соляные мосты;
- penaltie [ˈpen(ə)ltē] – штраф;
- exquisitely intertwined – изысканно переплетенный;
- to put together – собирать воедино;
- validation [ˌvaləˈdāSH(ə)n] – утверждение, проверка;
- merit [ˈmerət] – заслуга;

- propensity [prəˈpensədē] – склонность;
- drug-like properties – лекарственные свойства;
- conundrum [kəˈnəndrəm] – загадка;
- permeability [ˌpərmēəˈbilədē] – проницаемость;
- outlier [ˈoutˌlīər] – выброс;
- significantly [səgˈnifəkəntlē] – значительно;
- decisive factor – решающий фактор;
- thought-provoking – наводящий на мысли;
- due to – из-за;
- innate [iˈnāt] – природный, врожденный;
- proximity [präkˈsiməd̄ē] – близость;
- courtesy [ˈkərdəsē] – любезность;
- cleavage [ˈklēvij] – расщепление;
- acid residues – кислотные остатки;
- docking – стыковка;
- simultaneously [ˌsīməlˈtānēəslē] – одновременно;
- perturbation [ˌpərdərˈbāSH(ə)n] – возмущение;
- utility [yo͞oˈtiləd̄ē] – полезность;
- to resort to – прибегать к;
- to exert [igˈzərt] – прикладывать;
- aimed to – направленный на;
- loop [lo͞op] – петля;
- the lion's share – львиная доля;
- to permeate [ˈpərmēˌāt] – проникать;
- under-wrapped – скрытый;
- efflux [eˈfləks] – излияние;
- liver [ˈlivər] – печень;
- lead [lēd] – свинец;
- overemphasizing [ˌəʊvəˈremfəsaɪzɪŋ] – преувеличение;
- acknowledgement [əkˈnɒlɪdʒmənt] – благодарность.

Task 2. Summarize all the ideas of the article and write an essay.

Task 3. Make a presentation based on the article.

ARTICLE 2

Task 1. Read the text below.

Advances in lignocellulosic biotechnology: A brief review on lignocellulosic biomass and cellulases

(by Tanzila Shahzadi, Sajid Mehmood, Muhammad Irshad, Zahid Anwar, Amber Afroz, Nadia Zeeshan, Umer Rashid, Kalsoom Sughra)

Abstract

From the last few decades, there has been an increasing research interest in the value of lignocellulosic biomass. Lignoellulosic biomass is an inexpensive, renewable abundant and provides a unique natural resource for large scale and cost-effective bio-energy collection. In addition, using lignocellulosic materials and other low-cost biomass can significantly reduce the cost of materials used for ethanol production. Therefore, in this background, the rapidly evolving tools of biotechnology can lower the conversion costs and also enhance a yield of target products. In this context, a biological processing presents a promising approach to converting lignocellulosic materials into energy fuels. The present summarized review work begins with an overview on the physico-chemical features and composition of major agricultural biomass. The information is also given on the processing of agricultural biomass to produce industrially important enzymes, e.g., ligninases or cellulases. Cellulases provide a key opportunity for achieving tremendous benefits of biomass utilization.

Keywords

lignicellulosic biomass, ecofriendly, bioethanol, industrial enzyme

1. Introduction

Lignocellulosic materials are the most promising feedstock as natural and renewable resource. Among many of the developing countries, it's a routine practice that such agricultural wastes are not been fully discarded and then have become a major source of ecological pollution. Naturally, cellulose, hemicellulose and lignin are the major constituents of plant cell walls and among all of them, cellulose is the most common and abundant component of all plant matter. From the last several years, there is an increasing demand for industrial important enzymes. In such scenario, cellulase is being used in many of the industrial applications mainly but not limited in the field of cotton processing, paper recycling, agriculture and in the field of research and development. Besides all those applications, the production of fuel ethanol from lignocellulosic biomass through cellulase hydrolysis is a promising tool of the modern world. The most promising technology for the conversion of the lignocellulosic biomass to fuel ethanol is based on the enzymatic breakdown of cellulose using cellulase enzymes. Pakistan is an agricultural land that produces a large magnitude of lignocellulosic wastes. However, such wastes can be utilized for the production of

useful industrial enzymes or enzyme-based products. Enzymatic hydrolysis of such agricultural wastes provides an environmentally friendly means of depolymerizing cellulose and other carbohydrates at high yields.

2. Characteristics of lignocellulosic biomass

Lignocellulosic materials including agricultural wastes, forestry residues, grasses and woody materials have great potential for biofuel production. Typically, most of the agricultural lignocellulosic biomass is comprised of about 10% - 25% lignin, 20% - 30% hemicellulose, and 40% - 50% cellulose. Cellulose is a major structural component of plant cell walls, which is responsible for mechanical strength and chemical stability to plants. Hemicellulose macromolecules are often repeated polymers of pentoses and hexoses. Due to the genetic variability among different sources hemicellulose macromolecules also vary in structural composition. Lignin contains three aromatic alcohols (coniferyl alcohol, sinapyl alcohol and p-coumaryl alcohol) produced through a biosynthetic process and forms a protective seal around the other two components i.e., cellulose and hemicelluloses (Fig. 1). In general, the composition of lignocellulose highly depends on its source whether it is derived from the hardwood, softwood, or grasses. Lignocellulosic biomass has a complex internal structure and comprises of a number of major components that have, in turn, also complex structures. Table 1 shows the typical chemical compositions of all these three components in various lignocellulosic materials that vary in composition due to the genetic variability among different sources.

3. Properties of cellulose

Plant biomass contains 40% to 50% of cellulose molecules which are fibrous in nature, insoluble, crystalline polysaccharide. Being the most abundant and easily available carbohydrate polymer all around the earth which is a major polysaccharide constituent of plant cell wall, it is composed of repeating (1,4)-D-glucopyranose units, which are attached by β-1,4 linkages with an average molecular weight of around 100,000. Naturally cellulose molecules exist as bundles which are aggregated together in the form of micro-fibrils, i.e., crystalline and amorphous regions. The structure of one chain of the cellulose polymer is presented in Fig. 1. Cellulose has attracted worldwide attention as a renewable resource that can be converted into biobased products of commercial interests. Therefore, cellulose has been used as a potential energy source for a wide variety of organisms including fungi and bacteria to extract many useful products e.g., enzymes.

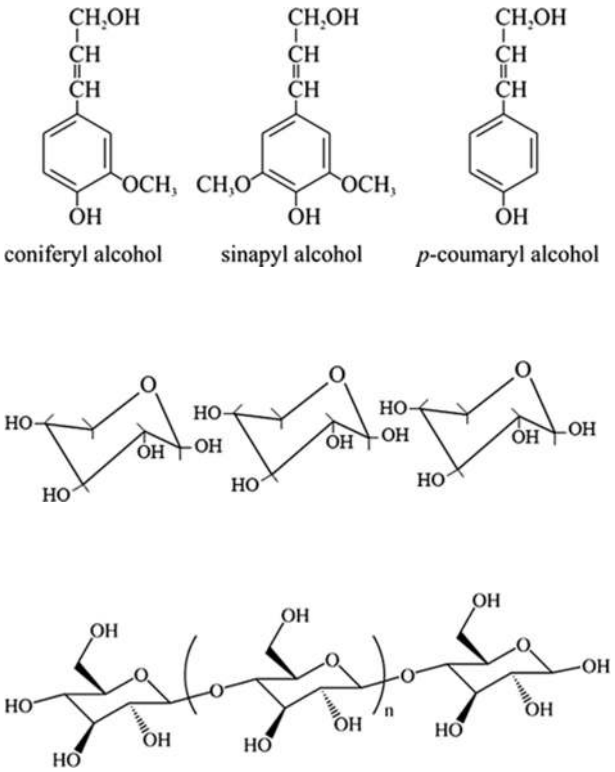

Fig. 1. Chemical structure of lignocellulosic material; (a) Building blocks/units of Lignin; (b) Xylose unit of hemicellulose; and (c) Cellulose. (Adopted from Iqbal *et al*.)

Lignocellulosic material	Lignin (%)	Hemicellulose (%)	Cellulose (%)	Reference*
Sugar cane bagasse	20	25	42	Kim & Day, 2011
Sweet sorghum	21	27	45	Kim & Day, 2011
Hardwood	18 - 25	24 - 40	40 - 55	Malherbe & Cloete, 2002
Softwood	25 - 35	25 - 35	45 - 50	Malherbe & Cloete, 2002
Corn cobs	15	35	45	Prassad *et al.* 2007
Corn stover	19	26	38	Zhu *et al.* 2005
Rice Straw	18	24	32.1	Prassad *et al.* 2007
Nut shells	30 - 40	25 - 30	25 - 30	Abbasi & Abbasi, 2010
Newspaper	18 - 30	25 - 40	40 - 55	Howard *et al.* 2003
Grasses	10 - 30	25 - 50	25 - 40	Malherbe & Cloete, 2002
Wheat straw	16 - 21	26 - 32	29 - 35	McKendry, 2002
Banana waste	14	14.8	13.2	John *et al.* 2006
Bagasse	23.33	16.52	54.87	Guimarães *et al.* 2009
Sponge gourd fibers	15.46	17.44	66.59	Guimarães *et al.* 2009

Table 1. Percent composition of lignocellulose components in various lignocellulosic materials (Adopted from Iqbal *et al*.).

4. Properties of hemicellulose

The second most abundant polymer after cellulose is hemicellulose which is heterogeneously branched in nature. The backbone of the hemicellulose polymer is built up by sugar monomers like xylans, mannans and glucans, with xylans and mannans being the most common, in this case xylanases are the enzymes involved in its degradation. Similar to cellulases the xylanases can act synergistically to achieve hydrolysis, predominant enzymes within this system are endo 1, 4 b-xylanases which attack the polysaccharide backbone and b-xylosidases. Hemicellulosic biomass contains 25% to 35% of hemicellulose, with an average molecular weight of <30,000. Cellulose and hemicellulose bind tightly with non-covalent attractions to the surface of each cellulose microfibril. Hemicellulose degrades quickly due to its amorphous nature. Among other important aspects of the structure and composition of hemicellulose are the lack of crystalline structure, mainly due to the highly branched structure, and the presence of acetyl groups connected to the polymer chain.

5. Properties of lignin

Lignin is generally the most complex and smallest fraction, representing about 10% to 25% of the biomass. It has a long chain, aromatic polymer composed largely of phenyl propane units. Lignin acts like a glue by filling the gap between and around the cellulose and hemicellulose complexion with the polymers. It is present in almost all kind of cellulosic plant biomass and acts as a protective sheet against cellulosic and hemicellulosic components of the biomass materials. Lignin consists of multifarious and large polymer of phenyl-propane, methoxy groups and non-carbohydrate poly-phenolic substance, which bind cell walls constituents together. Among them phenyl-propanes are the main blocks of the lignin share in biomass residues. These phenyl-propanes denoted as 0, I, II methoxyl groups attached to rings give special structure I, II and III. These groups depend on the plant source which they are obtained. Structure I exists in plants (grasses) and structure II is found in the wood (conifers) while structure III presents in deciduous wood.

6. Biotechnological importance of lignocellulosic biomass

A large magnitude of lignocellulosic biomass resources is available as potential candidates that are able to convert into high value bioproducts like bioethanol/biofuels. The detailed step by step information on the conversion of lignocellulosic biomass into fuel ethanol is illustrated in Fig. 2. From the last few decades there have been an increasing research and developmental interests in the value of lignocellulosic biomass. In this regard a considerable improvement from the green biotechnology related to lignocellulose biomass has appeared. The ever-increasing costs of fossil fuels and their greenhouse effects are a major concern about global warming. Therefore, all these issues are creating a core demand to explore alternative cheaper and ecofriendly energy resources.

7. From cellulose to cellulases

Cellulose is a fibrous, insoluble, crystalline polysaccharide. It is a major polysaccharide constituent of plant cell walls, composed of repeating D-glucose units linked by β-1,4-glucosidic bonds and being the most abundant carbohydrate polymer on earth. Cellulose has attracted worldwide attention as a renewable resource that can be converted into biobased products and bioenergy. But nowadays, enormous amounts of agricultural, industrial and municipal cellulose wastes have been accumulating or used in efficiently due to the high cost of their utilization processes. Therefore, it has become of considerable economic interest to develop processes for the effective treatment and utilization of cellulosic wastes as cheap carbon sources. Cellulose is used as a food source by a wide variety of organisms including fungi, bacteria, plants and protists, as well as a wide range of invertebrate animals, such as insects, crustaceans, annelids, mollusks and nematodes. These organisms possess cellulases and the complete enzymatic system of them include three different types, that is, exo-β-1, 4-glucanases (EC 3.2.1.91), endo-β-1,4-glucanases (EC 3.2.1.4), and β-1,4-glucosidase (EC 3.2.1.21). These enzymatic components act sequentially in a synergistic system to facilitate the breakdown of cellulose and the subsequent biological conversion to a utilizable energy source, glucose. The endo-β-1,4-glucanases randomly hydrolyze the β-1,4 bonds in the cellulose molecule, and the exo- β-1,4-glucanases in most cases release a cellobiose unit showing a recurrent reaction from chain extremity. Lastly, the cellobiose is converted to glucose by β-1,4-glucosidase.

8. Status and prospects of cellulases

Cellulase is an important and essential kind of enzyme for carrying out the depolymerization of cellulose into fermentable sugars. As a major resource for renewable energy and raw materials, it is widely used in the bioconversion of renewable lignocellulosic biomass. Glucose, received from appropriate hydrolysis of this lignocellulosic biomass under the treatment of advanced biotechnology, can be used in different applications such as production of fuel ethanol, single cell protein, feed stock, industrially important chemicals and so on. A number of fungi and bacteria capable of utilizing cellulose as a carbon source has been identified. Among the cellulolytic fungi, Trichoderma reesei has the strongest cellulose degrading activity, and its cellulase has been widely investigated. Many other industrially important enzymes produced by other fungi such as Trametes versicolor, Trichoderma, Aspergillus and Rhizopus species have also been extensively studied by several researchers.

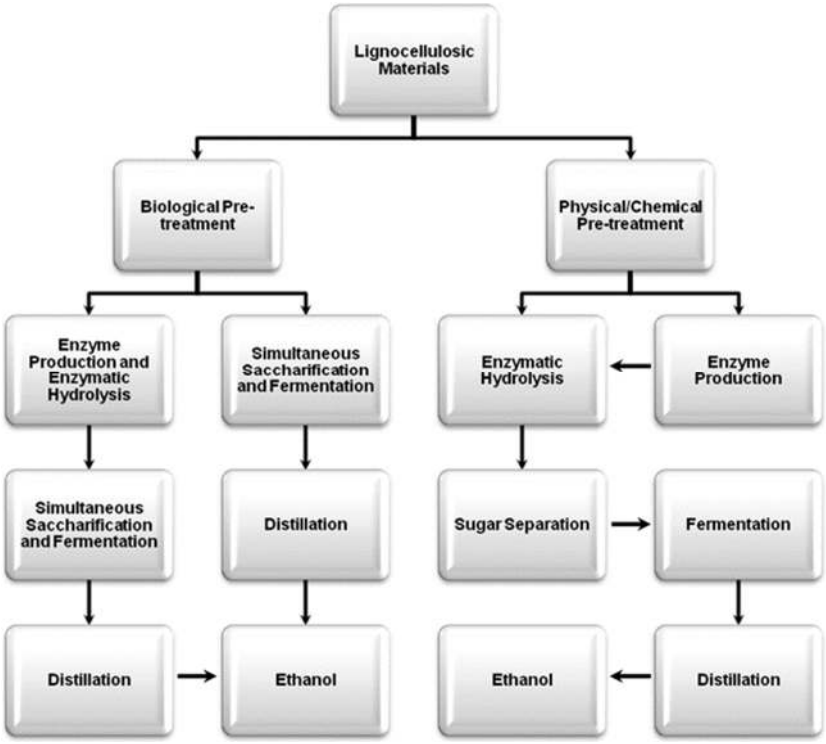

Fig. 2. Generalized schematic representation of lignocellulosic materials bioconversion into ethanol. (Adopted from Iqbal et al.)

9. Concluded remarks

The whole enzymatic process to hydrolyze lignocellulosic materials could be accomplished through a complex synergistically reaction of these various enzymatic components in an optimum proportion. Cellulases provide a key opportunity for achieving tremendous benefits of biomass utilization. Currently, two significant points of these enzyme-based bioconversion technologies are reaction conditions and the production cost of the related enzyme system. Therefore, there has been much research aimed at obtaining new microorganisms producing cellullase enzymes with higher specific activities and greater efficiency. In addition, using lignocellulosic materials, such as agricultural residues, grasses, forestry wastes, and other low-cost biomass can significantly reduce the cost of raw materials for ethanol production compared to corn. It is also predicted that the use of genetically engineered raw materials with higher carbohydrate content combined with the improvement of conversion technology could reduce the cost of ethanol a lot. All those will give a great help for solving the problems of energy and food in the world. In a word, the cellulase enzymes will be commonly used in many industrial applications, and the demand for more stable, highly active and specific enzymes is also growing rapidly.

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Words and word combinations:

- value [ˈvalyo͞o] – величина;
- key opportunity – ключевые возможности;
- feedstock [ˈfēdstäk] – сырье;
- abundant [əˈbəndənt] – обильный, распространённый;
- demand [dəˈmand] – спрос;
- protective seal – защитная пленка;
- worldwide [wərldˈwīd] – по всему миру;
- fungi [ˈfʌŋgiː] – грибковые образования, плесень;
- gap [gap] – зазор;
- deciduous [diˈsijo͞oəs] – лиственный;
- magnitude [ˈmagnəˌt(y)o͞od] – величина, размер;
- decade [ˈdekād] – десятилетие;
- invertebrate [inˈvərdəbrət] – беспозвоночный;
- crustacean [krəˈstāSH(ə)n] – ракообразный;
- annelid [ˈanəˌlid] – кольчатый червь;
- essential [əˈsen(t)SHəl] – существенный;
- enzyme [ˈenzaɪm] – фермент.

Task 2. Summarize all the ideas of the article and write an essay.

Task 3. Make a presentation based on the article.

Часть IV. БЕСЕДА ПО СПЕЦИАЛЬНОСТИ

SUMMARY

Task 1. Read the following instructions offered by Virginia Kearney, a university expert in writing essays (https://owlcation.com/academia/How-to-Write-a-Summary-Analysis-and-Response-Essay, 05.2019).

A summary is telling the main ideas of the article in your own words.

Steps in Writing

These are the steps to writing a great summary:

1. Read the article, one paragraph at a time.
2. For each paragraph, underline the main idea sentence (topic sentence). If you can't underline the book, write that sentence on your computer or a piece of paper.
3. When you finish the article, read all the underlined sentences.
4. In your own words, write down one sentence that conveys the main idea. Start the sentence using the name of the author and title of the article (see format below).
5. Continue writing your summary by writing the other underlined sentences in your own words. Remember that you need to change both the words of the sentence and the word order.
6. Don't forget to use transition words to link your sentences together. See my list of transition words below to help you write your summary more effectively and make it more interesting to read.
7. Make sure you include the name of the author and article and use "author tags" (see list below) to let the reader know you are talking about what the author said and not your own ideas.
8. Re-read your piece. Does it flow well? Are there too many details? Not enough? Your summary should be as short and concise as possible.

Sample Format

Author Tag: You need to start your summary by telling the name of the article and the author. Here are three examples of how to do that (pay close attention to the punctuation):

1. *In "How the Civil War Began," historian John Jones explains...*
2. *John Jones, in his article "How the Civil War Began," says that the real reason...*
3. *"How the Civil War Began," by historian John Jones, describes....*

First Sentence: Along with including the article's title and author's name, the first sentence should be the main point of the article. It should answer the question: What is this essay about? (thesis).

Example:

In "How the Civil War Began" by John Jones, the author argues that the real reason for the start of the Civil War was not slavery, as many believe, but was instead the clash of cultures and greed for cash.

Rest of Summary: The rest of your essay is going to give the reasons and evidence for that main statement. In other words, what is the main point the writer is trying to make and what are the supporting ideas he or she uses to prove it? Does the author bring up any opposing ideas, and if so, what does he or she do to refute them?

Here is a sample sort of sentence:

_____ is the issue addressed in "(article's title)" by (author's name). The thesis of this essay is _____ . The author's main claim is _____ and his/her sub claim is _____ . The author argues _____ . Other people argue _____ . The author refutes these ideas by saying _____ . His/her conclusion is _____ .

Author Tag List

Author's Name	Article	Words for "Said"	Adverbs to Use With "Said"
James Garcia	"whole title"	argues	carefully
Garcia	"first couple of words"	explains	clearly
the author	the article (book etc.)	describes	insightfully
the writer	Garcia's article	elucidates	respectfully
the historian (or other profession)	the essay	complains	stingingly
essayist	the report	contends	shrewdly

Transition Words List

Contrast	Adding Ideas	Emphasis
Although	In addition	Especially
However	Furthermore	Usually
In contrast	Moreover	For the most part
Nevertheless	In fact	Most importantly
On the contrary	Consequently	Unquestionably
Still	Again	Obviously

RESPONSE

Response answers: What do you think? Does this article persuade you?

How to Write

Generally, your response will be the end of your essay, but you may include your response throughout the paper as you select what to summarize and analyze. Your response will also be evident to the reader by the tone that you use and the words you select to talk about the article and writer. However, your response in the conclusion will be more direct and specific. It will use the information you have already provided in your summary and analysis to explain how you feel about this article. Most of the time, your response will fall into one of the following categories:

- You will agree with the author and back your agreement up with logic or personal experience.
- You will disagree with the author because of your experience or knowledge (although you may have sympathy with the author's position).
- You will agree with part of the author's points and disagree with others.
- You will agree or disagree with the author but feel that there is a more important or different point which needs to be discussed in addition to what is in the article.

How will this article fit into your own paper? How will you be able to use it?

Here are some questions you can answer to help you think about your response:

1. What is your personal reaction to the essay?
2. What common ground do you have with the author? How are your experiences the same or different from the author's and how has your experience influenced your view?
3. What in the essay is new to you? Do you know of any information the article left out that is relevant to the topic?
4. What in this essay made you re-think your own view?

5. What does this essay make you think about? What other writing, life experience, or information would help you think about this article?
6. What do you like or dislike about the essay and/or the ideas in the essay?
7. How much of your response is related to your personal experience? How much is related to your own worldview? How is this feeling related to the information you know?
8. How will this information be useful for you in writing your own essay? What position does this essay support? Or where might you use this article in your essay?

Sample Format

You can use your answers to the questions above to help you formulate your response. Here is a sample of how you can put this together into your own essay:

Before reading this article, my understanding of this topic was _____. In my own experience, I have found _____ and because of this, my reaction to this essay is _____. Interestingly, I have _____ as common ground with the author/audience. What was new to me is _____. This essay makes me think _____. I like/dislike _____ in the essay. I will use this article in my research essay for _____.

VOCABULARY

article – статья;

summary – краткое изложение, конспект;

rendering – реферирование;

uncommon – редкий;

finding – находка, открытие, полученные данные;

to pay attention – уделять/обращать внимание;

conclusion – умозаключение, вывод;

to highlight – выделять;

to comprehend – понимать, осмысливать;

rough draft – эскиз, набросок;

firm grasp – чёткое понимание;

assignment – предписание, инструкция, задание;

to explain – объяснять;

in plain language – простым языком;

referring to – ссылаясь на;

meaning – значение, смысл;

to convey – выражать, передавать (идею, смысл);

appropriate – подходящий, соответствующий;

to feature in – принимать участие;

concisely – кратко, сжато, лаконично, выразительно;

cut and paste – «вырезать и вставлять» (объёмно цитировать без ссылки на источник, компилировать);

jumble – куча; беспорядочно сваленные в кучу вещи;

borders on – граничить grade – оценка, отметка;

option – вариант, альтернатива; опция.

Task 2. Read and translate the text. Use its main ideas for rendering scientific articles:

How to write a Summary of a scientific article

Summarizing or rendering of a scientific article demonstrates your understanding of the material and presents this information to an audience that may not have a science background. It is not uncommon for a scientific article to describe an experiment and discuss its findings. To write an effective summary, you must be able to focus on the main ideas of the article. This also helps to understand scientific research better.

Instructions:

1. Read the entire article. Pay attention to the experiment methods and the conclusions presented. Read the article more than once, if necessary.
2. Look up any words or methods you do not understand.

3. Go through the article, and highlight its main ideas. Make sure you understand the main points in each para graph. Take notes so you have a starting point for your summary.
4. Test your understanding of the artic le by asking yourself questions about it. Try explaining the concept of the article to a friend or family member in non-scientific language. Determine if you can clearly explain the article in a way that is easy to comprehend.
5. Start a rough draft of your summary, using the notes you've written. Review the article to ensure you have a firm grasp of the conclusion. Summarize the article's conclusion. Offer your own interpretation of the conclusion along with your opinion of the article's content.

Task 3. Look through the "George Mason University Recommendations" on the writing of a summary of a scientific article. Be ready to answer the questions:

This assignment is generally intended to help you learn to synthesize scientific materials and communicate the main points effectively, using plain language.

Start by making sure you understand the central points of what you read. Explain the article in plain language to someone else and answer questions without referring back to the article, to make sure you have grasped the essence of what you read. Dr. James Lawrey in the Biology Department uses this assignment to teach students to pick out the meaning of an article and convey the main points. The appropriate writing style for a summary of a scientific article is to use simple sentences that express one or two ideas. An example might be a story featured in the mainstream media that explains a recent scientific finding, bringing out the important aspects concisely and without too much scientific jargon. Do not "cut and paste" from the article. When students do not really understand what they read, their writing is a jumble of statements nearly straight from the article, with no interpretation or synthesis of the article's findings. This strategy is common among students who wait until the last minute to complete

assignments. Besides the fact that this practice borders on or actually is plagiarism, it shows that students do not understand what they are writing about, and their grades reflect this.

Task 4. Answer the questions:

1. Who is James Lawrey? 2. What should you do at first while writing a summary? 3. Does the author limit the number of times his students should read the scientific article they are to summarize? 4. When do students use "cut and paste" function while writing a summary? 5. How do you understand the term "plagiarism"?

Task 5. Retell the Instructions on writing a Summary of a scientific article.

Task 6. Read the definition of summarizing/rendering in Russian. Try to remember as many set phrases as possible. Use them in the rendering of scientific articles.

Реферирование научных статей на английском языке – важный навык, необходимый любому современному инженеру. Суть реферирования можно свести к анализу прочитанной англоязычной работы с выделением её главной идеи, описанием перечисленных автором фактов и доводов и подведением итогов.

С этой целью можно использовать ряд вводных языковых конструкций:

1. Название статьи, автор, стиль. The article I'm going to give a review of is taken from… – Статья, которую я сейчас хочу проанализировать из… The headline of the article is – Заголовок статьи… The author of the article is… – Автор статьи… It is written by – Она написана (кем)… The headline foreshadows… – Заголовок приоткрывает…

2. Тема. Логические части. The topic of the article is… – Тема статьи это… The key issue of the article is… – Ключевым вопросом в статье является… The article under discussion is devoted to the problem… – Обсуждаемая статья посвящена проблеме… The author in the article touches upon the problem of… – В статье автор

затрагивает проблему…. I'd like to make some remarks concerning… – Я бы хотел(а) сделать несколько замечаний по поводу… I'd like to mention briefly that… – Хотелось бы кратко отметить, что… I'd like to comment on the problem of… – Я бы хотел(а) прокомментировать проблему… The article under discussion may be divided into several logically connected parts which are… – Статья может быть разделена на несколько логически взаимосвязанных частей, таких как…

3. Краткое содержание. At the beginning of the article its author… – В начале статьи автор… …describes – описывает …depicts – изображает …touches upon – затрагивает …explains – объясняет …introduces – знакомит …mentions – упоминает …makes a few critical remarks on – делает несколько критических замечаний о The article begins (opens) with a (the)… – Статья начинается… …description of – описанием …statement – заявлением …introduction of – представлением …the mention of – упоминанием …the analysis of / a summary of – кратким анализом …the characterization of – характеристикой …(author's) opinion of – мнением автора …the enumeration of – перечнем In conclusion the author – в заключение автор …dwells on – останавливается на …points out – указывает на то …generalizes – обобщает …reveals – показывает …exposes – показывает …accuses / blames – обвиняет …gives a summary of – дает обзор…

4. Отношение автора к отдельным моментам. The author gives full coverage to… – Автор полностью охватывает… The author outlines… – Автор описывает… The article contains the following facts…./ describes in details… – Статья содержит следующие факты …. / подробно описывает… The author starts with the statement of the problem and then logically passes over to its possible solutions. – Автор начинает с постановки задачи, а затем логически переходит к ее возможным решениям. The author asserts that… – Автор утверждает, что … The author resorts to … to underline… – Автор прибегает к …, чтобы подчеркнуть… Let me give an example… – Позвольте мне привести пример…

5. Вывод автора. In conclusion the author says / makes it clear that…/ gives a warning that… – В заключение автор говорит / проясняет, что… / предупреждает, что… At the end of the article author sums it all up by saying … – В конце статьи автор подводит итог всего этого, говоря… The author concludes by saying that… / draws a conclusion that… / comes to the conclusion that… – В заключение автор говорит, что .. / делает вывод, что… / приходит к выводу, что…

6. Выразительные средства, используемые в статье. To emphasize … the author uses… – Чтобы акцентировать внимание … автор использует… To underline … the author uses… – Чтобы подчеркнуть … автор использует To stress… – Чтобы усилить/подчеркнуть… Balancing… – Балансируя…

7. Ваш вывод. Taking into consideration the fact that – Принимая во внимание тот факт, что The message of the article is that… /The main idea of the article is… – Основная идея статьи (послание автора)… In addition… / Furthermore… – Кроме того…

On the one hand…, but on the other hand… – С одной стороны …, но с другой стороны… Back to our main topic… – Возвращаясь к нашей основной теме… To come back to what I was saying… – Чтобы вернуться к тому, что я говорил(а)… In conclusion I'd like to… – В заключение я хотел(а) бы… From my point of view… – С моей точки зрения… As far as I am able to judge… – Насколько я могу судить… My own attitude to this article is… – Мое личное отношение к этой статье... I fully agree with… / I don't agree with… – Я полностью согласен / не согласен с… It is hard to predict the course of events in future, but there is some evidence of the improvement of this situation. – Трудно предсказать ход событий в будущем, но есть некоторые свидетельства улучшения ситуации. I have found the article dull / important / interesting /of great value – Я нахожу статью скучной / важной / интересной/ имеющей большое значение (ценность).

Task 7. Retelling

Read text of the article several times. Work in pairs or groups. Divide text into parts, so that each group will have at least several sentences. Select the key words in the texts, type them in Word it Out (https://worditout.com/) and generate a cloud. Retell the story with the help of the generated word clouds. If two words need to be together, imagine "suffer from", you only need to insert _ between the two words and they'll be kept together in the cloud.

Пример рассказа о научных интересах магистранта:

1. What is your name? - My name is Ivan Ivanovich Ivanov.

2. What educational institution did you graduate from? When? -I graduated from …in 20…

3. What is your speciality? -My speciality is …/ My profession is …

4. Why did you decide to take a post-graduate course? -I decided to take a post graduate-course because I had been interested in science since my 3-d year at the University / because scientific approach is very important in my profession.

5. What is the subject of your future scientific research? -The subject of my scientific research is … -My future scientific research is devoted to the problem of … - My future scientific research deals with the problem of …

6. Who is your scientific supervisor? -My scientific supervisor is Ivan Petrovich Petrov, Professor, Doctor of technical/ economic sciences, Head of the Chair of … / Head of the Department of … -He has got a lot of publications devoted to the problem of …

7. Have you ever participated in any scientific conferences? -Yes, I've participated in many conferences devoted to the most actual problems of economy/physics/geodesy/hydrology etc. -Not yet, but I hope, together with my supervisor, I'll prepare some reports for scientific conferences/I'll take part in several conferences in the near future.

8. Do you have any publications? -Yes, I've got some publications connected with my research. - Not yet, but I hope, together with my supervisor, I'll prepare some publications, they will be devoted to my research.

9.What methods are you going to use in your investigation? -Together with my supervisor we are going to apply such methods as theoretical, experimental, practical and computational methods because they will help me to complete my research.

10. What will your scientific research give the world? In what way can your investigation/research be useful to … science?

-I think / I hope / I dare say that the problem of our scientific research is very urgent and our scientific research will be very useful for … / it will help people in the field of …

Сокращения, встречающиеся в текстах

сокращение	читается/означает	перевод
%	percent (per cent) [pə'sent]	процент
° C	degrees Centigrade	градус (Цельсия)
° F	degrees Fahrenheit	градус (Фаренгейта)
etc.	[et'set(ə)rə]	и так далее
e. g.	for example	например
i. e.	that is	то есть

Температура читается:

25° C – twenty-five degrees Centigrade ['sentɪgreɪd] (по шкале Цельсия);

34° F – thirty-four degrees Fahrenheit ['færənhaɪt] (по шкале Фаренгейта).

Химические элементы: символы и произношение

Symbol	Name	Pronunciation
Ac	Actinium	/ækt'ɪnɪəm/
Ag	Silver	/'sɪlvə/
Al	Aluminium	/æljʊ'mɪnɪəm/
Am	Americium	/əmə'rɪsɪəm/
Ar	Argon	/'ɑːgɒn/
As	Arsenic	/'ɑːsnɪk/
At	Astatine	/'æstəti:n/
Au	Gold	/'gəʊld/
B	Boron	/'bɔːrɒn/
Ba	Barium	/ˈbəɛrɪəm/
Be	Beryllium	/bəˈrɪlɪəm/
Bh	Bohrium	ˈbɔːrɪəm/
Bi	Bismuth	/ˈbɪzməθ/
Bk	Berkelium	/ˈbɜːklɪəm/
Br	Bromine	/ˈbrəʊmiːn/
C	Carbon	/ˈkɑːbən/
Ca	Calcium	/ˈkælsɪəm/
Cd	Cadmium	/ˈkælmɪəm/
Ce	Cerium	/ˈsiːrɪəm/
Cf	Californium	/kælɪˈfɔːnɪəm/
Cl	Chlorine	/ˈklɔːriːn/
Cm	Curium	/ˈkjuːrɪəm/
Co	Cobalt	/ˈkəʊbɒlt/
Cr	Chromium	/ˈkrəʊmɪəm/
Cs	Caesium	/ˈsiːzɪəm/
Cu	Copper	/ˈkɒpə/
Db	Dubnium	/ˈdʌbnɪəm/
Ds	Darmstadtium	/dɑːmˈstætɪəm/
Dy	Dysprosium	/dɪsˈprəʊzɪəm/
Er	Erbium	/ˈɜːbɪəm/
Es	Einsteinium	/aɪnˈstaɪnɪəm/
Eu	Europium	/juːˈrəʊpɪəm/
F	Fluorine	/ˈflʊəriːn/
Fe	Iron	/ˈaɪən/
Fm	Fermium	/ˈfɜːmɪəm/
Fr	Francium	/ˈfrænsɪəm/
Ga	Gallium	/ˈgælɪəm/
Gd	Gadolinium	/gædəˈlɪnɪəm/
Ge	Germanium	/dʒəˈmeɪnɪəm/
H	Hydrogen	/ˈhaɪdrədʒən/
He	Helium	/ˈhiːlɪəm/
Hf	Hafnium	/ˈhæfnɪəm/
Hg	Mercury	/ˈmɜːkjʊrɪ/
Ho	Holmium	/ˈhəʊlmɪəm/

Химические элементы: символы и произношение

Hs	Hassium	/ˈhæsɪəm/
I	Iodine	/ˈaɪədiːn/
In	Indium	/ˈɪndɪəm/
Ir	Iridium	/ɪˈrɪdɪəm/
K	Potassium	/pəˈtæsɪəm/
Kr	Krypton	/ˈkrɪptən/
La	Lanthanum	/ˈlænθənəm/
Li	Lithium	/ˈlɪθɪəm/
Lr	Lawrencium	/ləˈrensɪəm/
Lu	Lutetium	/ljuːˈtiːʃəm/
Md	Mendelevium	/mendəˈlɪvɪəm/
Mg	Magnesium	/mægˈniːzɪəm/
Mn	Manganese	/ˈmæŋgəniːz/
Mo	Molybdenum	/məˈlɪbdənəm/
Mt	Meitnerium	/maɪtˈnɜːrɪəm/
N	Nitrogen	/ˈnaɪtrədʒən/
Na	Sodium	/ˈsəʊdɪəm/
Nb	Niobium	/naɪˈəʊbɪəm/
Nd	Neodymium	/niːəʊˈdɪmɪəm/
Ne	Neon	/ˈniːɒn/
Ni	Nickel	/ˈnɪkəl/
No	Nobelium	/nəʊˈbiːlɪəm/
Np	Neptunium	/nepˈtjuːnɪəm/
O	Oxygen	/ˈɒksɪdʒən/
Os	Osmium	/ˈɒzmɪəm/
P	Phosphorus	/ˈfɒsfərəs/
Pa	Protactinium	/prəʊtækˈtɪnɪəm/
Pb	Lead	/ˈled/
Pd	Palladium	/pəˈleɪdɪəm/
Pm	Promethium	/prəˈmiːθɪəm/
Po	Polonium	/pəˈləʊnɪəm/
Pr	Praseodymium	/preɪzɪəʊˈdɪmɪəm/
Pt	Platinum	/ˈplætɪnəm/
Pu	Plutonium	/pluːˈtəʊnɪəm/
Ra	Radium	/ˈreɪdɪəm/
Rb	Rubidium	/ruːˈbɪdɪəm/
Re	Rhenium	/ˈriːnɪəm/
Rf	Rutherfordium	/rʌðəˈfɔːdɪəm/
Rg	Roentgenium	/rɒntˈgenɪəm/
Rh	Rhodium	/ˈrəʊdɪəm/
Rn	Radon	/ˈreɪdɒn/
Ru	Ruthenium	/ruːˈθiːnɪəm/
S	Sulphur	/ˈsʌlfə/
Sb	Antimony	/'æntɪmənɪ/
Sc	Scandium	/ˈskændɪəm/
Se	Selenium	/səˈliːnɪəm/
Sg	Seaborgium	/siːˈbɔːgɪəm/

Химические элементы: символы и произношение

Si	Silicon	/ˈsɪlɪkən/
Sm	Samarium	/səˈmɛərɪəm/
Sn	Tin	/ˈtɪn/
Sr	Strontium	/ˈstrɒntɪəm/
Ta	Tantalum	/ˈtæntələm/
Tb	Terbium	/ˈtɜːbɪəm/
Tc	Technetium	/tekˈniːʃɪəm/
Te	Tellurium	/təˈlʊərɪəm/
Th	Thorium	/ˈθɔːrɪəm/
Ti	Titanium	/tɪˈteɪnɪəm/
Tl	Thallium	/ˈθælɪəm/
Tm	Thulium	/ˈθjuːlɪəm/
U	Uranium	/jʊˈreɪnɪəm/
Uub	Ununbium	/juːˈnʌnbɪəm/
Uuh	Ununhexium	/ˌjuːnənˈheksɪəm/
Uuo	Ununoctium	ˌ/juːnəˈnɒktɪəm/
Uup	Ununpentium	/juːnənˈpentɪəm/
Uuq	Ununquadium	/juːnənˈkwɒdɪəm/
Uut	Ununtrium	/juːˈnʌntrɪəm/
V	Vanadium	/vəˈneɪdɪəm/
W	Tungsten	/ˈtʌŋstən/
Xe	Xenon	/ˈzenɒn/
Y	Yttrium	/ˈɪtrɪəm/
Yb	Ytterbium	/ɪˈtɜːbɪəm/
Zn	Zinc	/ˈzɪŋk/
Zr	Zirconium	/zɜːˈkəʊnɪəm/

Чтение наиболее распространённых соединений:

CO_2	Carbon dioxide	['kɑːbəndaɪ'ɔksaɪd]	углекислый газ
CO	Carbon monoxide	['kɑːbənmə'nɔksaɪd]	угарный газ
NO_2	Nitrogen dioxide	['naɪtrədʒən ˌdaɪ'ɒksaɪd]	двуокись азота
N_2O	Dinitrogen oxide	[daɪ naɪtrədʒən 'ɒksaɪd]	динитрооксид
NO	Nitrogen oxide	[naɪtrədʒən 'ɒksaɪd]	оксид азота
N_2O_4	Dinitrogen tetroxide	[daɪ naɪtrədʒən tɛ'trɒksaɪd]	динитротетроксид
SO_2	Sulphur dioxide	['sʌlfə ˌdaɪ'ɒksaɪd]	двуокись серы
SO_3	Sulphur trioxide	['sʌlfə traɪ'ɒksaɪd]	трёхокись серы
H_2SO_4	Sulphuric acid	[sel'fju(ə)rik 'æsɪd]	серная кислота
HCl	Hydrochloric acid	['haɪdrə'klɔrɪk 'æsɪd]	соляная кислота
HNO_3	Nitric acid	['naɪtrɪk 'æsɪd]	азотная кислота
PCl_5	Phosphorus pentachloride	['fɔsf(ə)rəs 'pentə'klɔːraɪd]	пентахлорид фосфора

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