Organic Chemistry III

後藤 佑樹 (Yuki Goto, Bioorganic Chemistry Lab.)

“Organic chemistry of biomolecules”

Q and A

糖の増炭反応や減炭反応はある程度想定されたとおりに開発されたのでしょうか？それとも偶然見つかったのでしょうか？

Ruff degradation (1898)
Kiliani–Fischer synthesis (1885/1889)

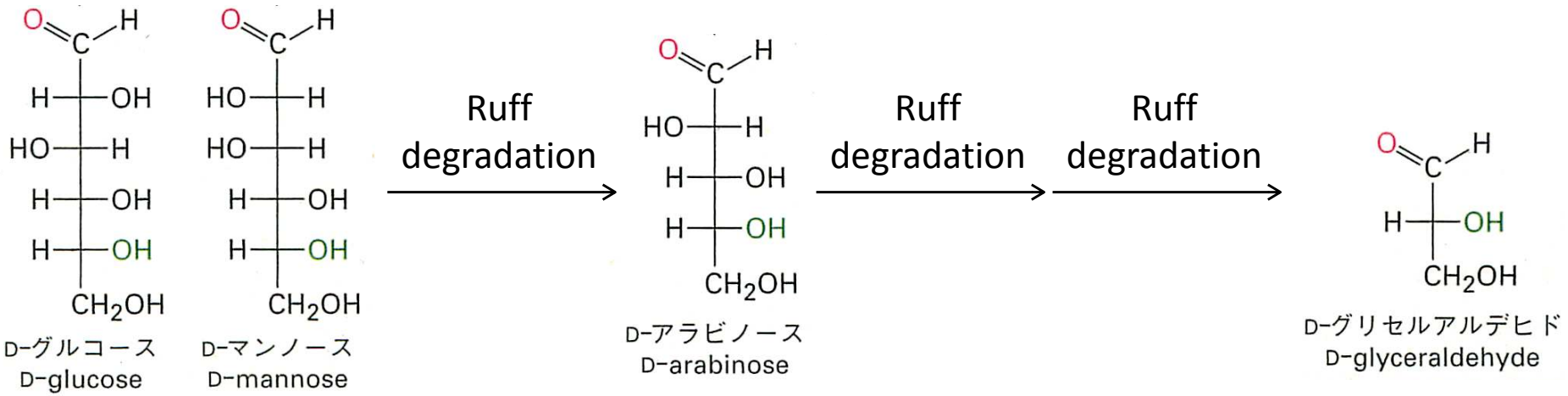
想像ですが、この時代の反応開発（というか発見）の殆どは、おそらく偶然の賜物が多いと思います。

ちなみに、この二反応は、糖の構造解析ツールとして超便利だった→1902年E. Fischer ノーベル賞

例えば、D-グルコースとD-マンノースの構造が分かっていないとしよう。

・Ruff degradationで同じ生成物（D-アラビノース）を与えた！
→D-グルコースとD-マンノースはC2だけの立体が違うジアステレオマー（エピマー）の関係と分かる

・さらにRuff degradationを繰り返していくと、既知のD-グリセルアルデヒドを与えた！
→C5位の立体化学が確定できる



2番. はさまざまなアイデアが見つけられそうだと思った.

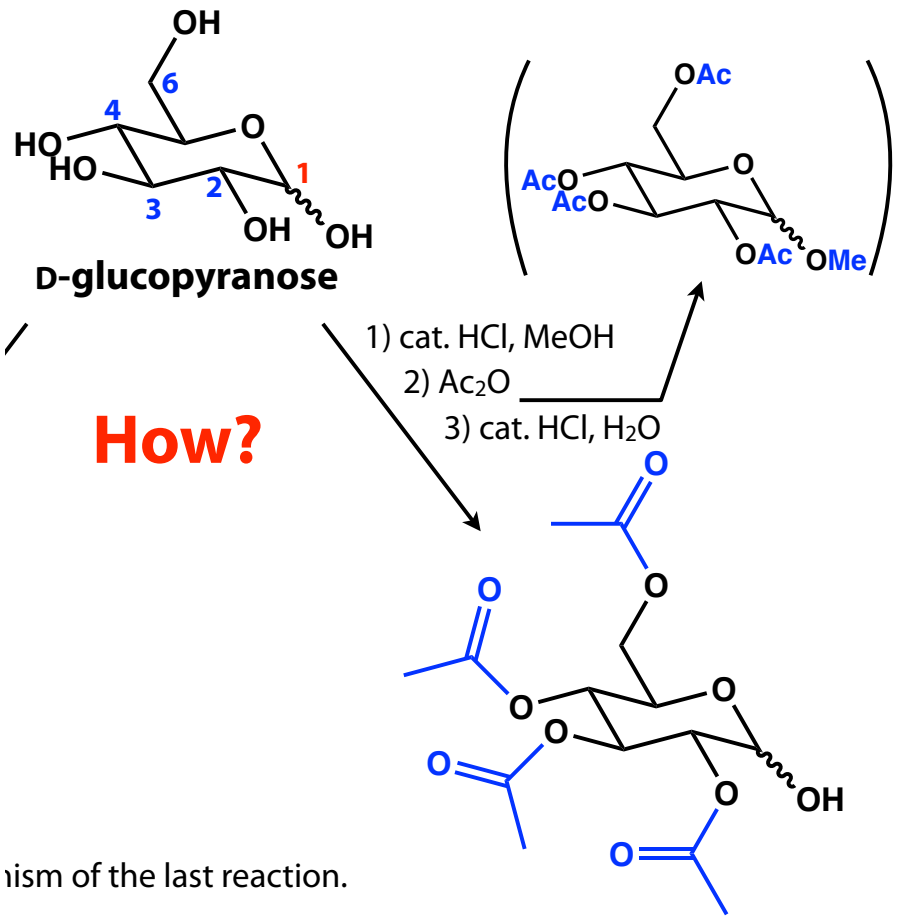
2番ができなかったので復習したいと思います.

2.の右の反応(3)で 1位の-OAcだけが-OHになったのも隣接基効果ですか?

多分何か勘違いしてる。1位は、OH→OMe→OMeのまま→OHと変化しています。

問2の右側が3段階必要な理由がよく分かりませんでした。

This student did not understand why the bottom transformation requires the 3-step reactions.



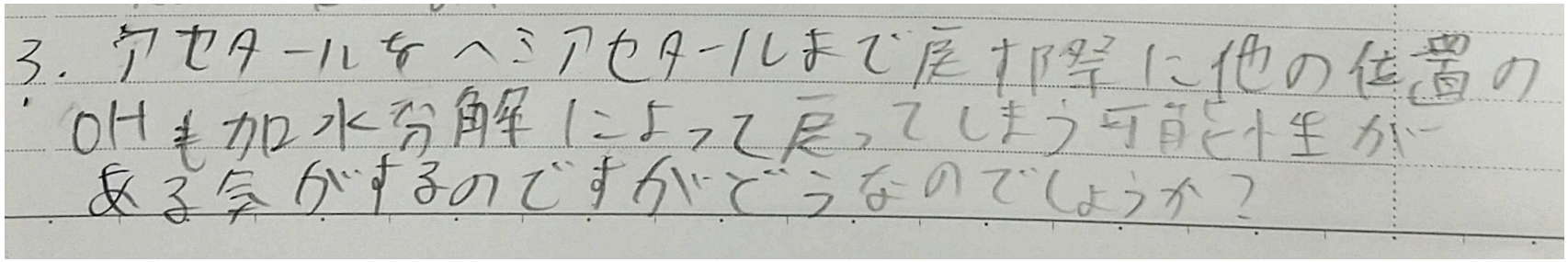
ism of the last reaction.

In the first step, only the anomeric position OH is converted into OMe (acetal).

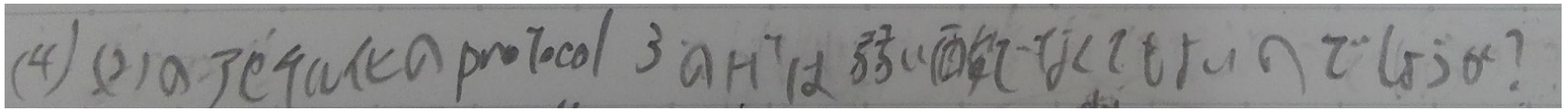
The second step acetylates the remaining four free OH groups while the OMe on C1 is intact.

The OMe (acetal) on the C1 is hydrolyzed to regenerate the OH (hemiacetal).

一段階目でC1のOHを選択的に「保護」しておいて、
二段階目のアセチル化後に
C1のOMeを脱保護している、とも言えます。

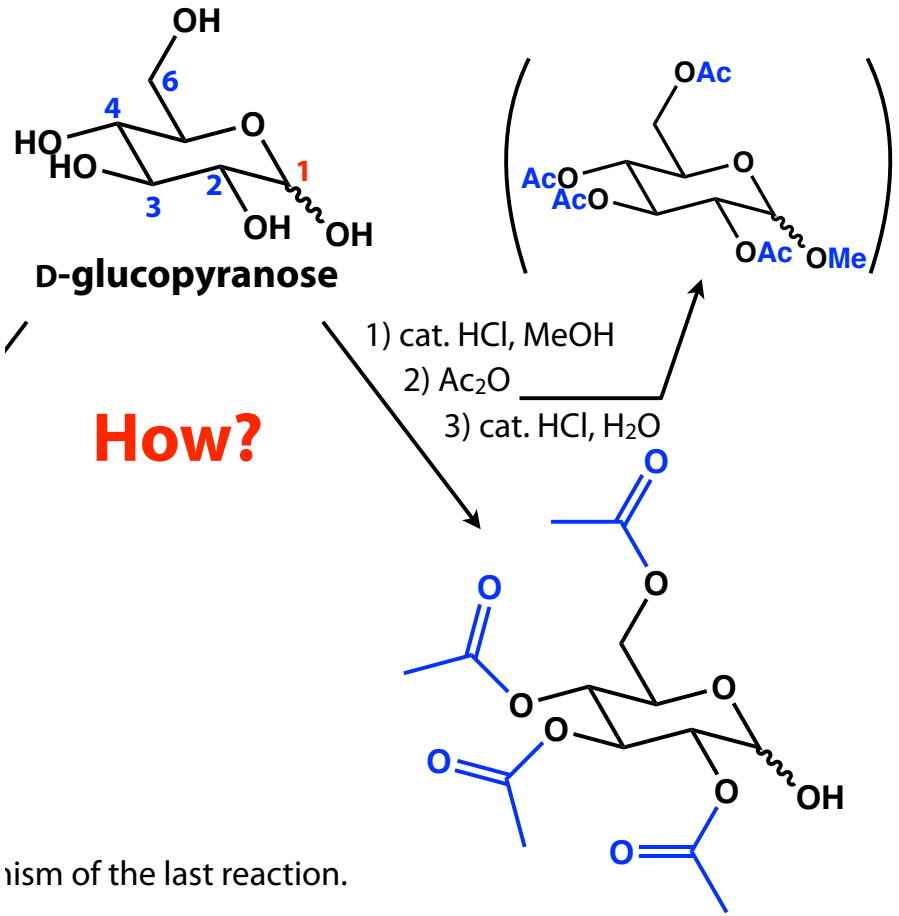


3. アセタールをヘミアセタールまで戻す際に他の位置のOHも加水分解によって戻ってしまう可能性が生じる気がするのですがどうなのでしょうか？



(4) 2のアセタール化のprotocol 3のOHは弱い酸でなくてもよいのでしょうか？

These students are concerned that the acetyl groups would be hydrolyzed in the step of acid-catalyzed hydrolysis of acetal.



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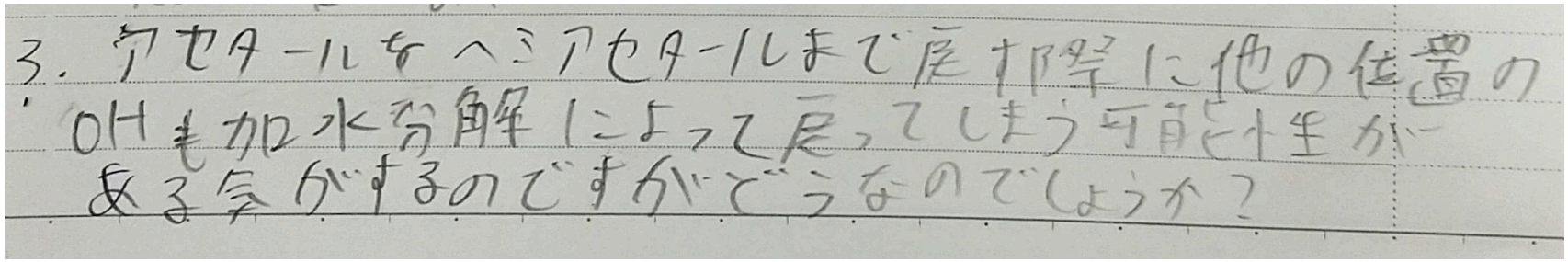
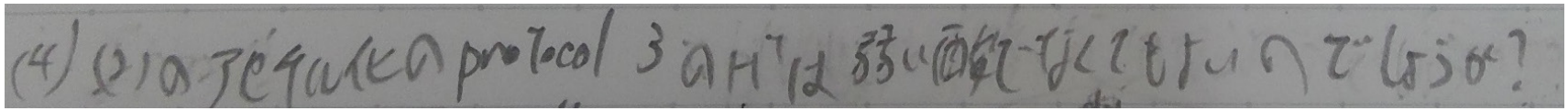
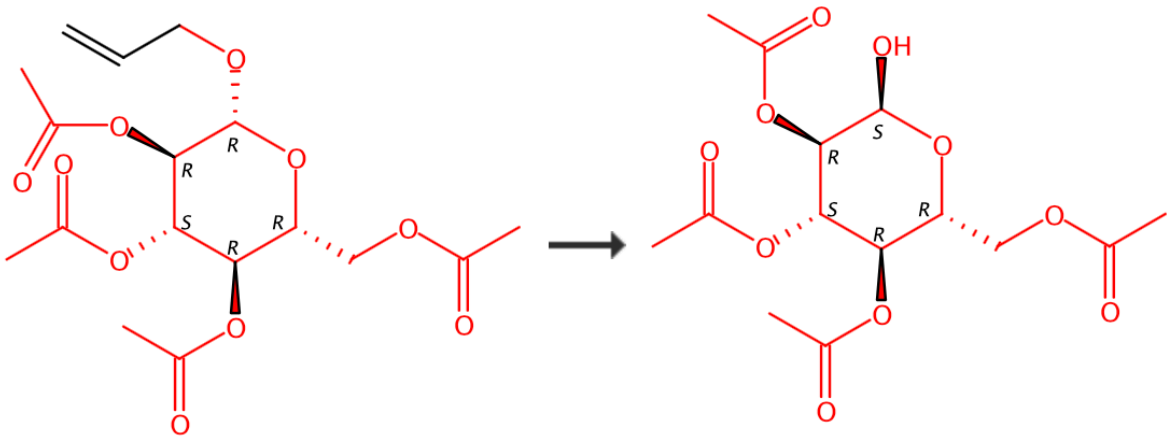
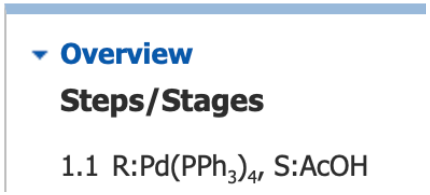


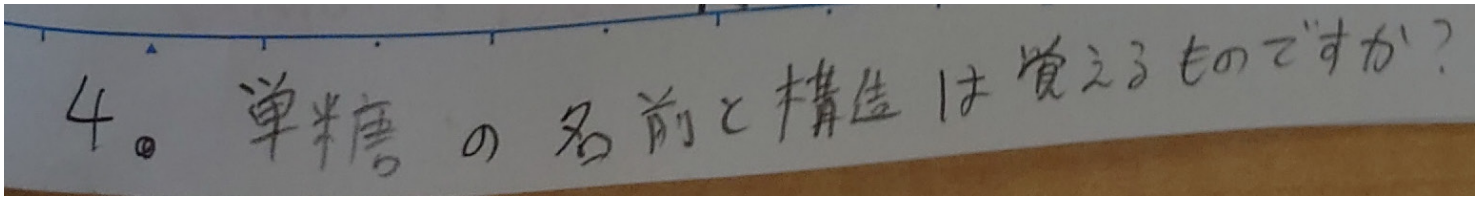


These students are concerned that the acetyl groups would be hydrolyzed in the step of acid-catalyzed hydrolysis of acetal.

Excellent questions.
Yes, deacetylation may compete with the hydrolysis of methyl acetal. However, there are indeed examples of reactions in the CAS database, in which the anomeric OMe is selectively removed in acid-catalyzed reaction conditions.
Nonetheless, these students' concern is correct, and thus acetal groups other than methyl are widely used for practical synthesis. For instance, allyl acetal can be removed by palladium catalysts, which do not cleave acetyl esters.
Because I guess the explanation using the simple OMe and OAc would be easier for you to understand the concept of selective protection, I showed these groups/conditions in this class.







No, you don't need to remember the names of sugars for this class.
I shared it just for your reference. Of course, you can remember them if you have interest or intend to pursue carbohydrate-related research in the future.

Tips from a textbook: How to remember the names of aldopentoses/aldohexoses

八つのD系列アルドヘキソースの名前と構造を覚えるには，次の方法が便利である．

段階 1　八つの Fischer 投影式を CHO 基を一番上に，CH_2OH 基を一番下にして書く

段階 2　C5 の八つの OH 基をすべて右に配置する（これでD糖になる）

段階 3　C4 の四つの OH 基を右に，残る四つを左に配置する

段階 4　C4 の OH 基を右にした四つに関して，C3 の二つの OH 基を右に，残る二つを左に配置する．左に配置したもう一組についても同様にそれぞれ配置する．

段階 5　C2 の OH 基を右，左，右，左と順番にそれぞれ配置する．

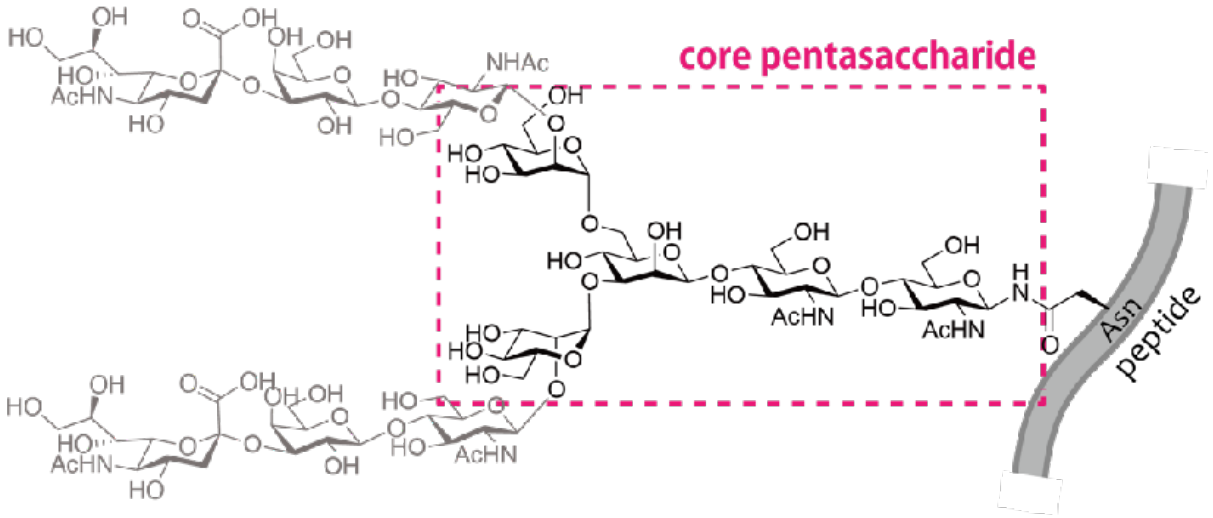
段階 6　8種の異性体を次の語呂合わせを使って名前をつける．“**All altruists gladly make gum in gallon tanks**（すべての利他的な人たちは喜んでガロンタンクの中でゴムをつくる）.”

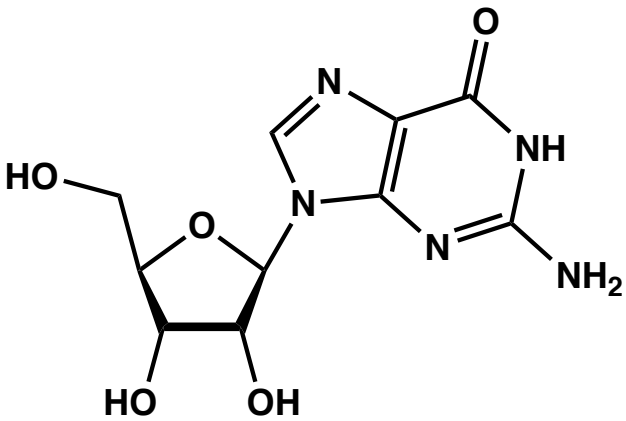
四つのD系列アルドペントースの構造はこれと同様にしてできる．名前の語呂合わせはコーネル大学の学部学生たちの作であるが，“**Ribs are extra lean**（リブ肉は特にひきしまっている）”である．

Q and A

椅子型の糖を描くときにOは右奥に書くのが普通ですか?

By convention, when drawing sugar structures in a chair form, we generally locate the ring-oxygen at the far right.

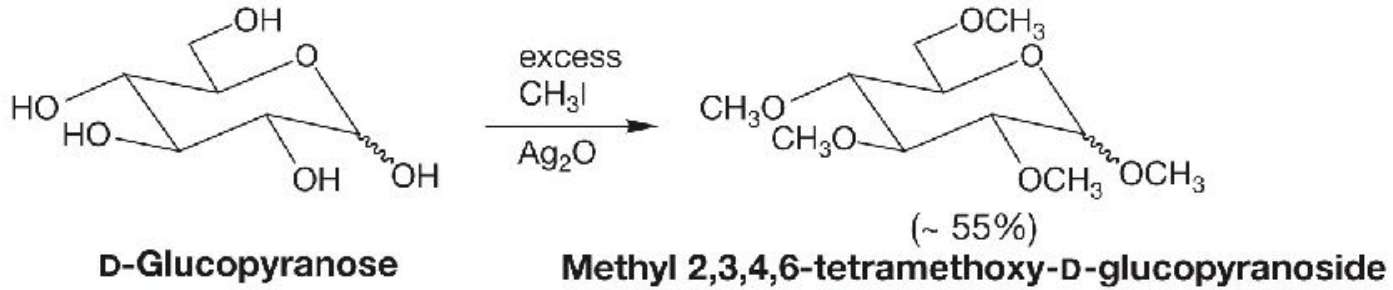




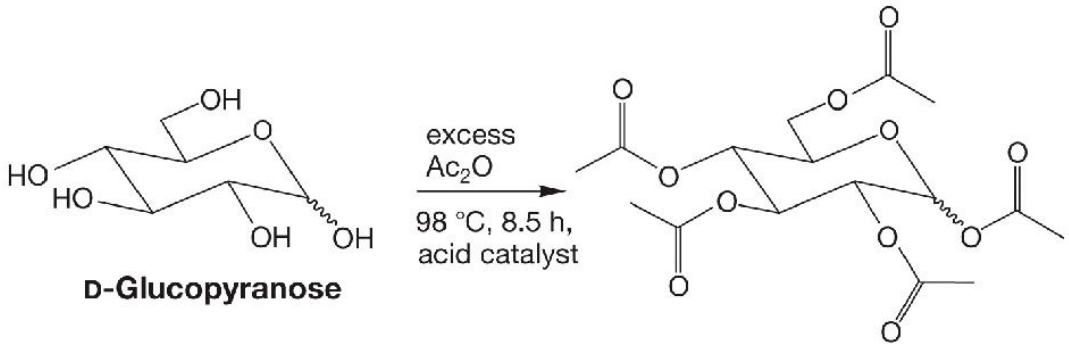
from Kajihara lab @ Osaka U.

Q and A

今日の講義で話しますが、セルロースを溶かすのはかなり厳しいです。
特別なイオン液体とかには溶かせるらしい。
同期が必死こいてセルロースを溶媒に溶かそうとしています。大変そうです。
アセチル化もメチル化も収率があまり高くないのですね。ほかに反応しそうな場所もなさそうなのにどんなものができているのでしょうか？それとも完全に進めるのが難しいのでしょうか？ Why the yields of the acetylation/methylation reactions are not so good?
Because of the multiple reaction sites, is the complete conversion simply difficult?



D-Glucopyranose — Methyl 2,3,4,6-tetramethoxy-D-glucopyranoside

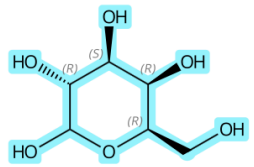


D-Glucopyranose — A pentaester (58%)

Actually, the reactions are not so difficult reactions. I don't know why the Jone's text book show these examples with low yields.

Actually, the reactions are not so difficult reactions. I don't know why the Jone's text book show these examples with low yields.

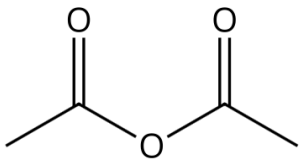
Scheme 1 (2 Reactions) Steps: **1** Yield: **100%**



Absolute stereochemistry shown

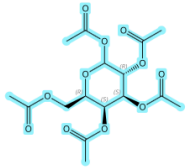
Suppliers (34)

+



Suppliers (79)

→



Absolute stereochemistry shown

Suppliers (50)

Reaction Summary Steps: **1** Yield: **100%**

1.1 Solvents: Pyridine; 0 °C; 0 °C → rt; overnight, rt

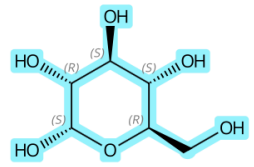
View Reaction Detail | Experimental Protocols

Facially amphipathic glycopolymers inhibit ice recrystallization

By: Graham, Ben; et al
Journal of the American Chemical Society (2018), 140(17), 5682-5685

Full Text

Scheme 1 (1 Reaction) Steps: **1** Yield: **88%**



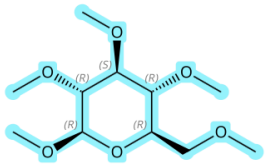
Absolute stereochemistry shown, Rotation (+)

Suppliers (50)

+

Suppliers (79)

→



Absolute stereochemistry shown

Suppliers (4)

Reaction Summary Steps: **1** Yield: **88%**

1.1 Reagents: Silver oxide (Ag_2O)
Solvents: Dimethylformamide

View Reaction Detail

Complete methylation of reducing carbohydrates

By: Walker, H. G. Jr.; et al
Journal of Organic Chemistry (1962), 27, 2100-2

Full Text

As Drawn (224)

Substructure (377)

Similarity (7,898)

Filter Behavior

Filter by | Exclude

Yield

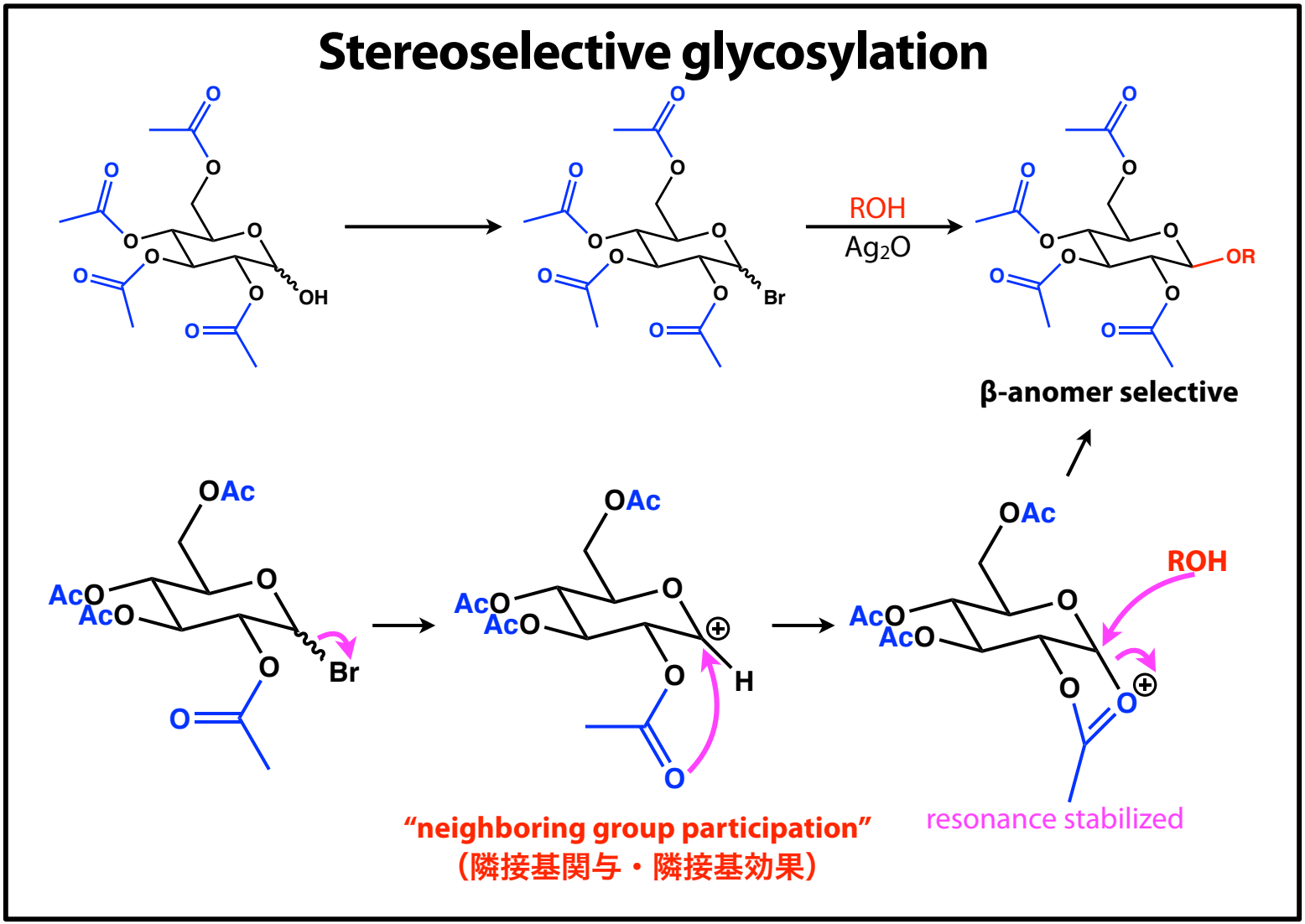
- [x] 90-100% (63)
- [ ] 80-89% (21)
- [ ] 70-79% (19)
- [ ] 50-69% (15)
- [ ] 30-49% (11)

View All

Q and A

保護基によって立体選択性をもたせているのが面白いしすごいと思った。

neighboring group effectが面白かったです。



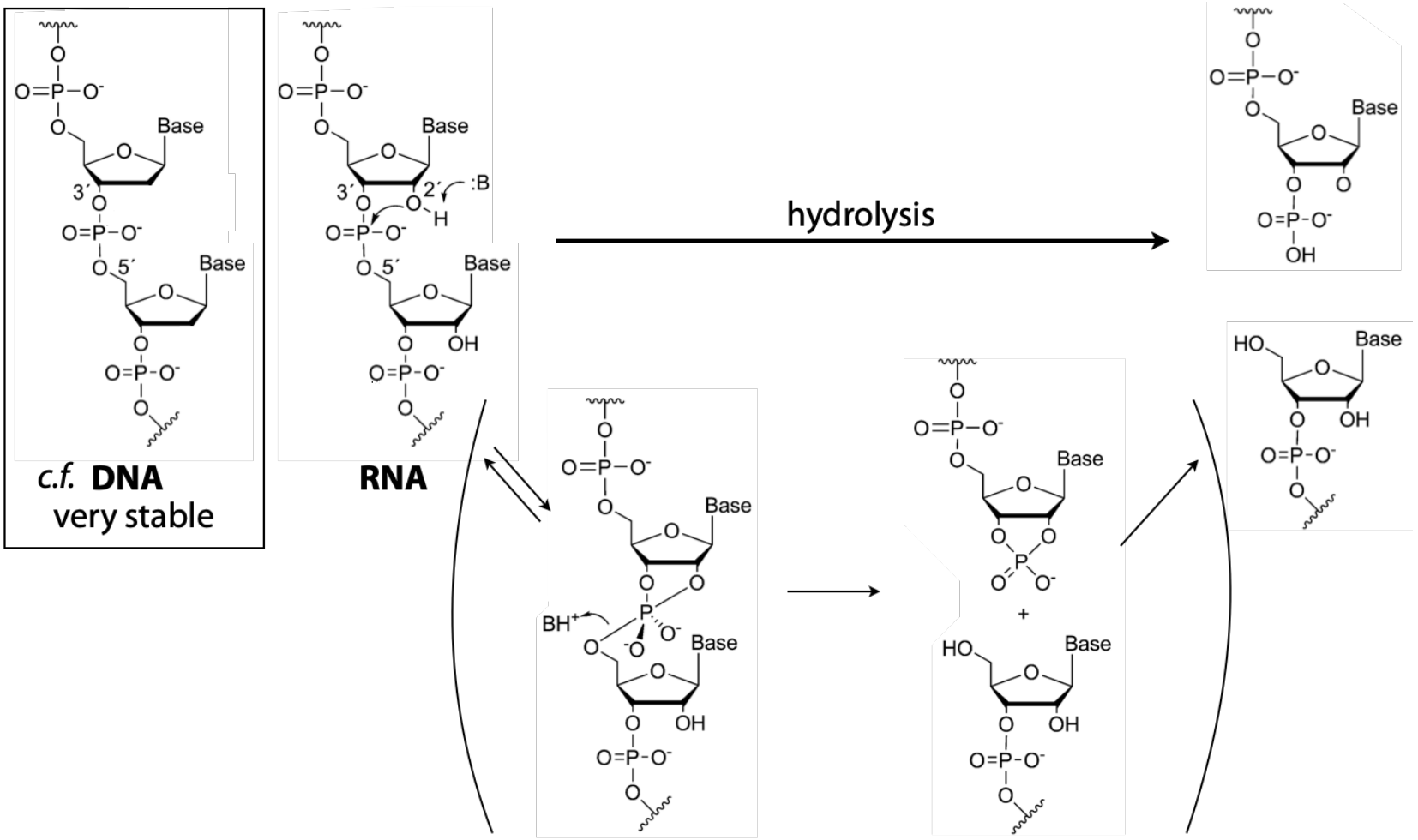
隣接基効果、おしゃれですよね。僕は大好きです

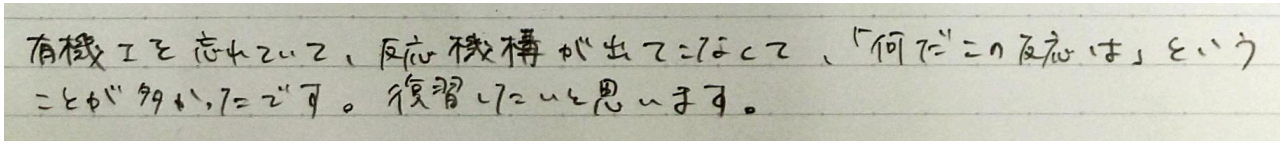
Q and A

保護基によって立体選択性をもたせているのが面白いしすごいと思った。

neighboring group effect が面白かったです。

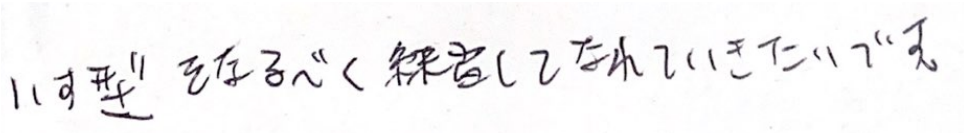
Another famous example for neighboring group participation

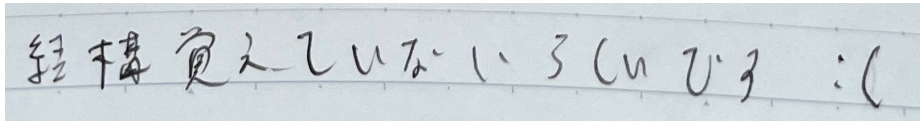




ありがとうございました.
反応の復習しようと思います...

前回の内容に関する問題を出して頂けると復習になってありがたいです





Yes, as you have experienced thus far, I try to design my lectures to encourage reviewing the previous organic chemistry knowledge. Please try to deal with the review quizzes suggested in the slides by yourself.

comment: sorry for the inconvenience, but please teach more in English.

Thanks for the comment.
Although I sometimes speak in Japanese during the classes, the Japanese talks are mainly for repeating the contents that have been or will be explained in English. I have given Japanese explanations specially for the important/complicated issues and when the topic changes, in order to raise the overall level of understanding of the students.
I know that this might be uncomfortable for some English speakers, but I would thank you for your understanding.
I promise that I will not fail to deliver any class content in English (except for Q/A).

Final Exam

July 22nd (Fri)10:25〜11:55

on-site (Chemistry main bldg., 3F lecture room)

guidelines

- There will be a 15-minute "cheating time" during 10:55–11:10. During this time, you may see the textbook, lecture handouts, notes, memos, etc. that you brought.
- However, viewing/using electronic devices such as PCs, tablets, and cell phones is prohibited.
- Consultation/discussion with other students is also prohibited.

- 開始30分後からの15分間、「cheating time」を設けます。この間は、持参した教科書・講義資料・ノート・メモ等を参照しても構いません。
- ただし、PC・タブレット・携帯などの電子デバイスの閲覧/使用は禁止。
- 他の人との相談も禁止。

Topics in the previous class

- structure of monosaccharide
  - classification
  - Fischer projection
  - cyclic sugars

- reactions of monosaccharide
  - several examples of monosaccharides
  - glycoside formation (glycosylation)
  - protection strategies of monosaccharides

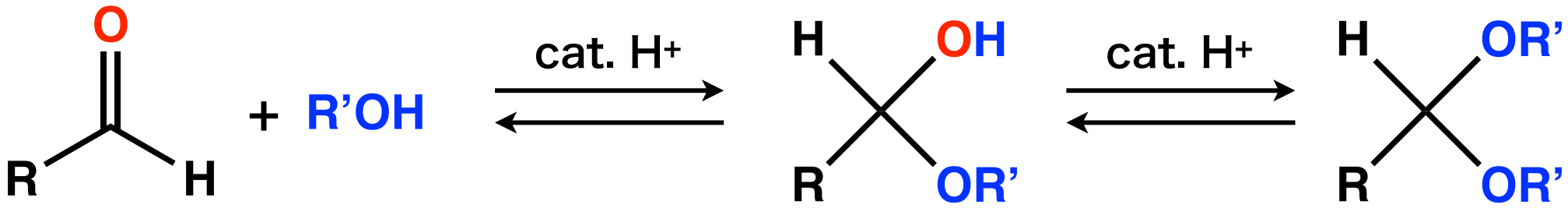
- structure and functions of oligo and polysaccharide

Reaction of monosaccharides - 5

Synthesis of glycosides

If glucose is reacted with alcohols, what can occur?

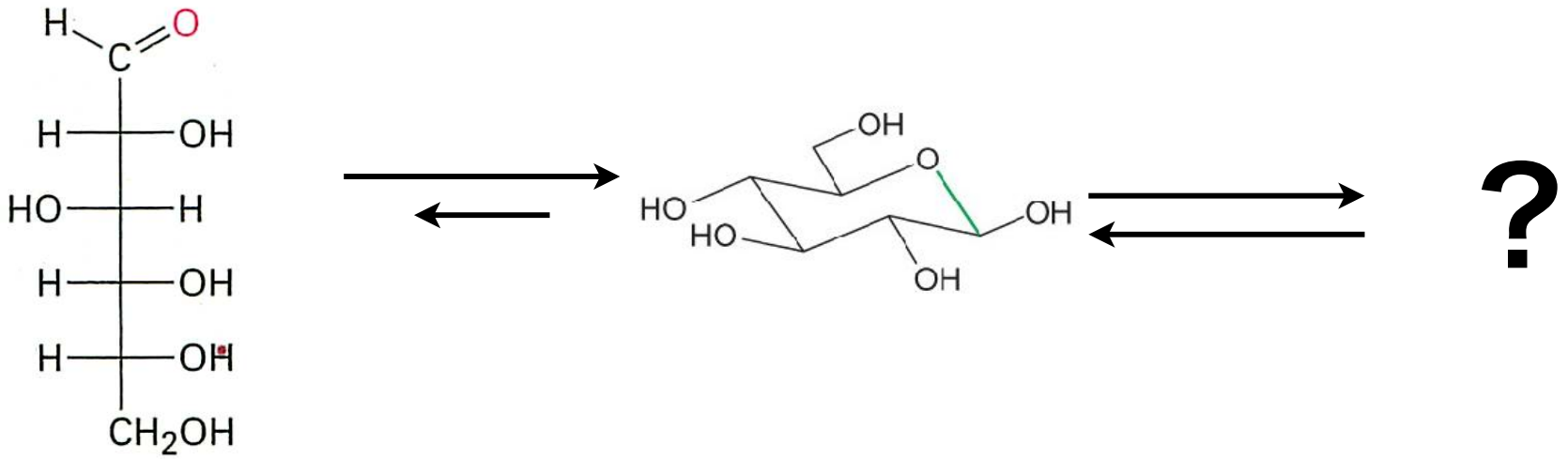
Remind this



hemiacetal

acetal

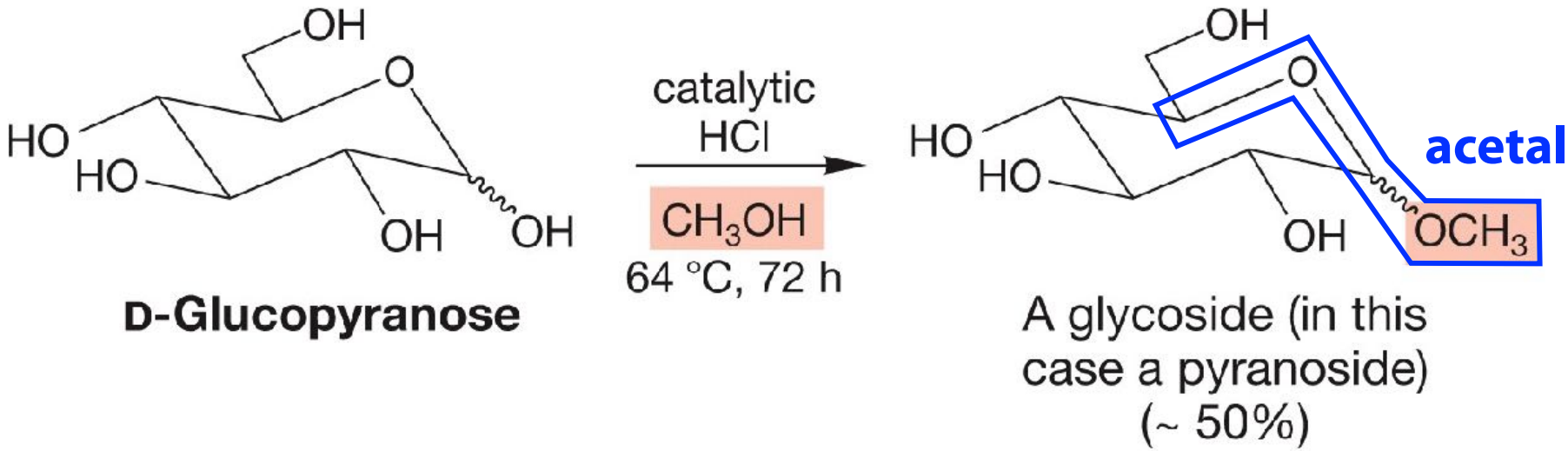
in sugar chemistry, **cyclic form** **glycoside**



Reaction of monosaccharides - 5

Synthesis of glycosides

If glucose is reacted with alcohols, what can occur?



glycosides: (in a narrow sense,) acetal forms of sugars on the anomeric position

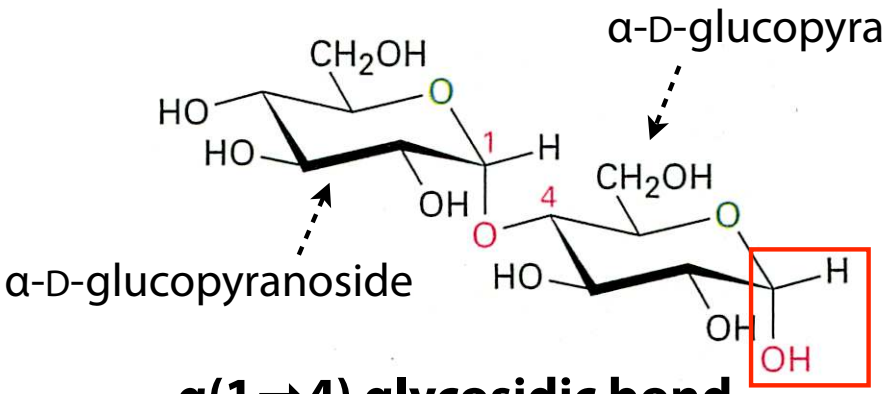
nomenclature - giving the alkyl group followed by the sugar name with the "-ose" replaced with "-oside"

e.g. the name of the glycoside above is "methyl D-glucopyranoside"

Review quiz: Draw the mechanism of the glycoside formation under acidic conditions.

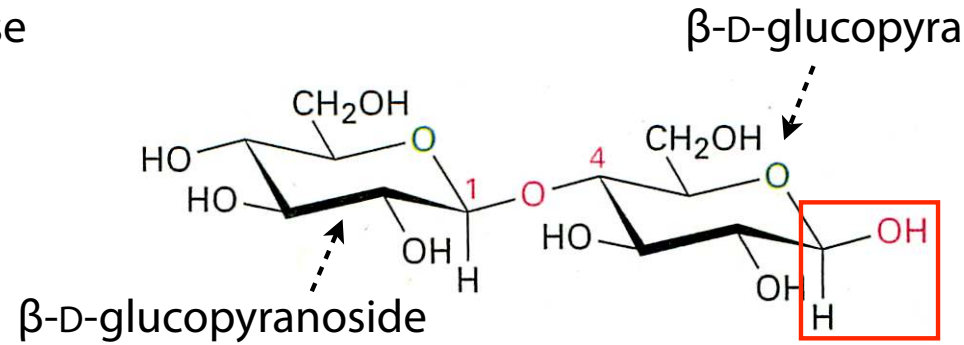
If ROH in glycosylation is a sugar … disaccharides

Dimers of D-glucopyranose



α(1→4) glycosidic bond

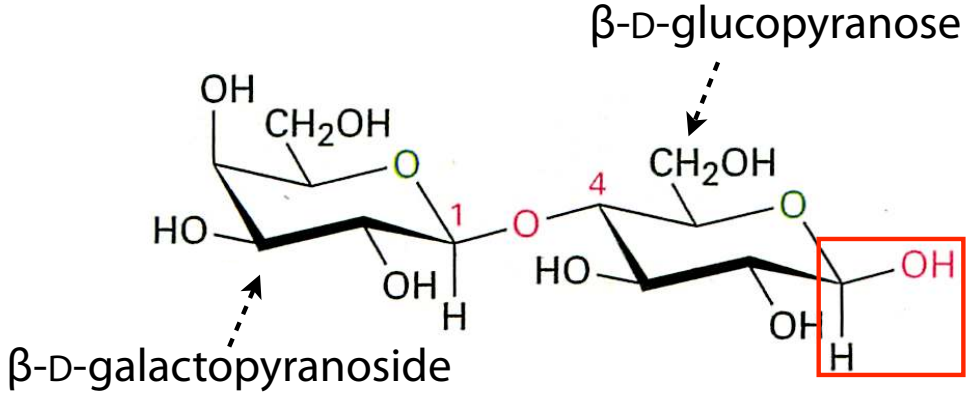
(maltose)



β(1→4) glycosidic bond

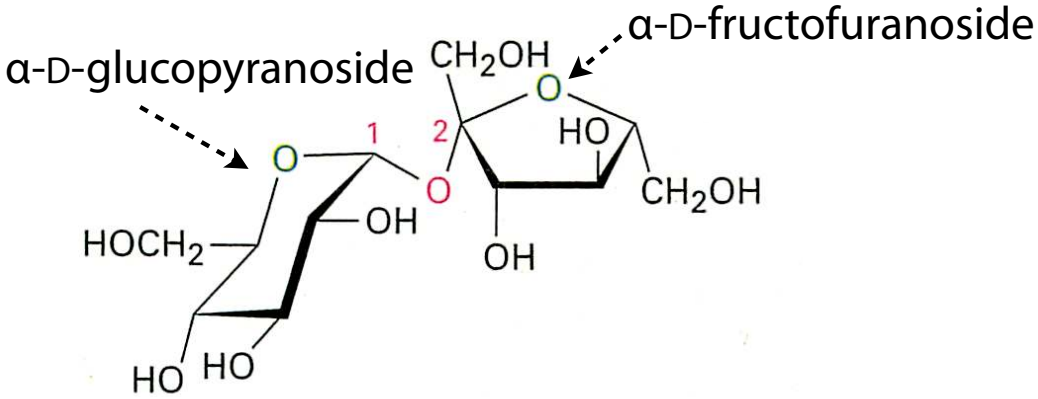
(cellobiose)

lactose （乳糖）



β(1→4) glycosidic bond

sucrose（ショ糖、砂糖）



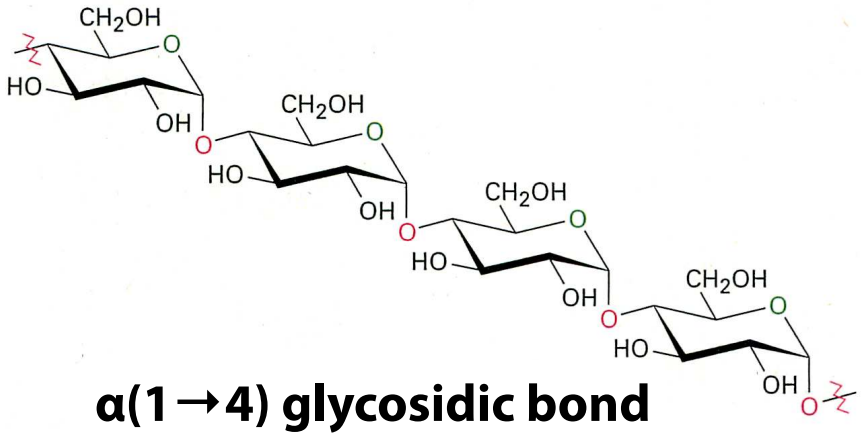
α(1→2) glycosidic bond

Two important polysaccharides

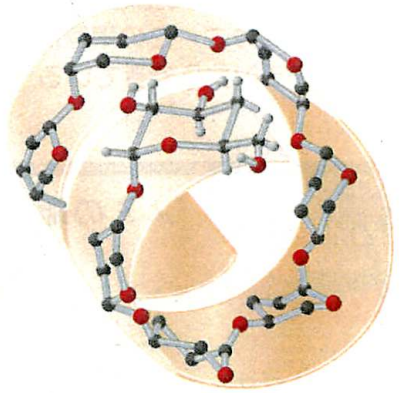
Both are polymers of D-glucopyranose

see 3D structures

amylose（デンプンの構成要素）

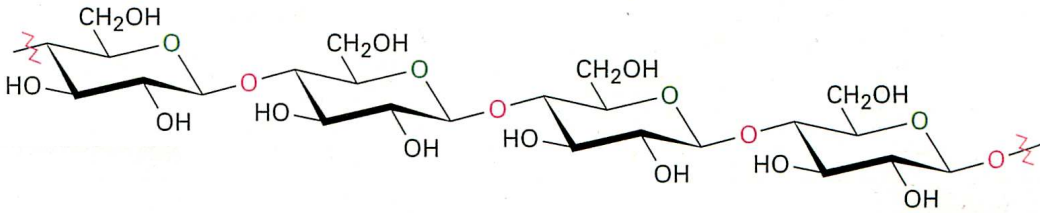


α(1→4) glycosidic bond

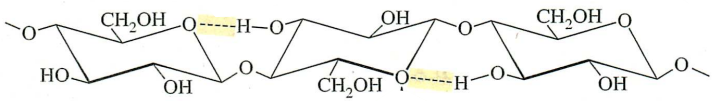


helical structure of amylose
(good energy source)

cellulose



β(1→4) glycosidic bond



planar structure of cellulose
(we cannot digest this)

topics- roles of polysaccharides in organisms

energy storage - amylose, glycogen, etc.

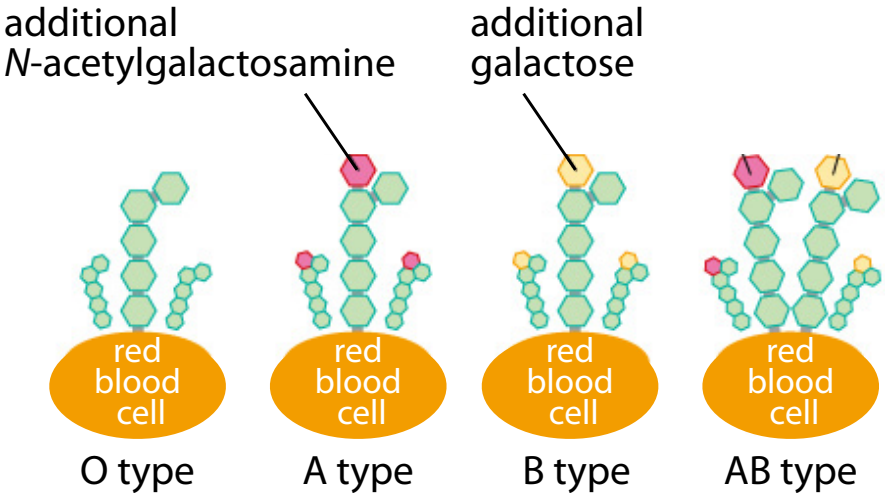
structural skeleton - cellulose, chitin, etc.

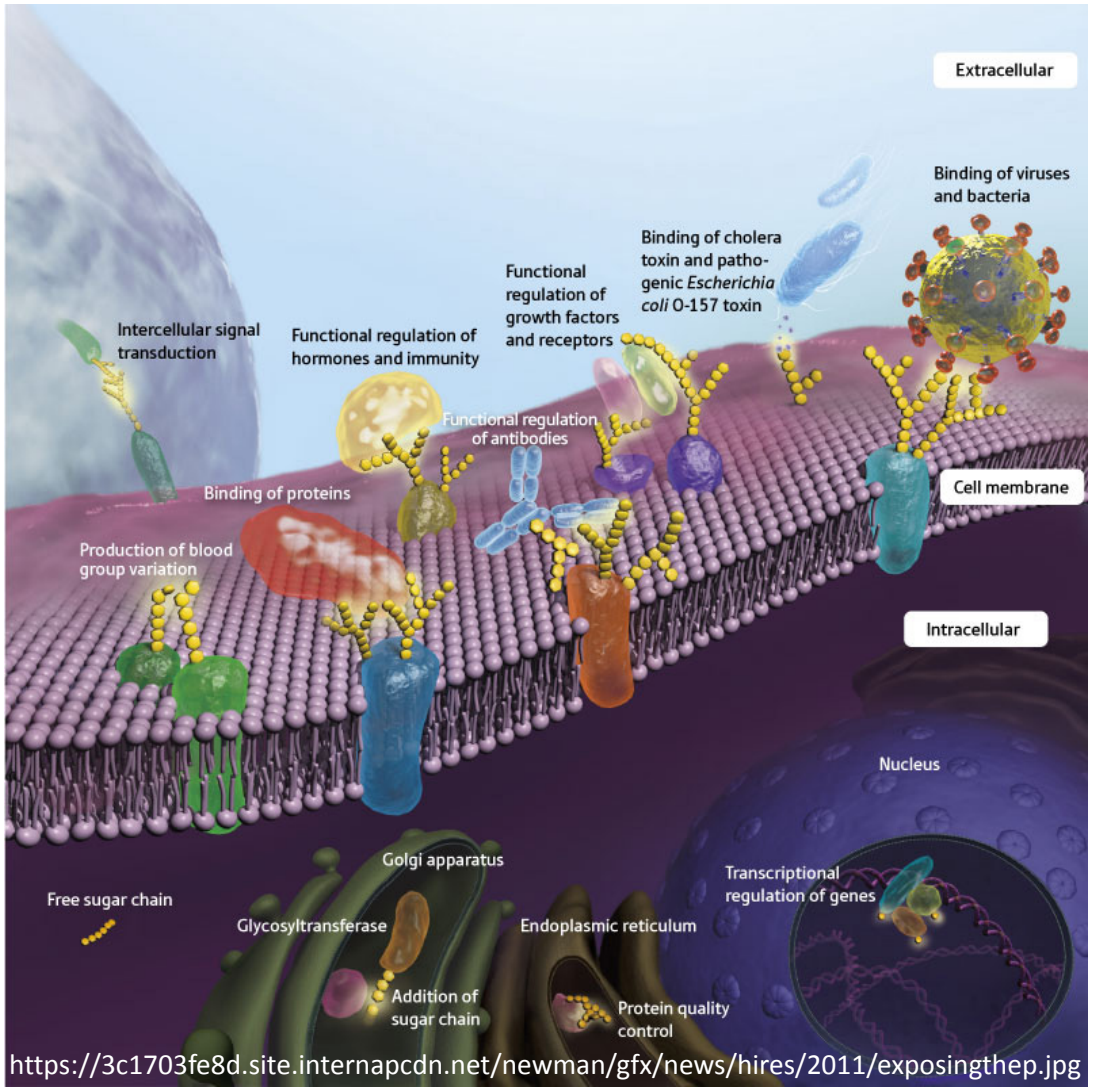
regulation of cellular events

Many different polysaccharide chains are found on exterior surface of cells.

Different cells display different poly saccharine chain on the surface.

They play important roles in
- definition/recognition of cellular types
- infection of viruses
- regulation of growth factors





Amino acids

Topics

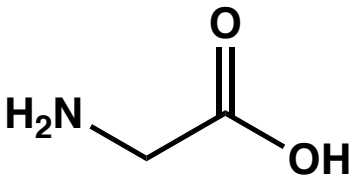
- **structure of amino acids**
  - classification and examples
  - acidity and basicity of amino acids

- **synthesis of amino acids**
  - amine synthesis
    - **synthesis of amines**
      - by S_N2 reactions
      - Gabriel synthesis
      - reductive amination
  - side chain addition
  - COOH synthesis
  - enantioselective synthesis

What are amino acids

amine + acid

α-amino acids

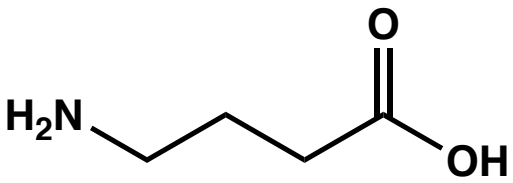


(glycine)

栄養成分表示　１本(200 ml)あたり

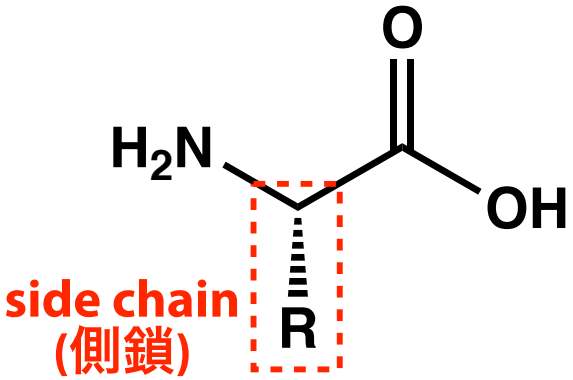
エネルギー	139	kcal
たんぱく質	6.8	g
脂　　質	0.8	g
炭水化物	10.0	g
ナトリウム	85	mg
カルシウム	227	mg

γ-amino acids



(γ-amino butyric acid, GABA)

Proteinogenic amino acids are

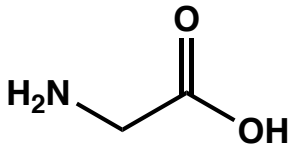


L-α-amino acids

Review
(Fischer projection)

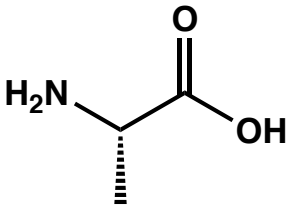
Examples/names of amino acids

e.g.)



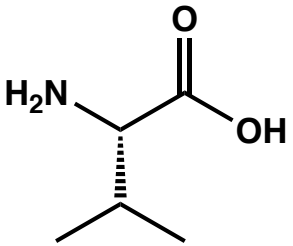
2-Aminoacetic acid
(glycine)

Gly
(G)



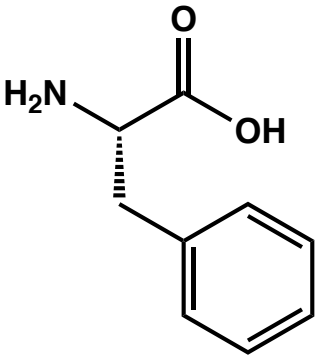
2-Aminopropanoic acid
(alanine)

Ala
(A)



2-Amino-3-methylbutanoic acid
(valine)

Val
(V)

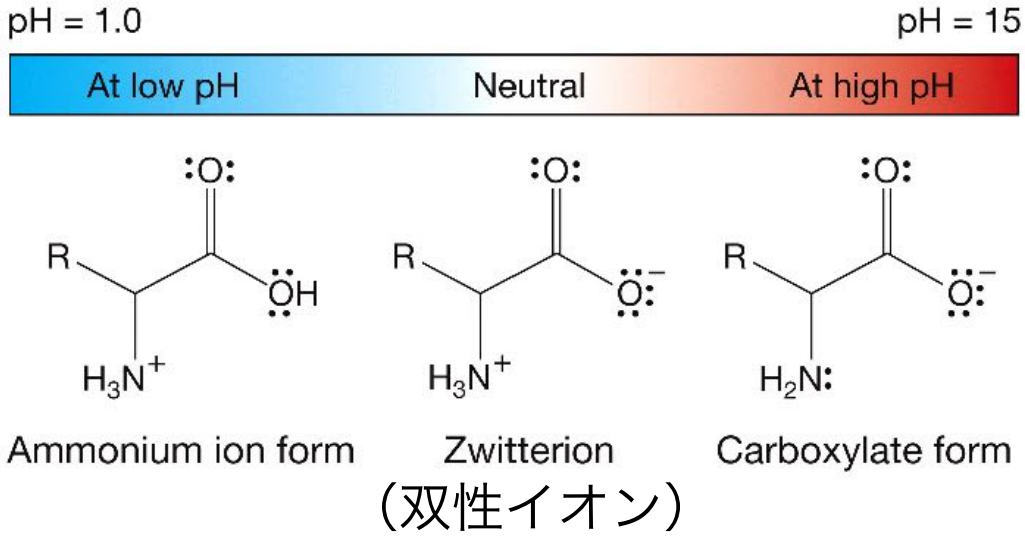


2-Amino-3-phenylpropanoic acid
(phenylalanine)

Phe
(F)

A total of 20 different amino acids is found in proteins.
See others in the appendix.

acidity/basicity of amino acids



Amino Acid	Abbreviation		pK_1	pK_2	pK_R	pI
	3-Letters	1-Letter	-COOH	$-NH_3^+$	R group	
Alanine	Ala	A	2.34	9.69	-	6.00
Arginine	Arg	R	2.17	9.04	12.48	10.76
Asparagine	Asn	N	2.02	8.80	-	5.41
Aspartic Acid	Asp	D	1.88	9.60	3.65	2.77
Cysteine	Cys	C	1.96	10.128	8.18	5.07
Glutamic Acid	Glu	E	2.19	9.67	4.25	
Glutamine	Gln	Q	2.17	9.13	-	5.65
Glycine	Gly	G	2.34	9.60	-	5.97
Histidine	His	H	1.82	9.17	6.00	
Isoleucine	Ile	I	2.36	9.60	-	6.02
Leucine	Leu	L	2.36	9.60	-	5.98
Lysine	Lys	K	2.18	8.95	10.53	9.74
Methionine	Met	M	2.28	9.21	-	5.74
Phenylalanine	Phe	F	1.83	9.13	-	5.48
Proline	Pro	P	1.99	10.60	-	6.30
Serine	Ser	S	2.21	9.15	-	5.58
Threonine	Thr	T	2.09	9.10	-	5.60
Tryptophan	Trp	W	2.83	9.39	-	5.89
Tyrosine	Tyr	Y	2.20	9.11	10.07	
Valine	Val	V	2.32	9.62	-	5.96

From Lehninger Principle of Biochemistry.

When the pH = pI (等電点: isoelectronic point), the net charge of amino acid becomes zero.

In this pH, the amino acid is mainly present as zwitterion.

Quiz Estimate the pI values of Glu, His, and Tyr.

Review Quiz

Explain the aqueous structures of alanine in buffers of pH = 2.34, 6.00, and 9.69.

Quiz

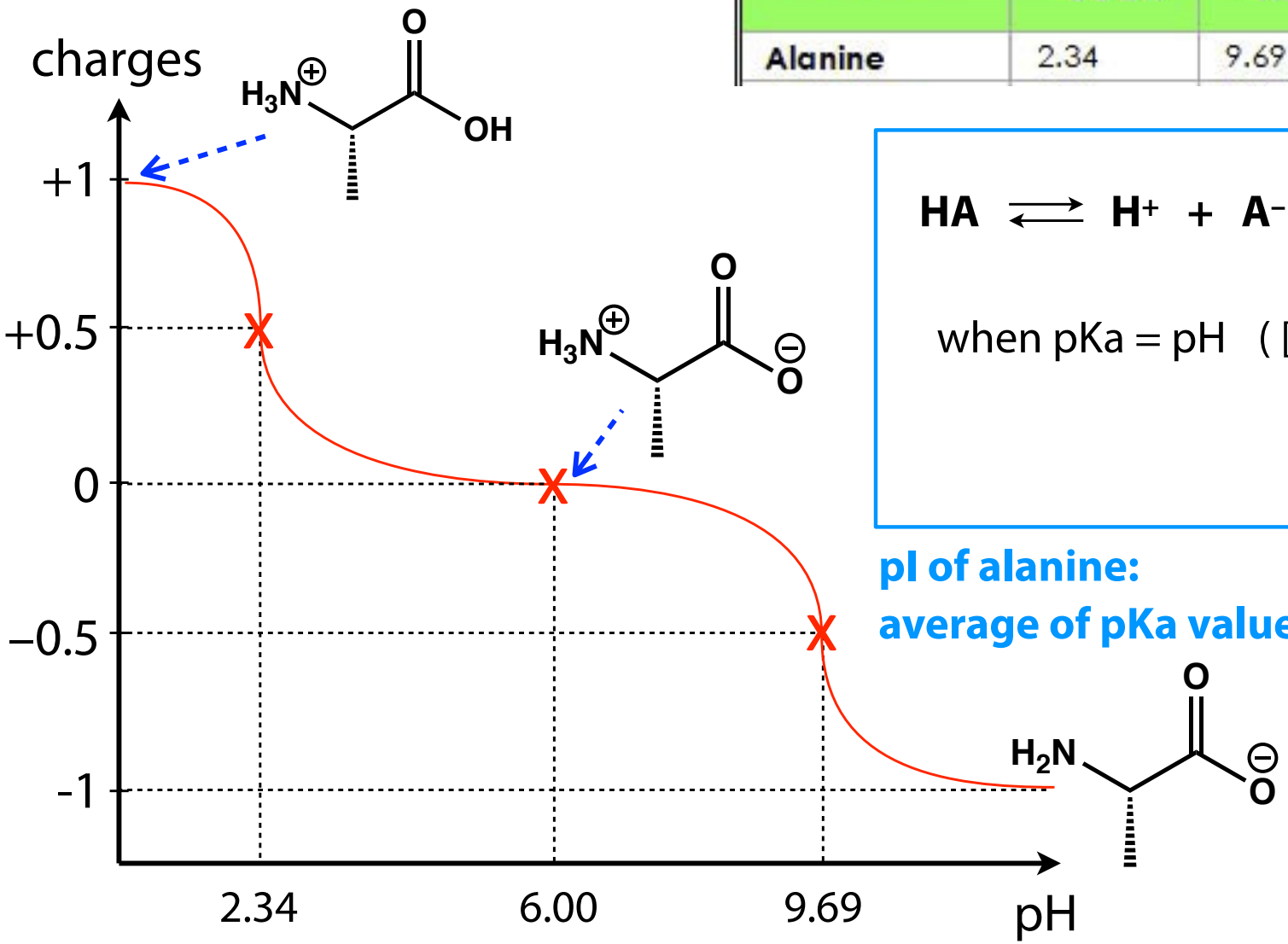
pKa values of general carboxylic acids are 4~5. Why the pKa values of COOH in amino acids are unusually small?

acidity/basicity of amino acids

Review Quiz

Explain the aqueous structures of alanine in buffers of pH = 2.34, 6.00, and 9.69.

Amino Acid	pK_1	pK_2	pK_R	pI
	-COOH	$-NH_3^+$	R group	
Alanine	2.34	9.69	-	6.00



$$HA \rightleftharpoons H^+ + A^- \qquad Ka = \frac{[H^+]\,[A^-]}{[HA]}$$

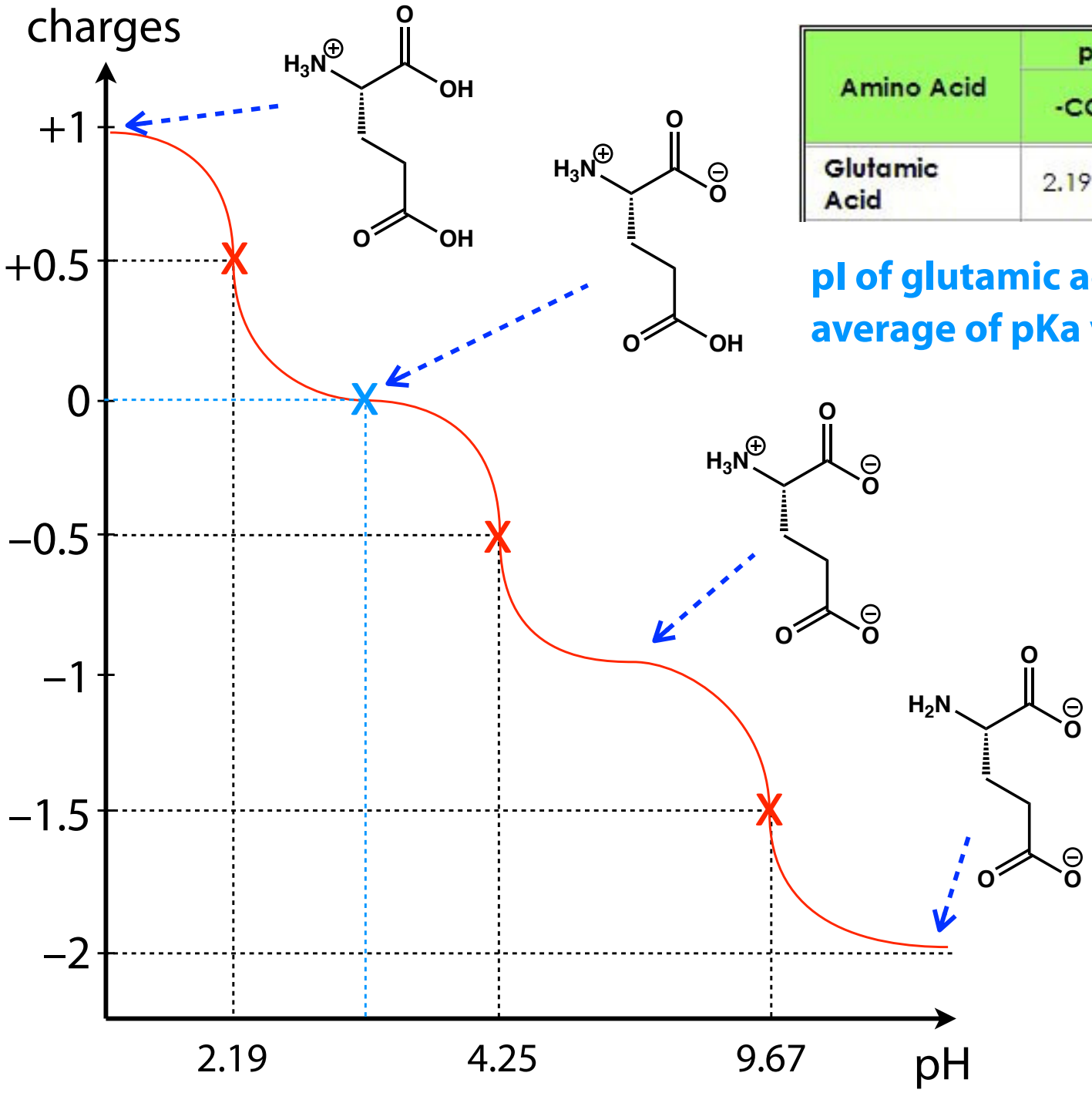
when pKa = pH ($[H^+] = 10^{-pH}$)

$$1 = \frac{[A^-]}{[HA]}$$

pI of alanine:

average of pKa values of NH_3^+ and COOH

acidity/basicity of amino acids



Amino Acid	pK_1 -COOH	pK_2 $-NH_3^+$	pK_R R group	pI
Glutamic Acid	2.19	9.67	4.25	

pI of glutamic acid:
average of pKa values of two COOH groups

Topics

- **structure of amino acids**
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- **synthesis of amino acids**
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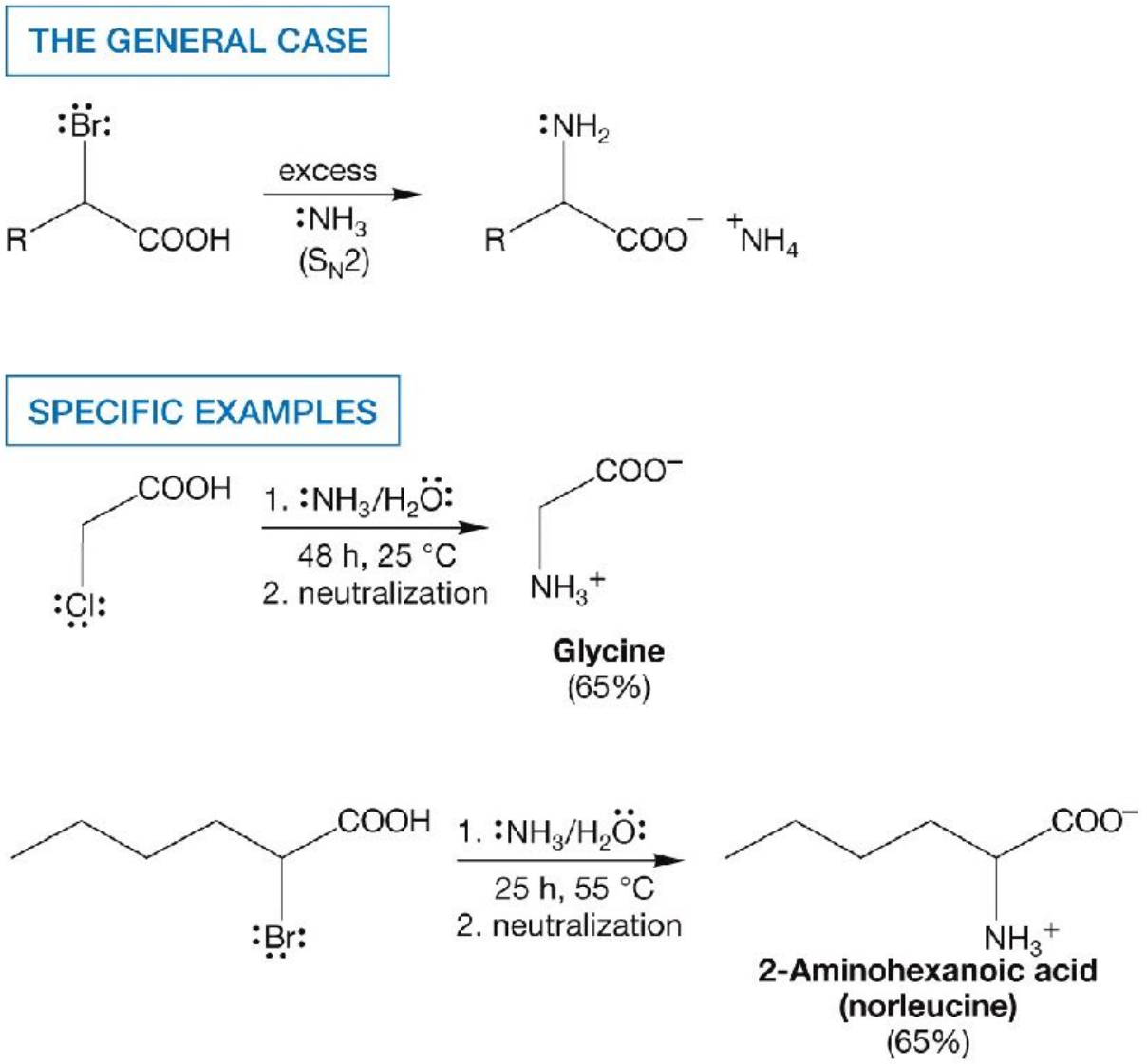
    - **synthesis of amines**
      - by S_N2 reactions
      - Gabriel synthesis
      - reductive amination
  - side chain addition
  - COOH synthesis
  - enantioselective synthesis

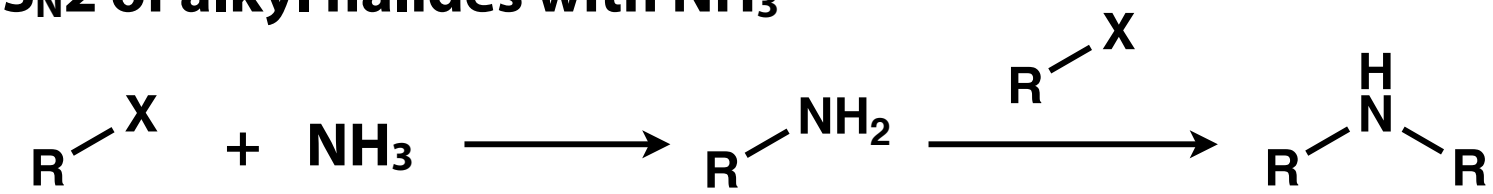
Synthesis of amino acids-1 amine synthesis

S_N2 of α-halo acids with NH_3

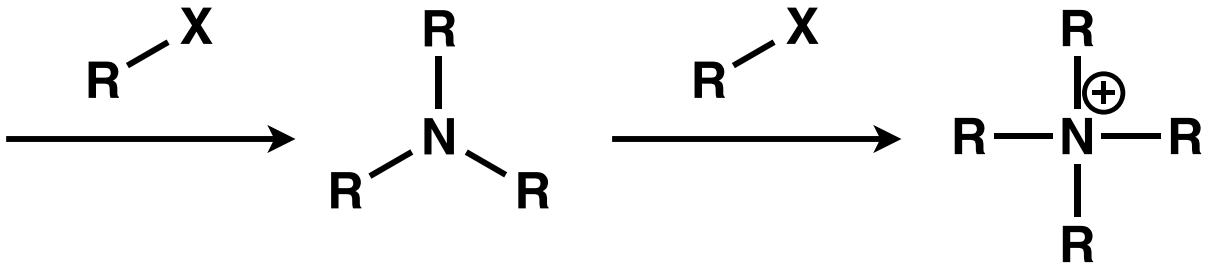


Synthesis of primary amines (general organic chemistry)

- **S_N2 of alkyl halides with NH_3**



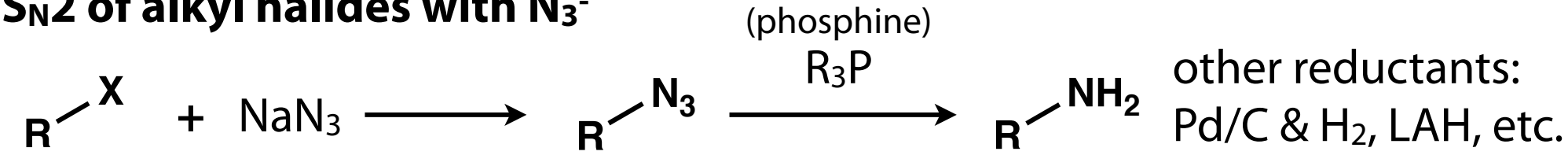
pKaH: **9.21** **10.63** **10.98**
(R = Et)



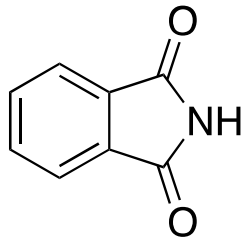
10.75

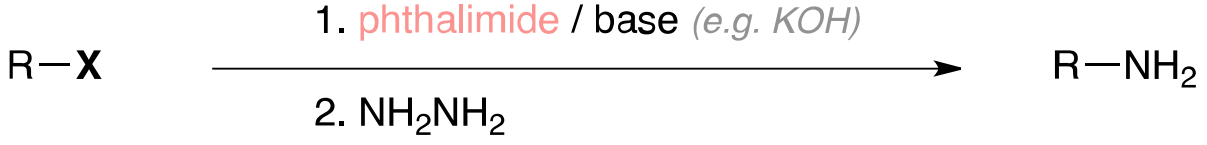
Synthesis of primary amines (general organic chemistry)

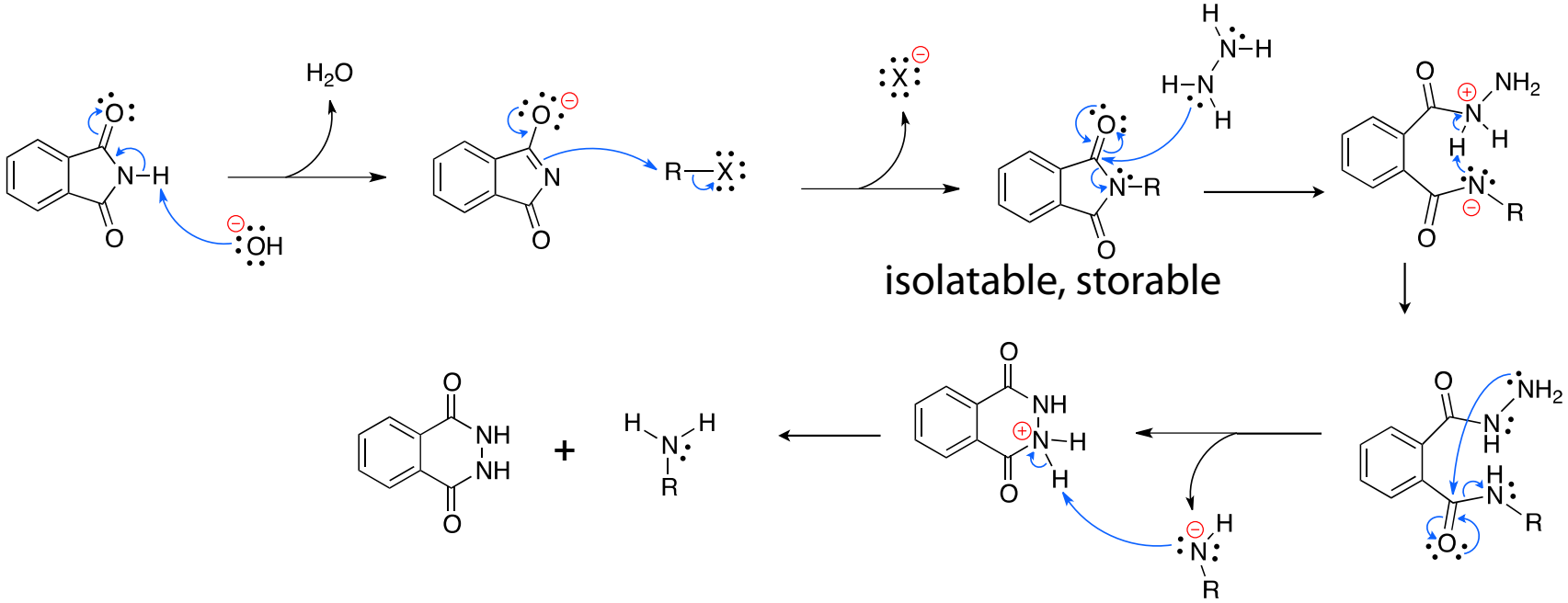
- **S_N2 of alkyl halides with N_3^-**



- **Gabriel synthesis**



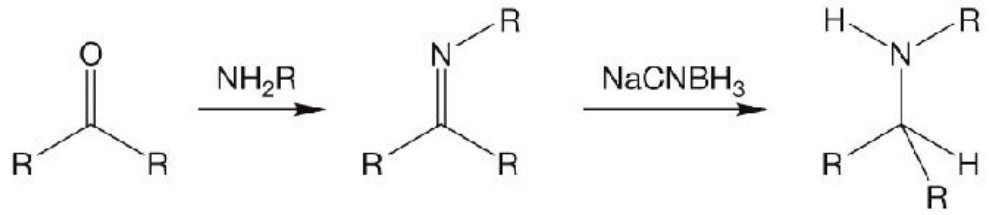




Synthesis of amines (general organic chemistry)

- **Reductive amination（還元的アミノ化）**

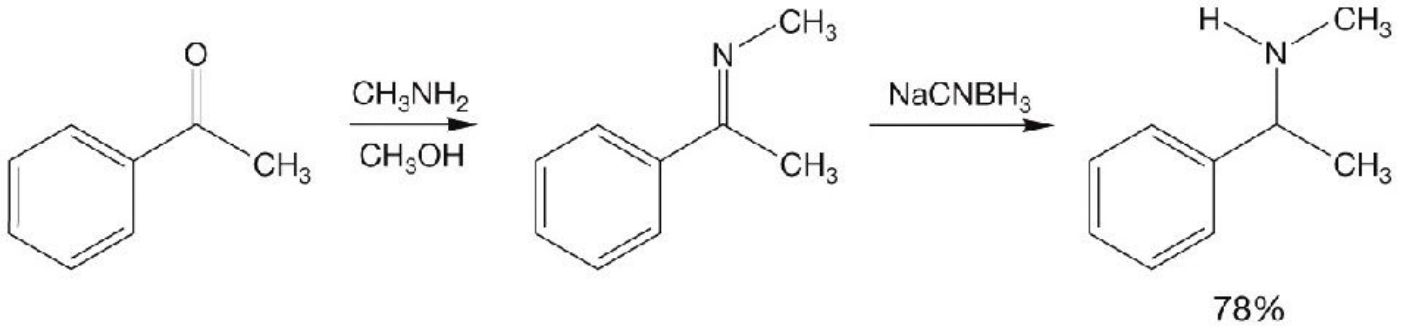
THE GENERAL CASE

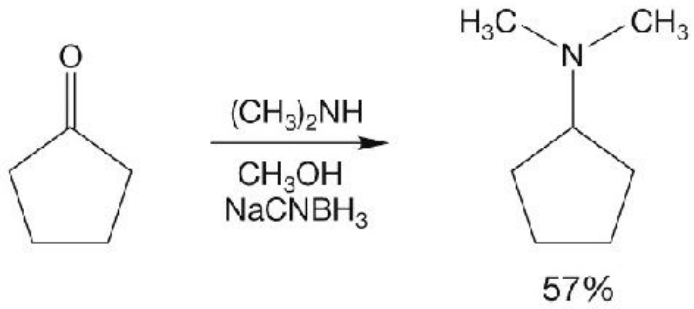


aldehydes can be also the SM.

can be performed in one-pot
often done in weak acidic cond.

SPECIFIC EXAMPLES





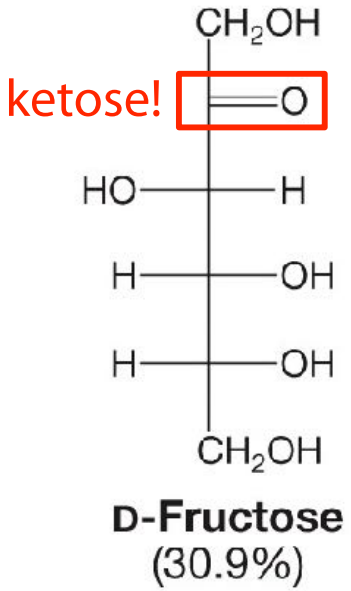
Review Quiz

Show the mechanism of imine formation and explain why reductive amination reactions are often performed in weak acidic conditions.

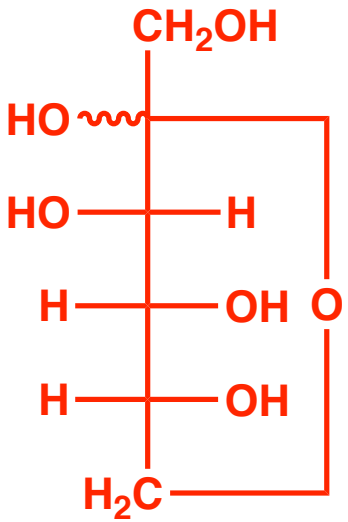
Reaction of monosaccharides - 4

Epimerization under basic conditions (Lobry de Bruijn-Alberda van Ekenstein reaction)

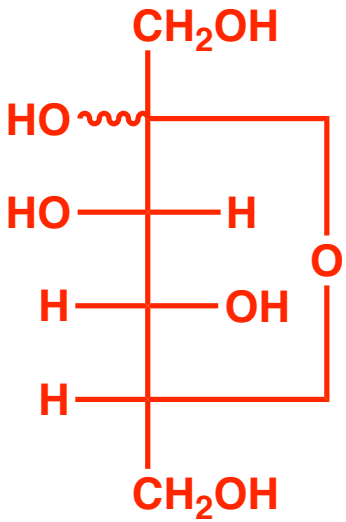
D-glucose can be slowly converted to D-mannose and D-fructose under basic conditions!



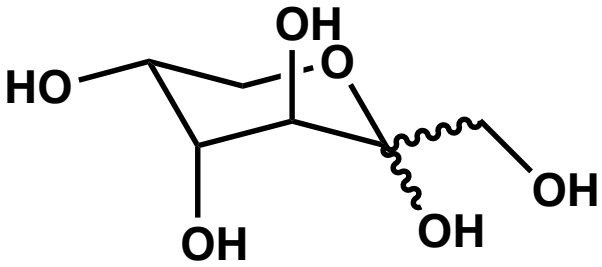
D-Fructose
(30.9%)



pyranose form

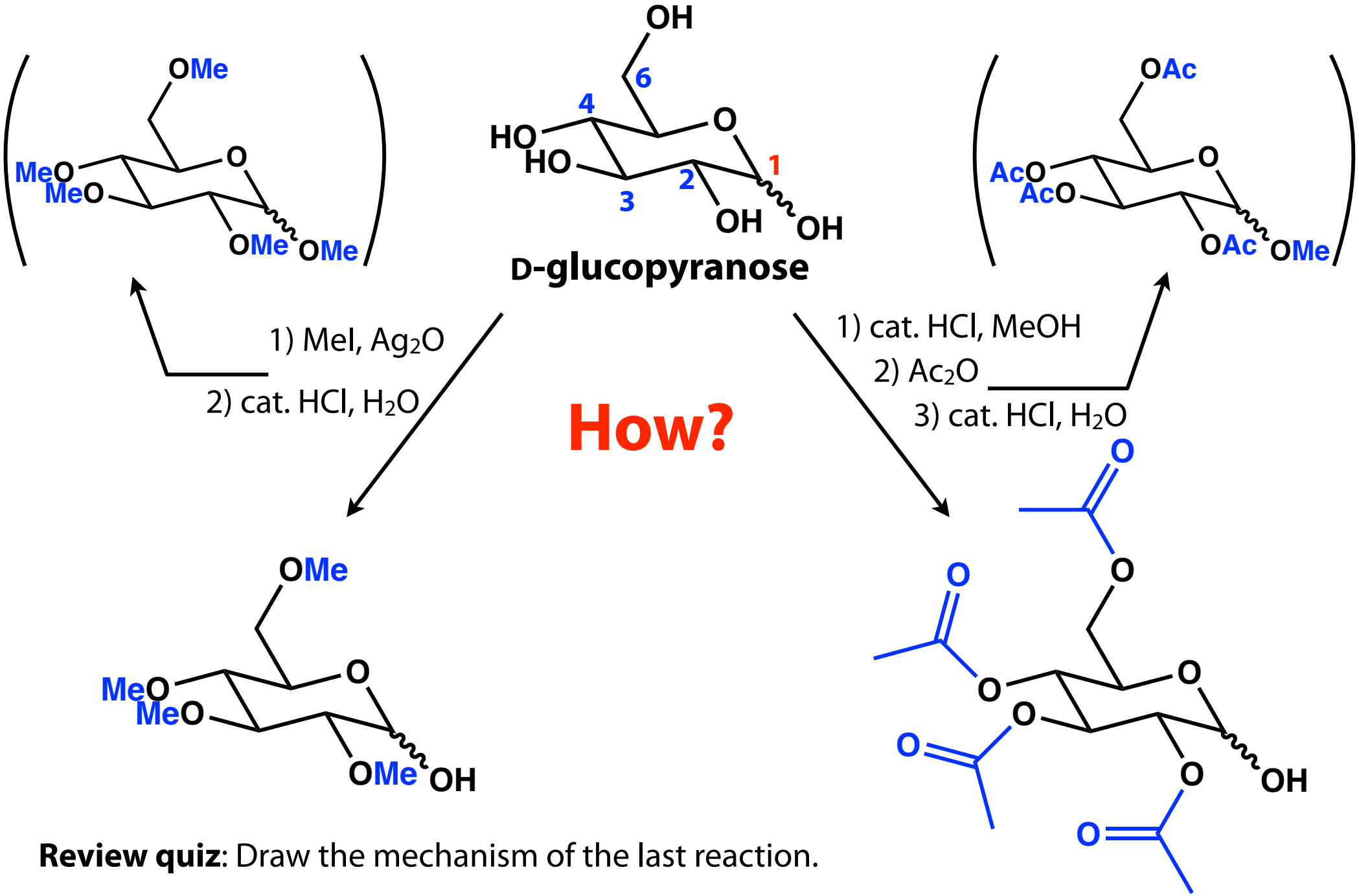


furanose form



Quiz-6: Although D-fructose (open chain form) is shown here to emphasize it is a ketose, it actually exists in the pyranose and furanose form. Draw Fischer projections for the pyranose and furanose forms of D-fructose.

Selective protection of monosaccharides



Review quiz: Draw the mechanism of the last reaction.