86. Ion-Molecule Reaction in the Gas Phase

Part VI[1])

Regioselective S_N2 Reaction from Terpenoid Diastereoisomeric Diols Using CI/NH_4^+

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Dedicated to Prof. *Tino Gäumann* on the occasion of his 60th birthday

(14.II.86)

A stereospecific and regioselective S_N2 mechanism (*Walden* inversion) is observed during studies involving modified terpenoid epimeric diols in a high-pressure ion source using ammonia as a reagent gas.

Introduction. – Mass spectrometric differentiation of stereoisomeric compounds on the basis of their respective decompositions in chemical ionization (CI) spectra is well-known [2]. Some years ago, *Winkler* and *Stahl* [3] demonstrated the power of ammonia chemical ionization (CI/NH_4^+) to distinguish between isomeric cyclic *cis/trans*-diols. Indeed, the relative stability of the adduct $[M + NH_4]^+$ ions is enhanced for those formed from the *cis*-isomers during the following process *(Eqn. 1)*:

$$M + NH_4^+ \rightleftarrows [M + NH_4]^+ \rightarrow MH^+ + NH_3 \qquad (1)$$

This stereochemical effect is due to the possible H-bonding, specific for the *cis*-isomers.

Note that the production of the MH^+ ion *(Eqn. 1)* must be an exothermic process ($PA(NH_3) \leqslant PA(M)$) [4] and thus, depends on the relative proton affinities of both reactants (*e.g.* M and NH_3). If the MH^+ formation is slightly endothermic ($PA(NH_3) > PA(M)$), then other decomposition pathways of adduct $[R{-}OH + NH_4]^+$ ions occur. For example, the alcohols (R–OH) react with the NH_3/NH_4^+ system to yield ammonium $R{-}NH_3^+$ species *via* an exothermic reaction *(Eqn. 2)* corresponding to nucleophilic substitution [4] [5].

$$R{-}OH + NH_4^+ \rightleftarrows [R{-}OH \cdots H \cdots NH_3]^+ \rightarrow R{-}NH_3^+ + H_2O \qquad (2)$$

To rationalize the formation of $R{-}NH_3^+$ (noted as M_sH^+) from the adduct ions, bimolecular (*e.g.* S_N1 and S_N2) [5–8] and unimolecular (*e.g.* S_Ni) [4] [9] processes have been proposed:

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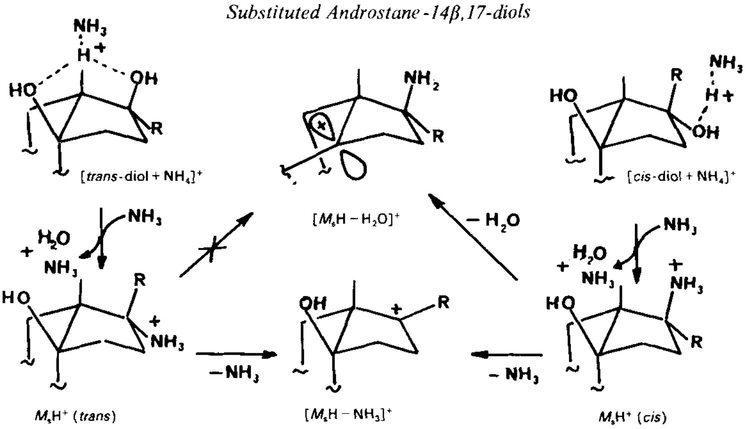
$$[R{-}OH + NH_4]^+ \xrightarrow[-H_2O]{-NH_3} R^+ \xrightarrow{+NH_3} R{-}NH_3^+\ (S_N1) \tag{3}$$

$$[R{-}OH + NH_4]^+ \xrightarrow{+NH_3} R{-}NH_3^+ + H_2O + NH_3\ (S_N2) \tag{4}$$

$$[R{-}OH + NH_4]^+ \xrightarrow[-H_2O]{} R{-}NH_3^+\ (S_Ni) \tag{5}$$

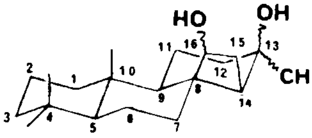
The analysis of the metastable decompositions of $[M + NH_4]^+$ is useful to distinguish the S_Ni from other processes. Indeed, only the S_Ni reaction can occur in the metastable region (field-free region or FFR) yielding to M_sH^+ by loss of water *(Eqn. 5)*. The only other possibility of decomposition is the loss of NH_3, because the bimolecular S_N1 and S_N2 pathways do not occur in the 2nd FFR. On the other hand, to distinguish between these processes, the configuration of the introduced NH_3^+ group in M_sH^+ may be determined; the reaction may be characterized by a racemization, an inversion or a retention of the $-NH_3^+$ configuration. The presence at proximity of a second nucleophilic site (double bond or heteroatom) susceptible to an interaction with the protonated site (OH_2^+ for MH^+ or NH_3^+ for M_sH^+) permits to differentiate epimeric ions and to determine the relative configuration of both functional groups. Among the different factors responsible for the stereochemical effects, the following ones are the most important: *i)* H-bond stabilization of molecular species ($[M + NH_4]^+$ and M_sH^+ or possibly MH^+) indicating a *cis*-geometry [3] and characterized by a larger abundance of these ions being displayed in the corresponding CI/NH_4^+ mass spectra (or in the MIKE or MIKE/CAD spectra), and *ii)* stereospecific decomposition in the 2nd FFR consisting in a loss of H_2O due to a possible H-transfer from $-NH_3^+$ which only occurs in the case of the *cis*-M_sH^+ species. For instance, the *Walden* inversion which occurs during the bimolecular S_N2 process (impossible in the 2nd FFR) has been demonstrated without ambiguity in the case of diastereoisomeric *cis*- and *trans*-androstane-14β,17-diols (substituted at C(17)) [10]. Indeed, during metastable decompositions, the M_sH^+ ion issued from the *trans*-isomer eliminates in competition NH_3 and H_2O on the contrary of the one derivated from *cis*-diol which loses only NH_3. On the other hand, only the *cis*-protonated M_sH^+ amino-alcohol can lose H_2O,

Scheme 1. *Regioselective* S_N2 *Process Involved under CI/NH_4^+ Conditions for Diastereoisomeric* cis- *and* trans-*17-Substituted Androstane-14β,17-diols*



while such migration being sterically impossible can not occur from *trans*-ionic form. So, we can conclude that *trans*-diols give rise to the formation of a *cis*-protonated amino-alcohol by an inversion of configuration during the S_N process. In addition, the MIKE/CAD spectra of the fragment ions $[M_sH - NH_3]^+$ *(Scheme 1)* produced from *trans*- and *cis*-M_sH^+ precursors are similar. Thus, a common structure does characterize these ions independently from their initial origin. This situation is consistent with a regioselective nucleophilic attack at the C(17) position during the formation of M_sH^+ [11]. This regioselectivity of the S_N2 displacement reaction is probably due to neighboring-group effects forced by the angular Me group on the C(13).

Here, we report on the study of the modified terpene diols **1**–**4** under CI/NH_4^+ conditions.



	OH-Configurations				
	C(13)	C(16)		C(13)	C(16)
1	*exo*	α	**3**	*endo*	α
2	*exo*	β	**4**	*exo*	β

These substrates are characterized by the presence of secondary and tertiary alcohol groups at the C(16) and C(13) positions, respectively, permitting a study of the molecularity of the nucleophilic substitution and of its specificity. Furthermore, the steric effect due to the presence of neighboring groups can *i)* hinder the electrophilic NH_4^+ attack (formation of adduct $(M + NH_4)^+$ ions) and *ii)* unfavor the reactivity of the adduct ion towards ammonia when an ion-molecule reaction (S_N2 pathway) occurs *(vide infra)*.

Results and Discussion. – The CI/NH_4^+ mass spectra *(Table 1)* of the diastereoisomeric diols **1**–**4** does not display major differences concerning their relative reactivities (except for the *endo*-α-isomer **3**).

Note that the MH^+ ions are absent in these spectra, indicating either very low stability, or the non-occurrence of the process described by *Eqn. 1*. The presence of the ammonium group in the different ions produced *(Table 1)* has been confirmed by D labelling under CI/ND_4^+ conditions. Indeed, the peak at *m/z* 306 (ion M_sH^+) is shifted at *m/z* 310 in the CI/ND_4^+ mass spectra which indicates that mainly the substituted $M_{d3s}D^+$ ion is produced in contrast to the isobar $M^{+\cdot}$ ion due a charge exchange reaction. Furthermore, the addition of ND_4^+ on a possible molecule $[M - H_2O]$ which is formed *via* a thermal process [12] and leading to $[M_{d2} - DHO + ND_4]^+$, *m/z* 311, is not detected.

Table 1. *Partial CI/NH_4^+ Mass Spectra*[a]) *of Epimeric Diols* **1**–**4**

Diol	$[M + NH_4 - 2H_2O - NH_3]^+$ (*m/z* 271)	$[M_sH - H_2O]^+$ (*m/z* 288)	$[M_sH - NH_3]^+$ or $[MH - H_2O]^+$ (*m/z* 289)	M_sH^{+b}) (*m/z* 306)	$[M + NH_4]^+$ (*m/z* 324)
exo-α (**1**)	22	5.4	65.8	6.4	0.4
exo-β (**2**)	38	4.5	54	3.3	0.2
endo-α (**3**)	18	24	43.8	15.1	0.1
endo-β (**4**)	24	5	64.6	3.8	0.6

[a]) The intensities of these peaks were normalized to 100% of total ionic current.

[b]) Under CI/ND_4^+ conditions, this peak was totally shifted by 4 amu. confirming the presence of OH and NH_3^+ groups. No charge exchange has been observed under those high-pressure ammonia conditions.

In each case, the more stable fragment ions correspond to $[M_sH - NH_3]^+$ (*m/z* 289) ions, which are formed in competition with $[M_sH - H_2O]^+$ (*m/z* 288). However, the *m/z* 289 ions may also correspond to $[MH - H_2O]^+$ structure.

1. *Origin of Ions* m/z *289 and* m/z *271; Non-occurrence of the* S_N1 *Process during the Formation of the Substituted* M_sH^+ *Ions.* The analysis of H. V. (high voltage) scan spectra of the ions *m/z* 289 in the 1st FFR (permitting the detection of parent ions for a selected daughter ion) shows that only two precursor ions M_sH^+ and $[M + NH_4]^+$ are involved. The contribution of the latter precursor is very low (< 8%) in comparison to the one of the M_sH^+ ions. Consequently, the ion *m/z* 289 is formed from M_sH^+ ions by loss of a NH_3 molecule, which indicates the structure $[M_sH - NH_3]^+$ rather than the $[MH - H_2O]^+$ one.

In addition, the H. V. scan spectra of *m/z* 271 $[M_sH - NH_3 - H_2O]^+$ cations indicate that the $[M_sH - NH_3]^+$ (*m/z* 289) and $[M_sH - H_2O]^+$ (*m/z* 288) ions are the main precursor ones, the contribution of the 'grand-parent' M_sH^+ ions being lower. Their relative abundance depends on the initial configuration of both OH groups *(Table 2)*.

Table 2. *Ratios of Parent Ions of the* m/z *271 Cations Measured in their Respective H. V. Scan Spectra* (for **1**–**4**)

	exo-α (**1**)	*exo-β* (**2**)	*endo-α* (**3**)	*endo-β* (**4**)
$\frac{[M_sH - H_2O]^+}{[M_sH - NH_3]^+}$	0.12	0.07	0.65	0.05

The occurrence of the S_N1 pathway involving an intermediate carbocation *(Eqn. 3)* should lead to a mixture of epimeric structures with the same abundance ratio for the M_sH^+ ion, independent of the initial configuration, and then its daughter ions should be produced with a similar abundance. On the other hand, the direct parent ions of the carbenium ion $[M_sH - NH_3 - H_2O]^+$ (*m/z* 271) which correspond to the fragment $[M_sH - NH_3]^+$ and $[M_sH - H_2O]^+$ ions must be characterized by a similar ratio for the four epimers which is not confirmed by our results. This allows to consider that the S_N1 pathway in the ion source must play a minor role.

2. *Comparison of the Different Structures of Ions* $[M_sH - NH_3]^+$ *(*m/z *289). Site Involved by the Nucleophilic Substitution.* The comparison of the daughter ion abundances of the isomeric fragment ions $[M_sH - NH_3]^+$, displayed by their MIKE/CAD spectra, should permit to determine which OH group is involved in the nucleophilic substitution, since its stereochemistry is lost during the production of *m/z* 289 ions.

Table 3 indicates that the MIKE/CAD spectra of the $[M_sH - NH_3]^+$ ions issued from the *endo-α*-**3** and *exo-α*-**1** epimers are identical with those produced from the *endo-β*-**4** and *exo-β*-**2** isomers, respectively. Thus, the structure of $[M_sH - NH_3]^+$ ions is independent of the α- or β-configuration of OH at C(13). This loss of stereochemistry shows that mainly the C(13) position is involved by the nucleophilic substitution leading to M_sH^+. This orientation will be explained below. However, it is difficult from these results to determine which pathway is followed to yield the M_sH^+ ions, S_N2 or S_Ni. Note that a complementary study of isomeric molecules formed in solution solvolysis *via* C(14)–C(15) bond migration into C(13)–C(15), shows that their MIKE/CAD spectra of M_sH^+ are significantly different to those obtained from **1**–**4**. Thus, the latter MH^+ species are not isomerized. In fact, a possible isomerization can only occur during decompositions by loss of H_2O and NH_3 yielding to carbonium ions *(vide infra)*.

Table 3. *MIKE/CAD*[a]) *Spectra of the* $[M_sH - NH_3]^+$ *Ions* (*m/z* 289) *for* **1–4**

m/z	*exo-α* (**1**)	*endo-α* (**3**)	*exo-β* (**2**)	*endo-β* (**4**)
189	2.0	1.4	2.2	1.0
193	4.2	8.8	4.4	9.0
201	4.2	9.1	4.2	8.9
203	1.9	1.9	2.1	2.2
205	0.5	–	0.7	0.1
207	2.4	2.1	2.9	1.7
215	6.9	9.6	5.9	10.2
219	3.1	3.5	3.7	3.1
229	1.2	1.4	1.5	1.2
231	11.0	5.1	9.6	5.1
233	2.2	2.9	2.3	2.5
245	8.5	14.7	8.1	13.8
271	51.9	39.5	52.4	41.2

[a]) The intensities of peaks were normalized to 100% of total ionic current, and the peaks with less 0.1% are not indicated.

[b]) The ion *m/z* 271 is only observed in the MIKE spectra of the various epimers.

3. *Minor Contribution of the* S_Ni *Mechanism on the Metastable Formation of* M_sH^+. *Structural Effects on the Stability of the* MH^+ *Ions Formed from Decomposition of the Adduct* $[M + NH_4]^+$ *Ions under Collision.* The metastable decompositions of the adduct ions (*m/z* 324) in the 2nd FFR, mainly consist in NH_3 elimination, yielding MH^+ (*Eqn. 1*). The contribution of the loss of H_2O (formation of M_sH^+ *via* the S_Ni process) is less than 5% of the total ion current, independent of to the initial configuration of the OH groups.

Thus, the role played by the S_Ni mechanism is very low in the 2nd FFR and most likely, this pathway must be even more negligible in the ion source. Indeed, recent investigations [13] of the behavior in CI/NH_4^+ of epimeric 1,2-indanediols show that the S_Ni process is more favored in the metastable region than in the ion source.

The S_Ni pathway is not enhanced under collision conditions (*Table 4(a)*), and the only additional decomposition concerns the metastable MH^+ ion, which eliminates a molecule of H_2O (*Eqn. 6*):

$$[M + NH_4]^+ \xrightarrow[-NH_3]{m^*} MH^+ \xrightarrow[-H_2O]{m^*} [MH - H_2O]^+ \qquad (6)$$

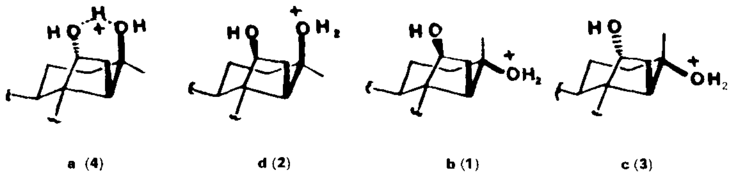
Table 4. $MH^+/[MH - H_2O]^+$ *and* $[M_sH - NH_3]^+/[M_sH - H_2O]^+$ *Daughter Ion Ratios Measured in the MIKE/CAD Spectra of Adduct Ions* $[M + NH_4]^{+a)}$ *and Substituted* $M_sH^{+b)}$ *Ions for* **1–4**

Daughter-ion ratios	*exo-α* (**1**)	*exo-β* (**2**)	*endo-α* (**3**)	*endo-β* (**4**)
(a) From $[M + NH_4]^+$				
$MH^+/[MH - H_2O]^+$	0.41	1.6	0.36	6.1
(b) From M_sH^+				
$[M_sH - NH_3]^+/[M_sH - H_2O]^+$	9.9	18.5	0.54	19.8
$([M_sH - NH_3]^+ + [M_sH - H_2O]^+)/M_sH^+$	$3.9 \cdot 10^{-3}$	$0.9 \cdot 10^{-2}$	$1.2 \cdot 10^{-3}$	$1.8 \cdot 10^{-2}$

[a]) M_sH^+ Ions are present in these spectra, but their relative abundance was less of 5% of the daughter ions MH^+.

[b]) In both MIKE/CAD spectra, the presence of $[M_sH - H_2O - NH_3]^+$ was less of 1% of total daughter-ion ionic current.

Scheme 2. *Isomeric Protonated Molecule* MH^+ *Structures Formed in the 2nd FFR from Adduct [*M *+* NH_4*]$^+$ Ions for the Diastereoisomeric Diols* **1**–**4**



The eventual loss of 2 H_2O which would produce the [*M*H – 2 H_2O]$^+$ ion is not observed in the MIKE/CAD spectra of the [*M* + NH_4]$^+$ ions.

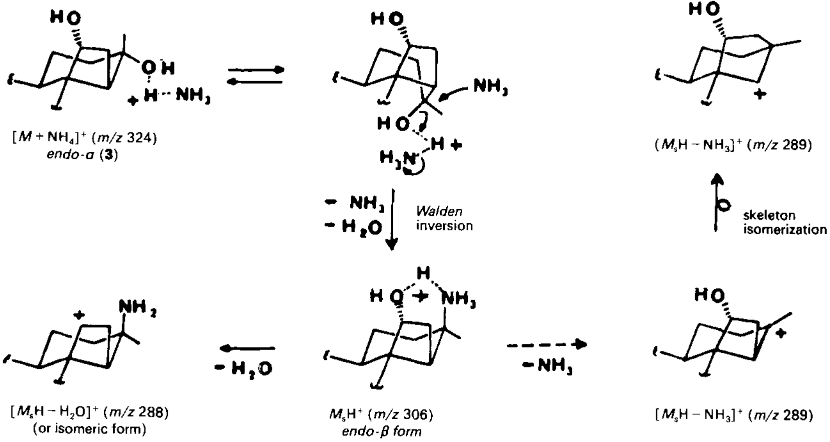
The relative abundance of both *M*H^+ and [*M*H – H_2O]$^+$ daughter ions depends strongly on the initial configuration of the OH groups. Considering that the stability of the daughter ions *M*H^+ can be described by the ratios ([*M*H^+])/([*M*H – H_2O]$^+$), *Table 4 (a)* indicates that the *M*H^+ ions issued from the *endo-β*-isomer **4** (structure **a** in *Scheme 2*) are more stable than those derived from the other diol epimers (forms **b**, **c**, and **d**). This result has been attributed to the possibility of an H-bond formation between both OH groups. In addition, the *exo-β*-isomer **2** leads to a more stable *M*H^+ ion (structure **d**) than the ions resulting from both *endo-α*- and *exo-α*-isomers which present a similar reactivity (structures **b** and **c**). With regard to these results, it appears that the ability of the metastable *M*H^+ ions to lose H_2O depends directly on the configuration of the OH group at C(13) and not on the configuration of the one at C(16) (except to favor an H-bonding). Note that the preferential role played by the OH group at C(13) during the formation of the epimeric fragment ions [M_sH – NH_3]$^+$ from $M_s$$H^+$ has already been shown (see *Sect. 3*).

4. *Structures of* M_sH^+ *and Determination of the* NH_3^+ *Configuration. Evidences in Favor of the* S_N2 *Process.* Previously, it has been shown that: *i)* the reaction occurs mainly on the tertiary alcohol at C(13), and *ii)* the S_N1 and S_Ni processes are unfavored pathways. Thus, the determination of the configuration of the introduced ammonium group at C(13) should give additional evidences that the S_N2 reaction is the main process.

For this purpose, a comparison between the behavior of the epimeric $M_s$$H^+$ ions concerning the competitive losses of H_2O (*m/z* 288) and NH_3 (*m/z* 289) in the metastable region (*Table 4 (b)*) has been performed. Note that the contribution on the consecutive losses of H_2O and NH_3 is very low, as observed during the decompositions induced by collisions on the *M*H^+ ions. This confirms the stability of the [M_sH – NH_3]$^+$ and [M_sH – H_2O]$^+$ daughter ions in the metastable region.

As shown in *Table 4 (b)*, the ratio of ([M_sH – NH_3]$^+$)/([M_sH – H_2O]$^+$) depends on the relative configuration of the diols [10] [14]. In particular, three main features can be observed *i)* only the *endo-α*-**3**-epimer yields a strong elimination of H_2O, *ii)* the abundance of daughter ions relative to parent ion (ratios ([M_sH – H_2O]$^+$ + [M_sH – NH_3]$^+$)/([$M_s$$H^+$]) in *Table 4 (b)*) is lower for this epimer, and *iii)* the $M_s$$H^+$ ions formed from the *β*-epimers (**2** and **4**) are more reactive than their counter parts, the *α*-isomers (**1** and **3**). This presents a remarkable contrast to the results obtained for *M*H^+ decompositions (also occurring in the 2nd FFR) which show pronounced decomposition for the isomers having an *α*-configuration over C(13) diols.

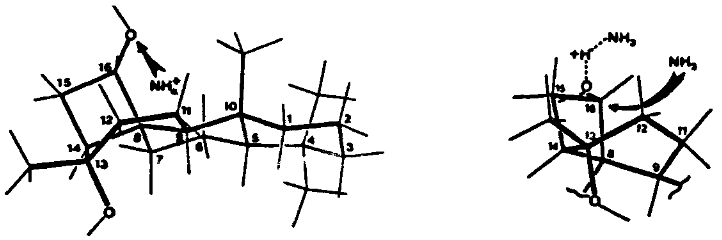
Scheme 3. *Regioselective* S_N2 *Process Involving OH–C(13) Groups* (for the isomeric *endo*-α-diol **3**) *Responsible for the Specific Loss of* H_2O *at C(16) from* M_sH^+



Among the different possibilities of mechanisms rationalizing the nucleophilic attack and orientation of the reaction at C(13) or C(16), only a S_N2 process occurring regioselectively on the OH group at C(13) is consistent with *i)* the ratio values of the *Table 4 (b)*, and *ii)* the reversed stabilities of *M*H and M_sH^+ ions (as expected in view of previous results). Moreover, the occurrence of H_2O loss is a test to show if both the OH and NH_3^+ groups are sufficiently close to permit a proton transfer in spite of its endothermic character. Such a situation only happens in the case of the *endo*-α-**3** epimer as shown in *Scheme 3*. Furthermore, the higher stability of M_sH^+ observed in the case of the latter epimer can also be explained by an eventual H-bonding *(Table 4 (b))*.

5. *Interpretation of the Regioselectivity Based on the Steric Effects.* Steric effects can explain the regioselectivity during the double-step process occurring on the tertiary OH group at C(13). The orientation appears during: *i)* NH_4^+ electrophilic attack and formation of reactive adduct $[M + NH_4]^+$ ion, and *ii)* nucleophilic substitution on the activated OH group (linked to NH_4^+) yielding M_sH^+. Indeed, the *Dreiding* models and *Allinger* calculations [15][3]) indicate that a steric hindrance *(Scheme 4 (a))* to a NH_4^+ electrophilic

Scheme 4. a) *Hindrance of the* NH_4^+ *Electrophilic Attack on the* endo-α-*Epimer* (**3**) *Leading to the Adduct* $[M + NH_4]^+$. b) *Hindered Nucleophilic Approach of* NH_3 *on the* exo-*Adduct Ions* (**1**) *during the Formation of* M_sH^+.



a

b

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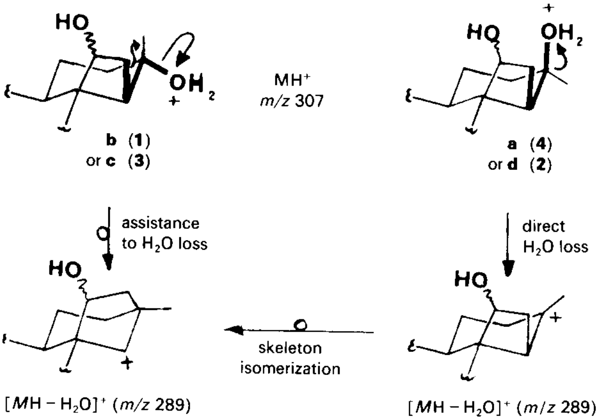
[3]) The *Allinger* calculations indicate that the boat conformation is favored for each diol epimer. Furthermore, for the OH–C(13) epimers **2** and **4** this conformation is stabilized by 3 to 3.5 kcal·mol^{-1} and for the epimers **1** and **3**, the stabilization is lower and corresponds to 0.2 to 0.3 kcal·mol^{-1}.

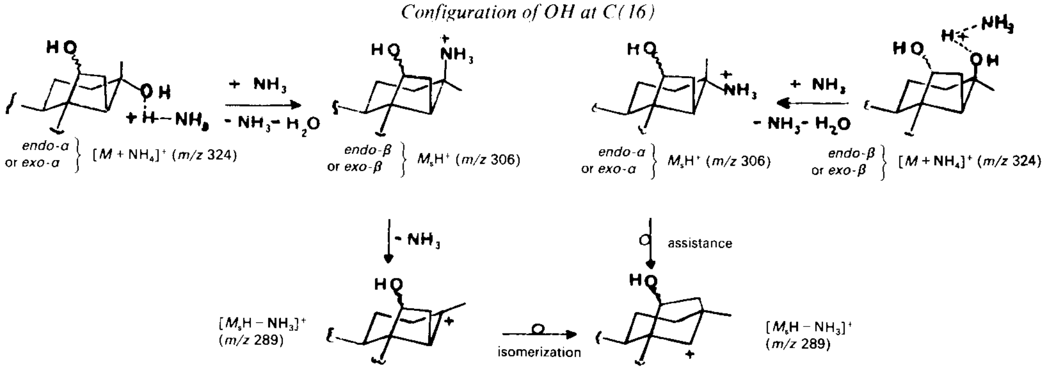
approach (the first step) on the *endo*-OH group at C(16) (epimers **3** and **4**) is forced by the presence of a neighboring H-atom at C(11) and by the Me group at C(10), as shown in *Scheme 4(a)* (case of the *endo*-α-epimer **3**). Furthermore, the *endo*-nucleophilic attack by NH_3 on the C(16)-activated OH group of the *exo*-adduct ions (*e.g.* epimers **1** and **2**) is sterically impossible *(Scheme 4(b))*. This steric hindrance is probably due to the presence of H_α–C(11). Thus, the formation of the ammonium adduct is regioselective with a NH_4^+ approach primarily oriented towards the OH group at C(13). The *Walden* inversion, which results from the nucleophilic substitution reaction between $[M + NH_4]^+$ (*e.g.* from *endo*-α-form, *Scheme 3*) and NH_3, produces a protonated amino-alcohol M_sH^+ presenting an *endo*-α-configuration. In this case, the proximity of both functional groups allows a competitive loss of NH_3 and H_2O *(Scheme 3)* [10] [14]. Such behavior and, therefore, a loss of H_2O is not expected from the other M_sH^+ epimers.

6. *Assistance during the Neutral Elimination from* M*H*$^+$ *and* M$_s$*H*$^+$ *Ions with an α-Configuration for the Protonated Group (OH$_2^+$ and NH$_3^+$).* Previously, it has been noted that the MH$^+$ ions formed from *endo*- (or *exo*)-α-diol epimers were less stable than those

Scheme 5. *C–C Migration Anchimeric Assistance to H_2O Elimination from* M*H*$^+$ *Formed in the 2nd FFR from Diastereoisomeric Adduct Ions [*M+*NH$_4$]*$^+$ (protonation on OH–C(13))



Scheme 6. *Formation of [*M$_s$*H – NH$_3$]*$^+$ *Ions Characterized by Identical Structure According to the* endo- *(or* exo-*) Configuration of OH at C(16)*



from β-diols *(Sect. 3, Table 4(a))*. In the same way, a facile decomposition of M_sH^+ ions characterized by an α-NH_3^+ (those formed from β-diols *via Walden* inversion) is observed *(Table 4 (b))*. This enhanced loss of H_2O (from α-MH^+) or NH_3 (from α-M_sH^+) can be attributed to the favorable anchimeric C(14)–C(15) bond assistance during the elimination of neutral (NH_3 or H_2O), as described in *Schemes 5* and *6*. This assumption is an additional element corroborating the already demonstrated attack at C(13). It is worthnoting that this particular group assistance is independent of the *endo*- or *exo*-configuration of OH at C(16). Such electronic assistance, similar to a *Wagner-Meerwein* rearrangement, has already been found responsible for the higher reactivity of the α-diols **1** and **3** observed during their condensed phase solvolysis [16]. Furthermore, this phenomena also explains the different rate constants for the solvolysis of bicyclic systems such as borneol and isoborneol isomers [17]. Finally, this also rationalizes the behavior of both the latter epimers when placed under the CI/NH_4^+ conditions which lead to the M_sH^+ ions [18].

Conclusion. – On the basis of our results, it has been shown that, under CI/NH_4^+, the modified terpenoid diols studied are converted into substitution product ions M_sH^+, likely following a mechanism similar to the one previously reported for androstane diol epimers; *i.e.* activation by formation in a first step of an adduct ion which subsequently reacts in a second step with NH_3. This gives rise to a nucleophilic displacement reaction at the activated C site ($\geqslant C-OH\cdots H^+\cdots NH_3$). A possible skeletal rearrangement as a *Wagner-Meerwein* isomerization during the M_sH^+ formation, which can occur like solution solvolysis, seems to play a minor role as shown by differences displayed in the MIKE/CAD spectra of M_sH^+ for isomeric diols characterized by bicyclo [4.2.0]- and -[3.3.1]octan systems on the C ring. The stereochemical effects observed on the stabilities of produced ions can be explained by the following assumptions. Each of these two steps (approach by NH_4^+ and by NH_3) must be sensitive to a steric hindrance due to neighboring H and Me groups, and then this suggests that the S_N2 reaction can be regioselective at C(13). Such an hypothesis is consistent with the metastable investigations.

The diastereoisomeric MH^+ ions which possess an α-OH moiety are less stable than the β-isomers (**2** and **4**) regardless of the *endo*- or *exo*-configuration of the OH group at C(16). The enhanced reactivity of the former during the elimination of H_2O for MH^+ (or NH_3 for M_sH^+) *via*, most likely, a skeleton rearrangement, can be attributed to an anchimeric assistance provided by the C(14)–C(15) bond *trans* to the $\geqslant C-OH_2^+$ (or $\geqslant C-NH_3^+$) bond. These observations were also made for the elimination of neutral molecules during solvolysis studies in solution.

Experimental. – A *ZAB-2F (VG Analytical Ltd.)* double-focusing mass spectrometer with reversed geometry was used for this study. A CI source was used at a pressure of about 0.7 Torr for ammonia. Accelerating voltage: 8 kV, total emission current (100 eV electron energy and zero repeller voltage): 500 µA, source temp.: 160°.

Metastable transitions in the 2nd FFR and collisionally activated decompositions (using He as collision gas) were studied by MIKE. Precursor spectra for a selected ion are recorded by scanning of the high-voltage source from 6 kV (main beam corresponding to the selected daughter ion) to 9 kV. Deuterated ammonia gas was obtained from *C.E.A. Saclay* (France).

The synthesis of the epimeric diols **1**–**4** will be published elsewhere.

Financial support of this work by the *CNRS* (France) is gratefully acknowledged, and the authors thank Prof. *M. Fetizon* for interesting discussions.

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