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ION-MOLECULE REACTIONS IN THE GAS PHASE. IX DIFFERENTIATION OF ENANTIOMERIC MENTHOLS USING A STEREOSPECIFIC SN2 PROCESS INDUCED BY A CHIRAL REAGENT.

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Abstract - Stereospecific ion-molecule reactions of chiral reagents such as amino-alcohol with Mr,s,r and Ms,r,s enantiomeric alcohols (both menthols with R- and S-hydroxylic groups, respectively) yield both diastereomeric $(Mr,r,s + AsH - H_2O)^+$ and $(Ms,r,s + AsH - H_2O)^+$ ions. This specific gas phase synthesis combined with Mass Spectrometry/Mass Spectrometry analysis was applied to differentiate enantiomeric alcohols. Indeed, respective MIKE/CID spectra present differences in the daughter ion abundances which are useful for distinguishing between the initial alcohol configurations.

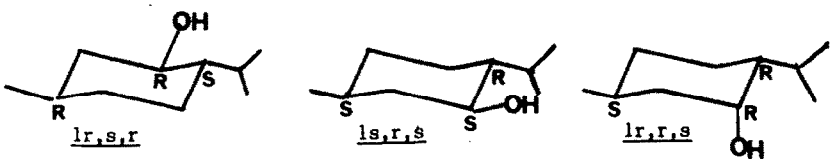
Mass spectrometry is a powerful tool for differentiation of cyclic diastereomers via analysis of decomposition products generated under either electron ionization (EI)[1] or positive and negative chemical ionization[2,3] conditions. For alicyclic compounds, generally characterized by non rigid conformations, it is more difficult to assign relative stereochemistry[4] as demonstrated by the lack of examples reported in the literature. Application of Mass Spectrometry/Mass Spectrometry (MS/MS) techniques[5] to the analysis of selected molecular species or fragment ions gives additional information about the molecular stereochemistry[2,3,6]. Diastereomeric molecular ions of (R,S) and (S,S)-N-Acet-Phe-Phe dipeptides were recently distinguished by comparing abundances of the respective daughter ions produced via Collision-Induced-Dissociation in the 2nd FFR of a reversed geometry mass spectrometer[7].

By analysis of a racemic mixture of deuterated diisopropyl-d_{14}-L- and diisopropyl-D-tartrates using Positive Chemical Ionization (PCI), Fales and Wright[8a] were able to distinguish the enantiomeric L and D tartrates. The abundance of the protonated "meso" DLH^+ dimer was found to be lower than those of the protonated DDH^+ and LLH^+ dimers. This chiral discrimination is attributable to geometric and steric factors[8b].

Recently, in a high pressure Chemical Ionization experiment in which the chiral (l)-amyl alcohol reagent was used, Chen et al.[9] distinguished enantiomeric (R)- and (S)- amino-acids by analysis of their respective $CI/C_5H_{11}OH_2^+$ conventional mass spectra. Among the observed differences, the relative abundances of the enantiomeric protonated molecules MH^+ and the diastereomeric adduct ions were used to characterize the chirality of the neutral amino-acids studied. These CI mass spectra, however, depend critically upon the source conditions (pressure and temperature), leading to difficulties in using this method for purposes of quantitative analysis.

We report herein another approach to reproducible differentiation of enantiomeric molecules such as enantiomeric Mr,s,r and Ms,r,s menthols (lr,s,r and ls,r,s ,molecular weight = 156) where the hydroxyl group is characterized by (R)- and (S)- absolute configurations, respectively. In this

study, a stereospecific gas-phase nucleophilic displacement of the hydroxyl group of the following enantiomeric 1r,s,r and 1s,r,s and diastereomeric 1r,r,s menthols is investigated.



This reaction is induced by (S)-2-amino-1-butanol (2s ,Mw = 89, noted As). Occurring without notable gas-phase racemization of the reactive site, this ion-molecule reaction is shown to be sufficiently stereospecific to produce diastereomeric $(Mr,s,r + AsH - H_2O)^+$ and $(Ms,r,s + AsH - H_2O)^+$ ions which can be distinguished by MS/MS analysis.

RESULTS and DISCUSSION

Under high pressure (~ 0.5 Torr) conditions, using a low source temperature (100°C), the CI mass spectrum of the chiral As amine reagent 2s displays mainly the protonated AsH^+ amine, m/z 90 (as base peak), along with the fragment $C_2H_6NO^+$, m/z 60 (5% of base peak), and $C_3H_8N^+$,m/z 58 (40%) ions. The protonated dimer As_2H^+ (m/z 179) was also detected (49% of base peak).

1. Relative stabilities of substituted $(M + As - H_2O)^+$ ions formed in the source during ion-molecule reaction induced by the As/AsH^+ system. Origin of the nucleophilic substitution process .

The chiral As/AsH^+ system reacts with the enantiomeric menthols (1r,s,r and 1s,r,s) yielding diastereomeric adduct $(M + AsH)^+$,m/z 246, ions and diastereomeric substituted $(M + AsH - H_2O)^+$ (m/z 228) ions (table 1).

Table 1. Main ions* observed in the CI mass spectra of enantiomeric 1r,s,r and 1s,r,s and diastereomeric 1r,r,s menthols

-OH Configuration of epimeric Menthols	$(M-H)^+$ m/z 155	MH^+ m/z 157	As_2H^+ m/z 179	$(M + AsH - 2H_2O)^+$ m/z 210	$(M + AsH - H_2O)^+$ m/z 228	$(M + As)^+$ m/z 246
(R)-OH (1r,s,r)	4	1	100	35	51	93
(S)-OH (1s,r,s)	2	1.5	100	42	38	60
(R)-OH (1r,r,s)	6	4	100	24	11	79

*Only the molecular species are reported. The ion abundances are related to base peak As_2H^+.

These CI mass spectra (recorded under our experimental conditions) indicate that:

(i) the $((M + AsH - H_2O)^+) / ((M + AsH)^+)$ ratio is 0.55 and 0.63 for 1r,s,r and 1s,r,s stereoisomers, respectively. The weak dependence of this ratio upon the hydroxyl group configuration indicates that the yield of the asymetric gas-phase synthesis of both diastereomeric substituted ions (using (S)-aminoalcohol as reagent gas) is low. This weak discriminatory effect is too sensitive to experimental conditions (source parameters, temperature and chiral reagent pressure) to be used to distinguish unambiguously epimeric menthols.

(ii) the relative abundances of the substituted $(Mr,r,s + AsH - H_2O)^+$ and $(Ms,r,s + AsH - H_2O)^+$ ions as well as the more highly fragmented $(M + AsH - 2H_2O)^+$ ions depend upon the relative configuration of the radical (methyl and iso-propyl) and hydroxylic groups in the studied menthol epimer. In particular, the value of the $((M + AsH - 2H_2O)^+) / ((M + AsH - H_2O)^+)$ ratio is significantly higher for the 1r,r,s epimer. This difference suggests that the substituted $(M + As - H_2O)^+$ ions produced from the diastereomeric 1s,r,s and 1r,r,s molecules do not have the same structure (or distribution of diastereomeric structures as dictated by the reaction pathway). A purely step-

wise S_N1 mechanism (equation 1) epimerizing the reactive electrophilic site, by contrast, would have led to identical diastereomeric distributions of both $(Mr,r,s + AsH - H_2O)^+$ and $(Ms,r,s + AsH - H_2O)^+$ derived from the ls,r,s and lr,r,s epimers:

Equation 1 $$M + AsH^+ \rightleftharpoons (M + AsH)^+ \xrightarrow[-(H_2O + As)]{} (MH - H_2O)^+ \xrightarrow{As} (MH - H_2O + As)^+ \qquad (S_N1)$$

Furthermore, the measured $((M + AsH - 2H_2O)^+)$ / $((M + AsH - H_2O)^+)$ ratio should have been independant of the (R)- and (S)-OH relative configuration for both lr,r,s and ls,r,s ,respectively if the reaction was truly S_N1. Thus, the stepwise mechanism must be rejected in view of the results given in table 1. Consequently, the process can be considered at least partially stereospecific (similar to unimolecular S_Ni or bimolecular S_N2).

(iii) as anticipated, the proton transfer process (equation 2) yielding the protonated MH^+ menthols via direct fragmentation of the adduct $(M + AsH)^+$ ions appears to be a minor pathway in comparison to Nucleophilic Substitution, which leads to the more abundant $(M + AsH - H_2O)^+$ ions.

Equation 2 $$M + AsH^+ \longleftarrow (M...H...As)^+ \not\longrightarrow MH^+ + As$$

The proton affinity of the menthol lr,s,r , ls,r,s and lr,r,s epimers is thus probably lower than that of the amino-alcohols 2 , rendering proton transfer from AsH^+ to M (lr,s,r , ls,r,s and lr,r,s) a necessarily unfavored endothermic process[10] . This situation is the reverse of what takes place when a chiral amyl alcohol system[9] was used. In this latter case, mainly the protonated MH^+ amino-acids were observed in the CI mass spectra. The proton affinity of the chiral amyl alcohol reagent is thus lower than those of amino-acids.

2. The unimolecular S_Ni decomposition of the adduct $(M + AsH)^+$ ions occurs as a minor process in the ion source .

Several mechanisms have been proposed[11] to account for nucleophilic attack induced by the NH_3/NH_4^+ system. They may vary depending upon on the structure of the investigated alcohol. In particular, the bimolecular S_N2 pathway is favored for saturated or unsaturated cyclic compounds[12-14] in the absence of steric hindrance effects[15] . The unimolecular S_Ni reaction is preferred for bicyclic alcohols[11] bearing a hydroxyl group at the bridge-head carbon , as well as for benzylic alcohols[10,17,18] . The latter process occurs only if a planar transition state can be achieved by the adduct ions[18] . In several dihydroxy compounds such as sterols or their analogs, the process has been shown to be regioselective[13,15,18] .

Concerning our study, the analysis of metastable decompositions of the adduct ions $(M + AsH)^+$ formed from enantiomeric lr,s,r and ls,r,s and diastereomeric lr,r,s menthols gives additional insight into the pathway followed by the nucleophilic substitution process. In the MIKE (Mass-Analyzed Ion Kinetic Energy) spectra of these adduct ions, AsH^+ appears as the sole daughter ion derived from the adduct $(M + AsH)^+$ ion (equation 3):

Equation 3 $$(M + AsH)^+ \xrightarrow{m^*} M + AsH^+$$

(i) The absence of the metastable MH^+ daughter ion confirms that the proton affinity of the amino-alcohol As reagent is higher than those of the menthols[19] . On the other hand, in the source, the acid-base process leading to formation of protonated MH^+ molecules must then be endothermic. Consequently, other exothermic source reactions such as Nucleophilic Substitution[10,13] must be preferred, favoring the formation of diastereomeric substituted $(Mr,s,r + AsH - H_2O)^+$, $(Ms,r,s + AsH - H_2O)^+$ and $(Mr,r,s + AsH - H_2O)^+$ ions.

(ii) Furthermore the absence of the daughter $(M + AsH - H_2O)^+$ ion indicates that the adduct $(M + AsH)^+$ ions do not follow the S_Ni unimolecular decomposition pathway (equation 4).

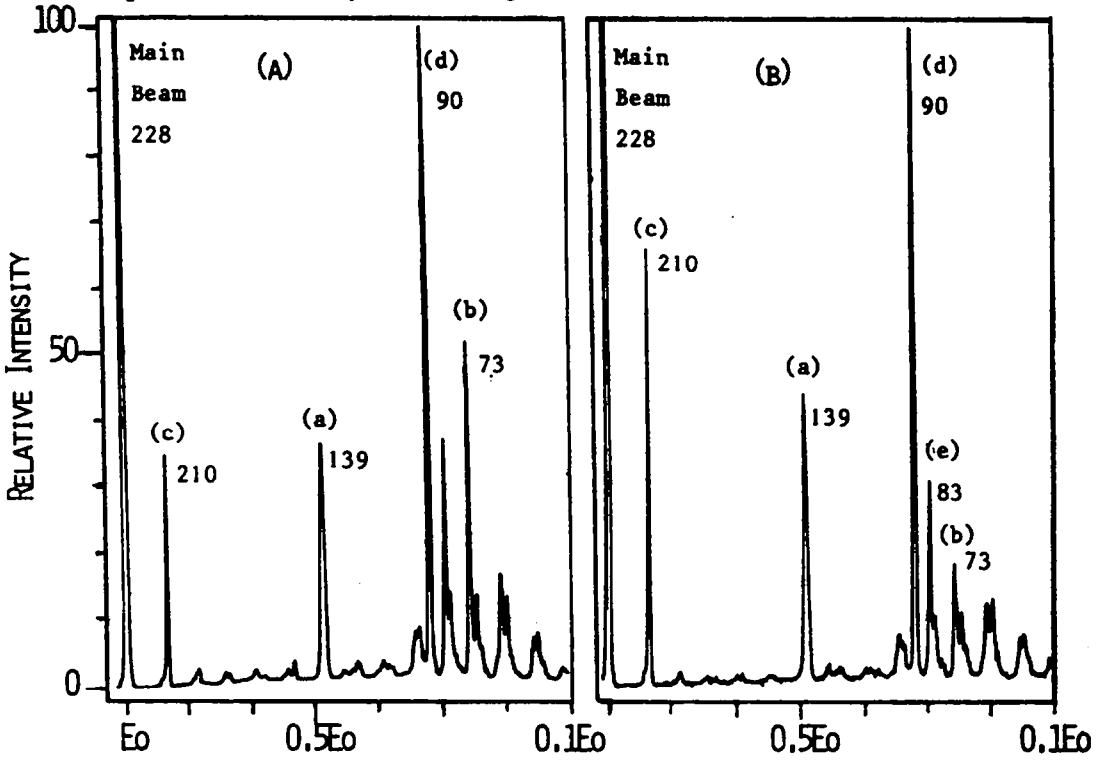
Equation 4 $(M + AsH)^+ \longrightarrow (M + AsH - H_2O)^+ + H_2O \quad (S_Ni)$

Although, it is difficult to determine the relative contribution of each SN pathway taking place in the ion source (yielding substituted ions from the adduct ion of the menthol epimers), it is possible to find out which one is principally involved. In the 2nd FFR[13], the S_Ni unimolecular process was not observed. Hence, within the high pressure ion source (where the adduct ions are thermolysed), S_Ni should also be less favored. Thus, only bimolecular processes should be observed. Because the bimolecular stepwise S_N1 pathway for formation of substituted $(M + AsH - H_2O)^+$ ions has been previously ruled out, the S_N2 process from the adduct ions consequently must be favored.

3. Structure of the substituted ions m/z 228. Indirect evidence for the bimolecular S_N2 pathway.

In order to demonstrate that the configuration of the various substituted $(M + AsH - H_2O)^+$ ions are different, the MIKE/CID spectra have been studied. Significant stereochemical effects are manifested in the abundances of daughter ions produced by collisional decompositions of the substituted $(M + AsH - H_2O)^+$ (m/z 228) ions of both enantiomeric 1r,s,r and 1s,r,s alcohols (figure 1).

Figure 1. MIKE/CID spectra of the substituted m/z 228 ions for the enantiomeric (a) 1r,s,r and (b) 1s,r,s menthol, formed under CI/chiral S-aminobutanol conditions (the m/z 210 and m/z 90 daughter ions are also produced during unimolecular decompositions of the m/z 228 ions).



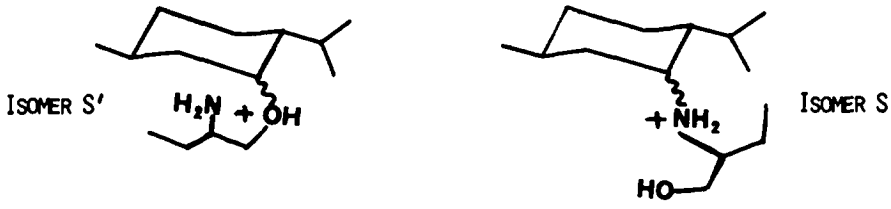
Furthermore, the MIKE/CID spectrum of m/z 228 (not shown) produced from the 1r,r,s diastereomer is different to those recorded for 1r,s,r and 1s,r,s . In particular, the daughter ion (m/z 210) / (m/z 90) ratio is 1.3. This ratio is significantly higher than those measured for the 1r,s,r and 1s,r,s enantiomers which are both less than 1. This difference observed for the subtituted $(M + AsH - H_2O)^+$ ions derived from 1r,r,s and 1s,r,s shows that their ion structures were different.

On the other hand, this result indicates that epimerization of the reactive site of the adduct ions is, at most, a minor event, further verifying previous considerations about the S_N1 process. This confirms that the major pathway followed under our CI conditions is the bimolecular S_N2 mechanism yielding diastereomeric $(M + AsH - H_2O)^+$ ions according to equation 5:

Equation 5 $M + AsH^+ \rightleftharpoons (M...H...As)^+ \xrightarrow{+As} (M + AsH - H_2O)^+ + As + H_2O \quad (S_N2)$

Nucleophilic substitution involves the carbon atom linked to $(-OH^+..As)$ in the adduct ions, which is activated by solvation. An ambiguity, however, can appear concerning the structure of the produced $(M + AsH - H_2O)^+$ ion. Indeed, each nucleophilic site (-OH and/or $-NH_2$) of the chiral amino-alcohol As can attack the activated alcohol of the adduct $(M + AsH)^+$ ion to yield isomeric ions, thereby forming either a protonated secondary $(M + AsH - H_2O)^+$ amino-alcohol (ion structure S) if the hydroxylic group of the neutral As reacts with $(M + AsH)^+$, or a protonated $(M + AsH - H_2O)^+$ amino-ether (ion structure S' as shown in scheme 1) if the amino site of As attacks the activated alcohol of the adduct ion.

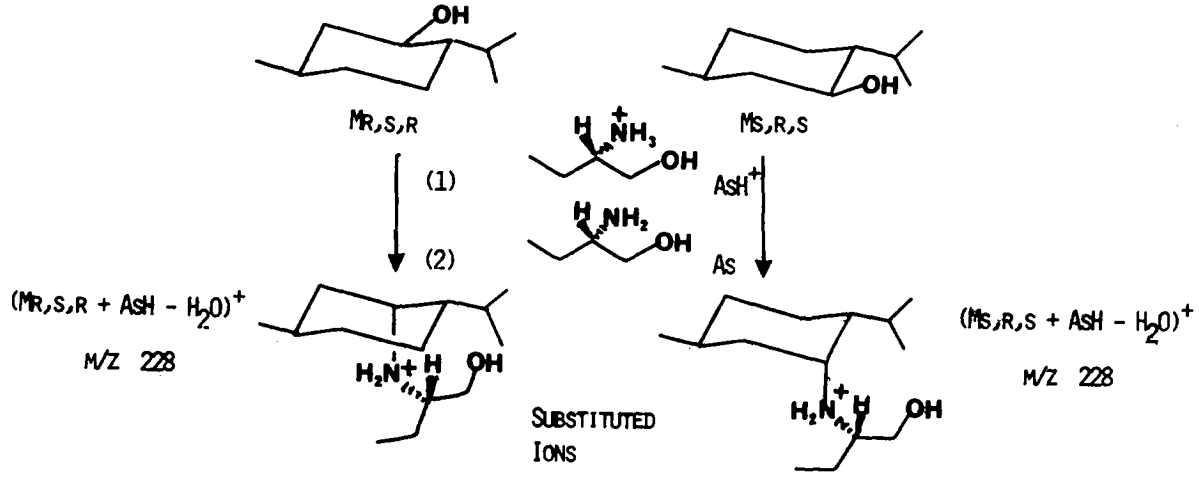
Scheme 1



The analysis of the MIKE/CID spectra of these substituted ions indicates that the former possibility takes place exclusively. Indeed, the loss of NH_3, which is expected from the structure S' for $(M + AsH - H_2O)^+$ was not observed, whereas the ion characterized by structure S must specifically lose H_2O as was detected in these MIKE/CID spectra. This behavior also suggests that the S_N2 reaction is regioselective[1,15].

Thus, during nucleophilic attack of the reagent chiral amine 2s, diastereomeric $(Mr,s,r + AsH - H_2O)^+$ and $(Ms,r,s + AsH - H_2O)^+$ ions are produced from the chiral menthols (1r,s,r, 1s,r,s) with Walden inversion of the hydroxylic group configuration (scheme 2). During this process, the (S)- configuration at the initial $\geq$C-N bond of the As nucleophilic reagent is preserved.

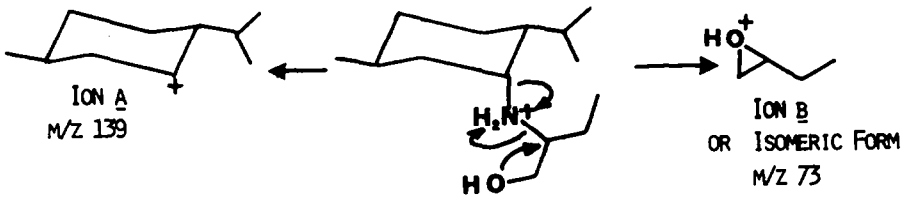
Scheme 2.



Furthermore, the secondary ammonium structure S proposed in scheme 1 for substituted $(Mr,s,r + AsH - H_2O)^+$ and $(Ms,r,s + AsH - H_2O)^+$ ions are consistent with the MIKE/CID spectra. The observed fragmentations can be explained by classical mechanisms such as:

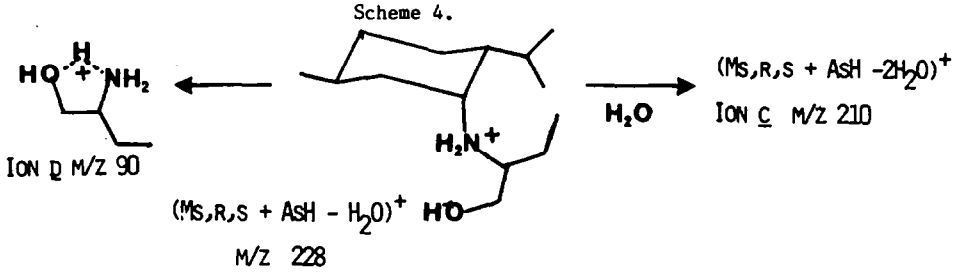
(i) simple cleavage of both $\geq$C-N bonds giving rise to the complementary a (m/z 139) and b (m/z 73) ions (scheme 3),

Scheme 3.



(ii) decomposition via hydrogen transfer inducing either the loss of water (ion c ,m/z 210) or C-N bond cleavage via a H transfer from the ring (menthol skeleton) yielding ammonium ion d (m/z 90) as the major ion (scheme 4).

Scheme 4.



The proposed origin for the transfered proton is confirmed by analysis of the MIKE/CID spectra of (d_3) labeled substituted ions (m/z 231 as selected ion) produced during the gas-phase S_N2 induced by (d_3) labeled amino-butanol (73% of d_3, 18% of d_2 and 9% of d_1)[20]. The ions b , c and d were mainly shifted at m/z 74 (93%), m/z 211 (95%) and m/z 93 (83%), whereas the ion at m/z 139 was not shifted. Thus, the elimination of water mainly involves a deuterium transfer from the labeled ammonium group yielding ion c (d_1) without prior notable H/D scrambling.

(iii) a more complex decomposition giving rise to the carbonium e ($C_6H_{11}^+$, m/z 83) ion.

The abundance of ion b , m/z 73, relative to the m/z 90 ion (base peak of MIKE/CID) is characterized by a larger stereochemical effect. This abundance was found to be 0.165 for ls,r,s and 0.510 for lr,s,r . A less dramatic effect is produced during the fragmentation via the elimination of H_2O leading to c , its abundance (relative to the main daughter ion m/z 90) being 0.675 for ls,r,s and 0.341 for lr,s,r .

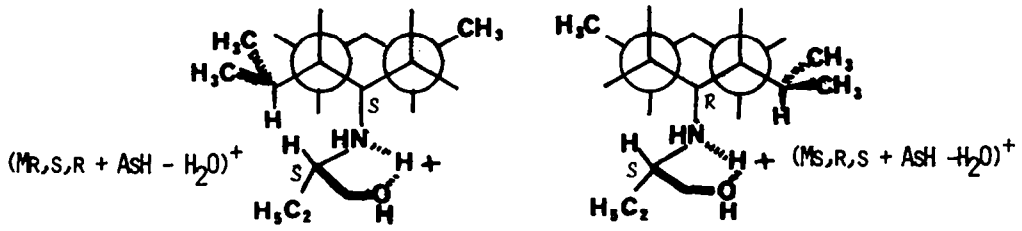
4. Steric hindrance as a possible explaination of the stereochemical effect observed for the water elimination from the substituted $(M + AsH - H_2O)^+$ ions formed from lr,s,r and ls,r,s enantiomers.

Even with the aid of metastable studies, which suggest a predominance of the S_N2 mechanism (thus precisely indicating the axial configuration of the formed C-N bond), we cannot yet rationalize the appreciable stereochemical effect accompanying the formation of daughter ion b . However, the stereochemical effect observed on formation of the $(M + AsH - 2H_2O)^+$ ion c via the loss of water from the diastereomeric substituted $(Mr,s,r + AsH - H_2O)^+$ and $(Ms,r,s + AsH - H_2O)^+$ ions can be explained from the following considerations.

The extent of the water elimination (yielding ion c) must depend upon the rate of proton transfer which takes place from the secondary $-NH_2^+$- ammonium to the hydroxylic group (scheme 4). Likely, the distance between the -O- and -N- heteroatoms, and the possibility of forming a planar transition state significantly influence this proton transfer rate. It appears from examination of Dreiding models of the more stable chair conformations (scheme 5) that the proximity of (i) the

neighboring-groups such as the isopropyl, methyl (equatorial groups in the menthol skeleton) and ethyl (amino-alcohol skeleton) and (ii) axial hydrogen atoms which are present on the substituted ions characterized by the S structure sterically hinder H transfer. This steric effect seems to be more important in the substituted $(Mr,s,r + AsH - H_2O)^+$ ion structure as shown in scheme 5:

Scheme 5



Consequently, the elimination of water is slightly disfavored in comparison to its diastereosomer $(Ms,r,s + AsH - H_2O)^+$ ion. Furthermore, based on this interpretation, it is possible to explain the larger abundance of ion b (m/z 73) arising from the diastereomeric $(Mr,s,r + AsH - H_2O)^+$ ion. Indeed, the more severe steric strain caused by the neighboring alkyl groups in this diastereomeric ion must promote the C-N bond cleavage and the formation of the ion b , m/z 73 is favored.

The determination of the driving-force that directs fragmentations sensitive to stereochemistry is very important to assign "a priori" the initial chirality of unknown alcohols. More studies are now in progress.

The use of chiral reagents such as aminoalcohol 2s also permitted us to distinguish enantiomeric mandelic acids. Concerning chiral ketones, acids and their derivatives, this technique has already produced some successful results[21]. Furthermore, other chiral reagents such as prolinol and 1-phenylethylamine can be used to give analogous results showing the strong potential of the method. Various studies reported in the literature[22] demonstrate the advantages of selected metastable ion monitoring for quantification of mixtures. This method, complementary in nature to GC/MS and LC/MS, is very promising for the analysis of enantiomeric compounds present in complex mixtures.

EXPERIMENTAL

A reversed geometry mass spectrometer ZAB-2F (VG micromass Lt) equipped with a high pressure source was used under the following conditions: T(source) = 100°C, filament current = 0.1mA, repeller voltage = 0V. (S)-2-amino-1-butanol (98%, Janssen Chimica) introduced by the inlet system was used as reagent gas at 5.10^{-5} Torr, measured in the source housing (corresponding to 0.5 Torr in the ion source). He was used as the collision gas and was added until the main beam was attenuated to 30%. 200 ng samples were introduced via direct probe without heating. The results reported are averages of five spectra (± 2% and ± 5% absolute errors for ion intensities displayed in conventional mass spectra and MIKE/CID spectra, respectively).

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