Substitution Reactions Under NH_3 Chemical Ionization Conditions in *cis*-/*trans*-1,2-Dihydroxybenzosuberans†

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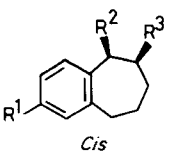
The nucleophilic substitution reaction under NH_3 chemical ionization (CI) conditions in *cis*- and *trans*-1,2-dihydroxybenzosuberans (1–4) has been studied with the help of ND_3 CI and metastable data. The results indicate that in the parent diols 1 (*cis*) and 2 (*trans*), the substitution ion, $[M_sH]^+$, is produced mainly by the loss of H_2O from the $[MNH_4]^+$ ion (S_Ni reaction) while in their 7-methoxy derivatives 3 and 4, the ion–molecule reaction between $[M-OH]^+$ and NH_3 seems to be the major pathway for the formation of $[M_sH]^+$. The substitution ion from 1 and 2 and the $[MH]^+$ ion from *trans*-1-amino-2-hydroxybenzosuberan give similar collision-induced dissociation mass-analysed ion kinetic energy spectra. Interestingly, their diacetates do not undergo the substitution reaction.

INTRODUCTION

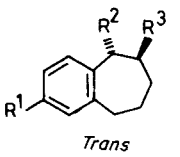
Many gas phase analogies of condensed phase organic reactions have been reported in the literature.[1,2] One of the reactions which has attracted the attention of several workers recently is the nucleophilic substitution of hydroxy group by amino group under NH_3 chemical ionization (CI) conditions.[3–10] Mechanisms such as S_N2,[3–5,10] S_N1[7] and S_Ni[8] have been proposed for these reactions. However, only the S_N2 reaction with Walden inversion has been proved in certain diastereoisomeric alcohols.[3–5] The presence of a double bond in the vicinity of the substitution centre has been found to enhance this process.[5,7] However, recent reports[4,9] indicate that this is not a prerequisite for the observation of abundant substitution ions. There has been no report on the substitution reaction in vicinal diols so far. Thus it was decided to examine the NH_3 CI spectra of the following isomeric pairs of vicinal diols (*cis*/*trans*-benzosuberan-1,2-diols), prepared in connection with a study on central muscle relaxants.[11] Under NH_3 CI conditions these diols have been found to undergo substitution of one of the hydroxyl groups with an amino group giving rise to ions isobaric with the molecular ion. The origin and structure of the substitution ion have been investigated with the help of ND_3 CI, collision-induced mass-analysed ion kinetic energy (CID MIKE), MIKE and B^2/E spectra and the results are presented in this paper.

RESULTS AND DISCUSSION

The NH_3CI data given in Table 1 clearly indicate a difference in the abundances of the $[MNH_4]^+$ ion in



Cis



Trans

1 : $R^1=H$, $R^2=R^3=OH$
2 : $R^1=H$, $R^2=R^3=OH$
3 : $R^1=OMe$, $R^2=R^3=OH$
4 : $R^1=OMe$, $R^2=R^3=OH$
5 : $R^1=H$, $R^2=R^3=OAc$
6 : $R^1=H$, $R^2=R^3=OAc$
7 : $R^1=H$, $R^2=NH_2$, $R^3=OH$

the *cis* and *trans* isomers. This difference is more marked in the methoxydiols **3** and **4**. It appears that the $[NH_4]^+$ adduct is stabilized by chelation with the functional groups and that this stabilization is greater in the *cis* compounds. This is also reflected by the faster decomposition of the adduct ion in the *trans* isomer.

Because of their comparatively low proton affinities relative to NH_3 proton transfer to these diols is not favoured and consequently $[MH]^+$ ions are insignificant and the substitution of OH with NH_2 leads to

Table 1. Ion abundances[a] (% total ionization) in the NH_3 CI spectra of 1–7

Ion	Compound (mol. wt)						
	1 (178)	2 (178)	3 (208)	4 (208)	5 (262)	6 (262)	7 (177)
$[M+N_2H_7]^+$	0.5	0.8	—	—	—	—	—
$[M+NH_4]^+$	77.2	64.8	19.0	9.6	78.6	54.3	5.6
$[M_sH+NH_3]^+$	1.1	1.8	2.4	2.5	—	—	—
$[MH]^+$	2.4	4.0	7.0	8.1	—	—	93.0
$[M_sH]^+$	17.8	31.4	52.6	59.1	—	—	0.7
$[M-OH]^+$	1.0	1.1	18.8	20.9	—	—	—
$[MH-NH_3]^+$	—	—	—	—	—	—	0.7
$[M-AcO]^+$	—	—	—	—	21.4	45.7	—

[a] Not corrected for ^{13}C contribution.

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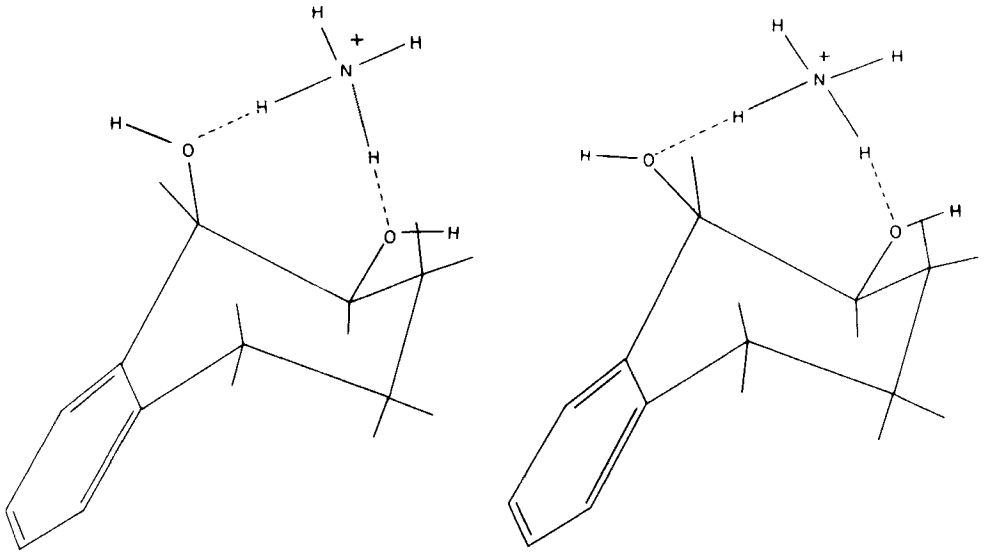


the substitution ion $[M_sH]^+$, isobaric with $[M]^{+\cdot}$. In the ND_3 CI spectrum of **2** the peak at *m/z* 178 shifts to *m/z* 182, consistent with the loss of D_2O from the $[MND_4]^+$ ion at *m/z* 202. $[NH_4]^+$ attachment to the thermally formed neutral, $[M-H_2O]$, is also indicated by the presence of ions at *m/z* 183 in the ND_3 CI spectrum. However, the contribution from $[M]^{+\cdot}$ is not significant.

The probable pathways for the formation of the $[M_sH]^+$ ion are shown in Scheme 1. These are:

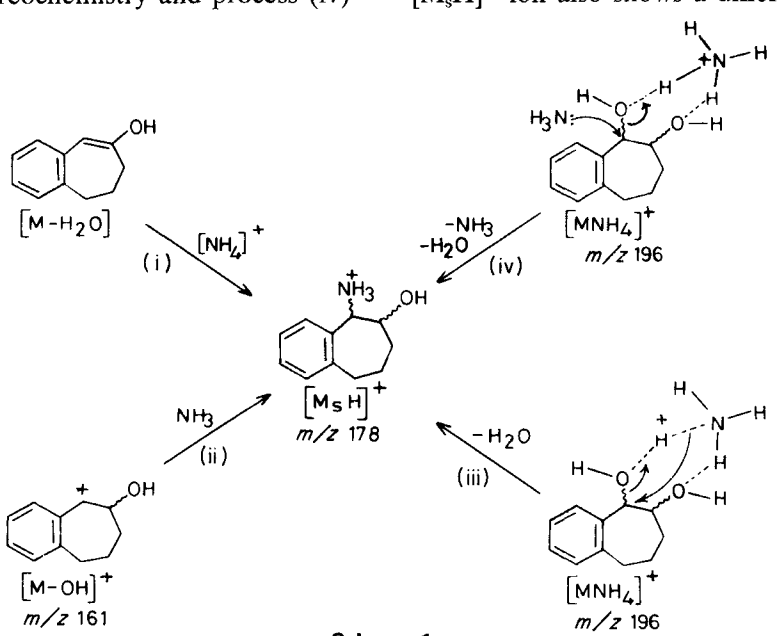
(i) $[NH_4]^+$ attachment to thermally formed $[M-H_2O]$.

(ii) Reaction of NH_3 with $[M-OH]^+$ formed by loss of (NH_3+H_2O) from $[MNH_4]^+$.

(iii) Transfer of NH_3 group from $[MNH_4]^+$ to the benzylic carbon during the loss of water.

(iv) S_N2 reaction between NH_3 and $[MNH_4]^+$.

Processes (i) and (ii) would result in a mixture of isomeric amino alcohols while (iii) would lead to retention of the diol stereochemistry and process (iv) would result in Walden inversion. Operation of process (i) is evident from the ND_3 CI spectrum. It was found that, in general, in the spectra taken on the VG-ZAB-HF instrument this thermal contribution is significant. However, in the spectra taken on the Jeol D-300 this process is insignificant as shown by the chloride ion negative chemical ionization (NCI) spectra of the diols **1–4** which give only $[M+Cl]^-$ ions. Processes (i), (ii) and (iv) would show a positive dependence on the NH_3 pressure while process (iii) would lead to a decrease in the abundance of the substitution ion with increase in NH_3 pressure. The pressure dependence of the substitution process in the diols **2** and **4** is shown in Fig. 1. The parent diol **2** shows a negative pressure dependence and the methoxydiol **4** shows a positive pressure dependence suggesting that different processes are predominant for the substitution process in these diols. The effect of source temperature on the abundance of the $[M_sH]^+$ ion also shows a difference in **2** and **4** (Table



Scheme 1

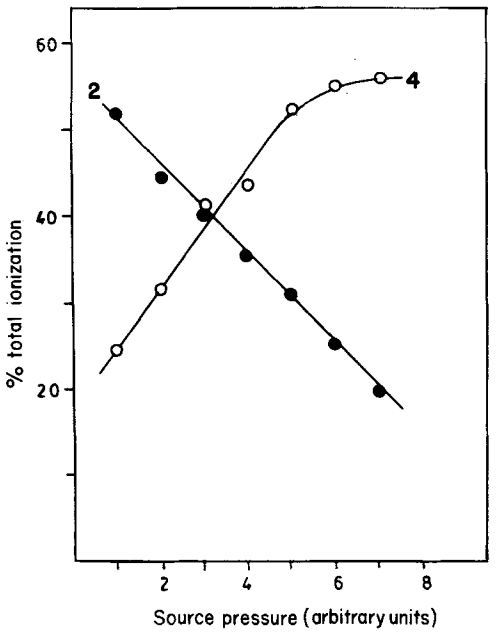


Figure 1. Effect of NH_3 pressure on the abundance of $[M_sH]^+$ in **2** and **4**.

2). In the diol **2** its abundance increases with temperature which is in accordance with its formation by loss of H_2O from $[MNH_4]^+$ while in **4** there is a very slow decrease with increase in temperature consistent with its formation from the $[M-OH]^+$ ion (process (ii)). This is further substantiated by the fact that while both **1** and **2** show $[MNH_4]^+$ and $[M-H_2O+N_2H_7]^+$ as the precursors (B^2/E scan) for the $[M_sH]^+$ ion, the diols **3** and **4** show only the latter ion as the precursor. Thus it appears that an S_Ni mechanism operates in the diols **1** and **2** along with small contributions from processes (i) and (ii) while in **3** and **4**, the contribution of process (iii) is insignificant. The operation of process (iv) could not be confirmed or ruled out on the basis of the available data. The net results of these processes would be that the $[M_sH]^+$ ion would consist of a mixture of stereoisomers in these diols. This is borne out by the identical CID MIKE spectra obtained for the $[M_sH]^+$ ion in both the *cis*- and *trans*-diols.

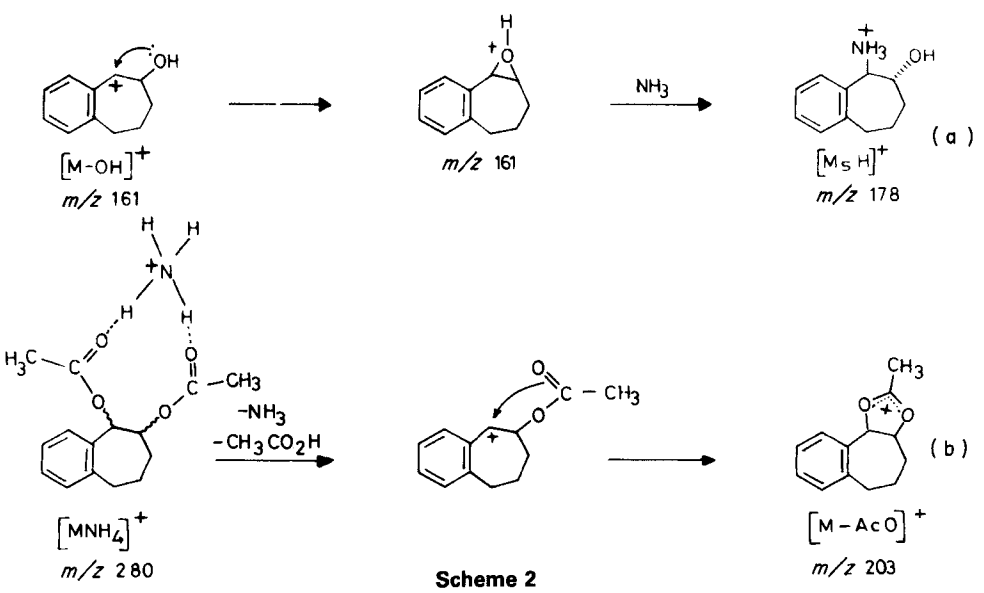
Table 2. Effect of ion source temperature on the abundance (%Σ) of $[M_sH]^+$ in 2 and 4

	Temperature (°C)				
Compound	150	175	200	225	250
2	35.9	49.2	57.6	63.6	72.9
4	63.1	61.5	60.6	58.8	51.8

It is obvious that, being benzylic, the OH at C(1) would be replaced by NH_2 in the substitution process. Loss of C(1)-OH results in a benzylic cation which on reaction with NH_3 could produce the substitution ion, $[M_sH]^+$ (process (ii)). Consistent with this is the observation that $[M_sH]^+$ is more abundant in the diols **3** and **4** having a methoxy group at the *para* position on the benzene ring. The benzylic cation could rearrange to the protonated epoxide which on reaction with NH_3 could lead to the amino alcohol (Scheme 2(a)). It may be pointed out here that the condensed phase reaction of nucleophilic reagents such as NaOMe or AcOH with 1,2-epoxybenzosuberan also results in 1-substituted benzosuberan-2-ols.[11]

The CID MIKE spectra of the $[M_sH]^+$ ion from **2** and the $[MH]^+$ ion from **7** are shown in Fig. 2. Except for the loss of (NH_3+H_2O) giving rise to $[M-OH]^+$ the two spectra are identical. The difference in the $[M-OH]^+$ ion is presumably due to the formation of a *cis*/*trans* mixture of amino alcohols from the diol. Loss of NH_3 is the only major decomposition pathway of the $[M_sH]^+$ ions as shown by their MIKE spectra.

The diacetates **5** and **6** do not show the substitution process. The only peaks in their spectra correspond to the $[MNH_4]^+$ and $[M-AcO]^+$ ions produced by $[NH_4]^+$ attachment and loss of (NH_3+AcOH) from $[MNH_4]^+$, respectively (Scheme 2(b)). The $[M-AcO]^+$ ion is stabilized by the possibility of formation of the dioxolanyl ion. This observation also indirectly supports the formation of the substitution ion via the protonated epoxide in the diols.



Scheme 2

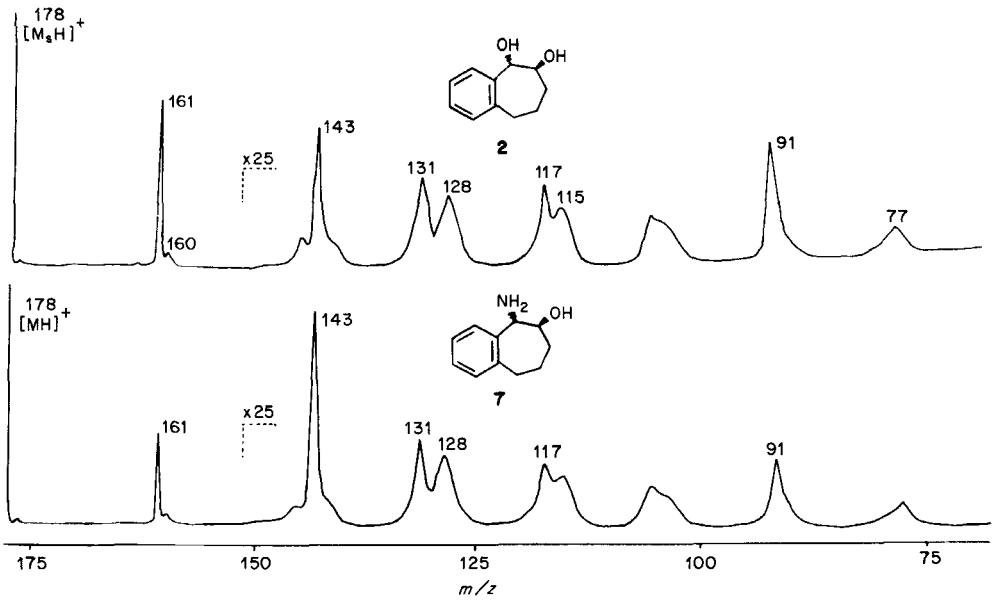


Figure 2. CID MIKE spectra of the *m/z* 178 ion from **2** and **7**.

Evidence for the operation of an S_Ni mechanism in the methoxydiols **3** and **4** can be obtained under CI conditions using a stronger base, $MeNH_2$. Both the *cis*- and *trans*-diols (**3** and **4**) show the substitution ion at *m/z* 222 (Table 3). Similar stereochemical differences as observed in **1** and **2** under NH_3 CI conditions are seen in these spectra also. A metastable peak corresponding to the transition, $[M + MeNH_3]^+ \rightarrow [M_sH]^+ + H_2O$ is observed at *m/z* 205.5 (calculated 205.35).

CONCLUSIONS

The adduct ion abundance is greater in the *cis* compounds because of the favourable spatial arrangements for chelate formation with $[NH_4]^+$. The major fragment ions observed in their spectra correspond to the loss of H_2O from the $[MNH_4]^+$ ion. In the parent diols **1** and **2** this substitution process occurs mainly through an S_Ni mechanism while a two-step S_Ni mechanism seems to be operating in **3** and **4**. With $MeNH_2$ as the reagent, even in these molecules an S_Ni mechanism operates. It thus appears that the substitution reaction under CI conditions could proceed through different mechanisms depending upon the nature of the molecule and the reagent ion.

Table 3. $MeNH_2$ CI spectra of 3 and 4

	Compound	
Ion	3	4
$[Me + MeNH_3]^+$	88.6	77.1
$[M_sH]^+$	9.3	19.3
$[M - OH]^+$	2.1	3.6

EXPERIMENTAL

Synthesis

The preparation of compounds **1–6** has been described elsewhere.[11] The amino alcohol **7** was prepared from 1,2-epoxybenzosuberan[11] through the azide as described below.

1,2-*trans*-1-Azido-2-hydroxybenzosuberan (8). 1,2-Epoxybenzosuberan[11] (0.16 g, 1 mmol) and NaN_3 (0.18 g, 3 mmol) in 50% aqueous Me_2CO were heated on a water bath and the mixture worked up to give the product, an oil, yield 90%. ^{1}H-NMR ($CDCl_3$): δ 3.64 (m, 1H, C(2)*H*), 4.62 (d, 1H, C(1)*H*, $J = 9$ Hz, *trans*).

1,2-*trans*-1-Amino-2-hydroxybenzosuberan (7). $LiAlH_4$ reduction of **8** (0.2 g) in dry Et_2O for 3 h at r.t. gave **7**, 0.15 g, yield 84%, m.p. 153 °C. ^{1}H-NMR ($CDCl_3$): δ 3.20 (m, 1H, C(2)*H*), 3.95 (d, 1H, C(1)*H*, $J =$ 9.5 Hz, *trans*).

Mass spectrometry

The CI spectra were recorded on a Jeol D-300 mass spectrometer attached to a JMA-2000 data system. Reagent gases used were of >99% priority. A 40% solution of $MeNH_2$ in water was used as the source of $MeNH_2$. Unless otherwise stated all the CI spectra were recorded at a source housing pressure of 1.5×10^{-5} Torr. The effect of NH_3 pressure on the substitution process was studied by varying the NH_3 pressure from 5×10^{-6} to 2×10^{-5} Torr. The other ion source conditions were as follows: electron energy, 200 eV; emission current, 600 μA; temperature, 150 °C.

The ND_3 CI, MIKE, CID MIKE and B^2/E spectra were recorded on a VG-ZAB-HF mass spectrometer at an accelerating voltage of 8 kV and a mass resolution of 1000–1500. The other source conditions were: electron energy, 50 eV: emission current, 500 μA; temperature, 150–160 °C. Helium was used as the collision gas for the CID MIKE spectra.

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