Direct evidence for anchimeric assistance in alcohol elimination from gas-phase MH^+ ions of 1,4-dialkoxycyclohexanes under chemical ionisation. Experiment and theory

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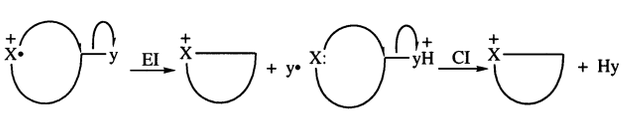
***trans*-1,4-Dialkoxycyclohexanes afford very abundant $[MH - ROH]^+$ ions upon chemical ionisation (CI), in contrast to the *cis*-isomers, suggesting anchimeric assistance in the alcohol elimination from the MH^+ ions of the *trans*-diethers. Collision induced dissociation (CID) measurements of the $[MH - ROH]^+$ ions, obtained from various suitably deuterium labelled stereoisomeric 1-ethoxy-4-methoxycyclohexanes, indicate formation of symmetrical bicyclic ethyl and methyl oxonium ions by an anchimerically assisted alcohol elimination from the *trans*-diethers. On the other hand these measurements suggest that the *cis*-isomers afford isomeric monocyclic *O*-protonated 4-alkoxycyclohexene cations, in which the hydrogens at positions 2 and 3 (as well as those at positions 5 and 6, and 1 and 4) are not equivalent. The two results, namely the symmetrical bicyclic structure and the high abundance of the $[MH - ROH]^+$ ions in the CI mass spectra of the *trans*-diethers, in contrast to the non-symmetrical monocyclic structure and low abundance of these ions in the *cis*-isomers, are suggested to be direct evidence for anchimeric assistance in a gas-phase ion dissociation process. *Ab initio* calculations at the MP3/6-31G*//6-31G* level support the anchimerically assisted elimination mechanism observed in *trans*-1-ethoxy-4-methoxycyclohexane, but also show that the energy difference between the anchimerically assisted and non-assisted elimination mechanisms is small (*ca*. 2–3 kcal mol^{-1}) (1 cal = 4.184 J).**

Introduction

Anchimeric assistance has been suggested to play an important role in the mechanisms of numerous fragmentation processes of gas-phase cations obtained under electron ionisation (EI) and chemical ionisation (CI) conditions. Such intramolecular backside nucleophilic attacks (Scheme 1), which have well-defined

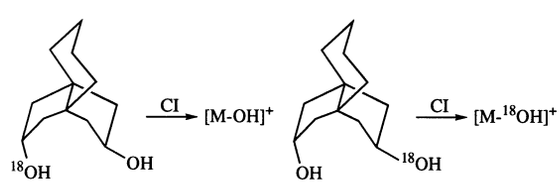


Scheme 1

configurational requirements, provide explanations for different ion abundances, often observed in the mass spectra of stereoisomers.[1–6]

Anchimerically assisted eliminations should result in cyclic product ions. In 1,2-disubstituted ions such eliminations are expected to result in three-membered ring product ions, in analogy to the intermediates proposed for neighbouring group assisted substitution reactions in the condensed phase.[7] A three-membered cyclic structure of a product of a supposedly anchimerically assisted fragmentation in the gas phase has been experimentally determined by a collision induced dissociation (CID) study of $[M - PhO]^+$ ions obtained from deuterium labelled 2-phenoxyethylamine under EI conditions.[8,9] Similar tandem mass spectral studies of suitably deuterium labelled substrates indicate formation of five- and six-membered ring product ions from linear diethers, bissulfides and dihaloalkanes.[10–12] However, no evidence has been presented that could exclude the possibility, that cyclisation occurred in a subsequent step after the elimination rather than by an anchimerically assisted single step process. Formation of cyclic fragment ions by anchimerically assisted processes of various 1,ω-disubstituted molecular ions has often been proposed based on ion abundance arguments,[13,14] but no direct evidence was presented that would support these proposed pathways.

There has been one report of a case where the fragmentation behaviour suggested occurrence of an anchimerically assisted process, while a detailed CID analysis of suitably isotopically labelled analogues excluded the expected cyclic structure of the product ion.[15a] A study of ^{18}O-labelled stereotopic *syn,anti*-[4.3.3]propellane-8,11-diols showed that the *syn*-hydroxy group is preferentially lost upon isobutane chemical ionisation (Bu^i-CI), suggesting occurrence of internal backside nucleophilic attack in this process (Scheme 2).



Scheme 2

However, a CID study of deuterium and ^{18}O-doubly labelled analogues showed that the expected symmetrical cyclic ether structure has not been formed in that process (Scheme 3). The two stereotopomers exhibit different behaviour under CID conditions, which indicates formation of isomeric non-symmetrical $[M - OH]^+$ ions.[15a] A non-bonding interaction in the transition structure or occurrence of other processes involving hydrogen transfer were proposed as explanation for the highly stereospecific nature of the above elimination.[15a]

The above results in the propellanediol system show that high stereospecificity of an elimination reaction does not necessarily imply occurrence of anchimeric participation in the process. On the other hand, formation of a cyclic product from a linear substrate cannot be considered as compelling evidence for the involvement of anchimeric assistance in the elimination pro-

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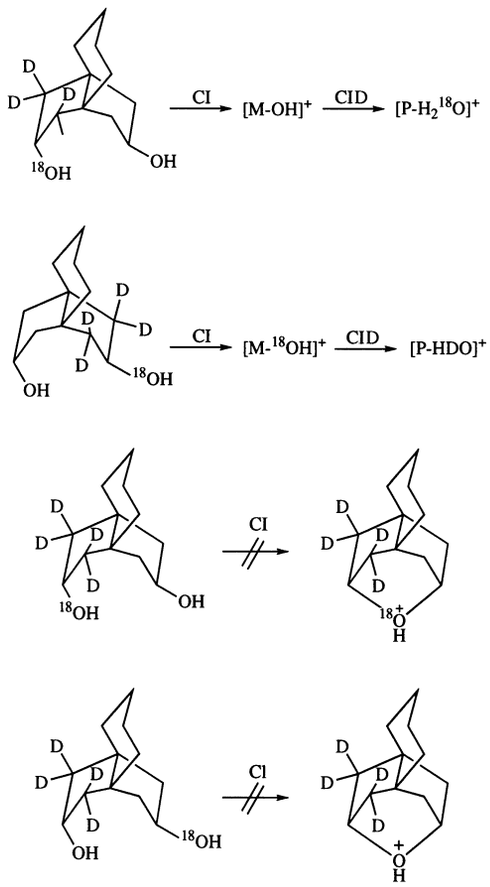


Scheme 3

cess. Thermochemical factors may cause cyclisation in a later stage of the fragmentation, without intervention of anchimeric assistance in the elimination step. These results show that it is unjustified to postulate anchimeric assistance merely on the basis of ion abundance variations, at least in the propellane system.[15]

The present study was initiated in an attempt to provide direct evidence for anchimeric assistance in an elimination process, by choosing a system where both stereospecificity of the fragmentation process and ring closure of the product could be demonstrated. We report both experimental and computational results, which to the best of our knowledge provide the strongest evidence yet available in the literature for the occurrence of anchimeric assistance in a gas-phase ion elimination process.

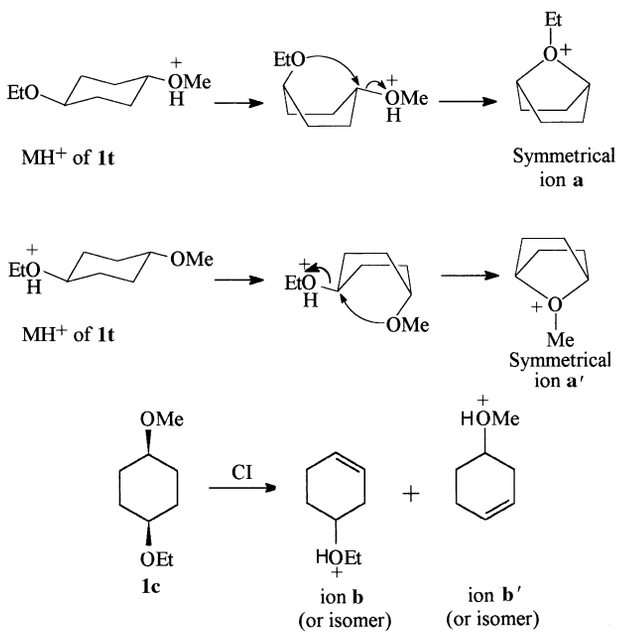
Results and discussion

The 1-ethoxy-4-methoxycyclohexane system was chosen in the present study for testing the occurrence of anchimeric assistance. The MH^+ ion of the *trans*-isomer **1t** is expected to afford the bicyclic oxonium ions **a** and **a′** by elimination of methanol and ethanol respectively under Bu^i-CI and CID conditions, if anchimeric assistance is involved in this process. On the other hand, the epimeric *cis*-diether **1c** should give rise to monocyclic $[MH - MeOH]^+$ and $[MH - EtOH]^+$ fragment ions, if cyclisation does not follow the simple non-assisted elimination process. The instability of the cyclohexyl cation in the gas phase[16] leads us to the conclusion that formation of a 4-alkoxycyclohexyl carbocation structure by a simple cleavage of the C–O bond is improbable. Protonated 4-alkoxycyclohexene structures **b** and **b′** may be proposed based on previous works.[17] These assumed fragmentations are shown in Scheme 4. Structural assignments of ions **a** and **b** will be necessary in order to examine the above assumptions. CID measurements of the $[MH - MeOH]^+$ and $[MH - EtOH]^+$ ions formed from suitably deuterium labelled analogues upon CI should be helpful in such

Table 1 CI Mass spectral data of *cis*- and *trans*-1-ethoxy-4-methoxycyclohexanes **1**

		Bu^i-CI		NH_3-CI	
		1c	**1t**	**1c**	**1t**
m/z	Ion	RA (%)	RA (%)	RA (%)	RA (%)
176	$[MH + NH_4]^+$	—	—	*a*	28
160		8	*a*	8	2
159	MH^+	100	3	100	25
157	$MH - H]^+$	1	4	*a*	*a*
128		1	9	*a*	2
127	$[MH - MeOH]^+$	7	100	1	22
126		1	6	2	*a*
114		3	6	1	8
113	$[MH - EtOH]^+$	11	80	1	100
112		*a*	3	1	10
111		*a*	1	*a*	1
98		*a*	*a*	*a*	2

[a] Relative abundance below 1%.



Scheme 4

structural assignments. The bicyclic ion **a′** was proposed as an intermediate in the acetolysis of 4-methoxycyclohexyl toluene-*p*-sulfonate (tosylate) in solution, where 4-methoxycyclohexene was the major product.[18]

The Bu^iCI and NH_3-CI mass spectral data of **1c** and **1t** are given in Table 1. The high abundance of the MH^+ ion and the low abundance of the $[MH - ROH]^+$ ions in the CI mass spectra of **1c** indicate stabilisation of the MH^+ ion, possibly by formation of an intramolecular hydrogen bond between the two *cis* ether groups. The very low abundance of the MH^+ ion (3%) and the highly abundant $[MH - MeOH]^+$ and $[MH - EtOH]^+$ ions (100 and 80%, respectively) in the Bu^i-CI mass spectrum of the *trans*-isomer **1t**, as compared with the isomeric *trans*-1-ethoxy-3-methoxycyclohexane **2t** (100% for MH^+, see Scheme 5), suggest anchimeric assistance in the elimination of MeOH or EtOH from the *trans*-1,4-diether. The difference between **1c** and **1t** is even more pronounced under low energy NH_3-CI conditions. For the *cis*-isomer **1c**, the $[MH - ROH]^+$ ions are of negligible abundance.

An extensive CID and deuterium labelling study has been undertaken in order to determine whether the $[MH - ROH]^+$ ions obtained from **1t** attain the bicyclic methyl- and ethyl-oxonium structures (ions **a** and **a′** respectively, in Scheme 4), expected to result from the anchimerically assisted elimination processes. The results of the CID measurements of [MH –

Table 2 CID[a] mass spectral data[b] of $[MH - MeOH]^+$ ions obtained from stereoisomeric 1-ethoxy-4-methoxycyclohexanes **1** upon CI

		NH_3-CI[c]		Bu^i-CI				CH_4-CI			
		1t		**1t**		**1c**		**1t**		**1c**	
m/z	Ion	30 eV	20 eV	30 eV	20 eV	30 eV	20 eV	30 eV	20 eV	30 eV	20 eV
127	Parent [P]	43	208	14	123	4	52	14	116	1	76
99	$[P - C_2H_4]^+$	2	6	1	2	*d*	1	3	3	1	3
85		2	4	1	4	1	1	2	1	1	*d*
84		1	1	*d*	*d*	*d*	*d*	*d*	*d*	*d*	*d*
81	$[P - EtOH]^+$	100	100	100	100	100	100	100	100	100	100
79		1	*d*	1	1	*d*	1	*d*	*d*	*d*	*d*
57		4	2	1	3	1	3	1	*d*	*d*	*d*
55		8	2	6	2	*d*	1	1	1	1	*d*
47		1	2	1	2	1	2	1	1	1	1
43		7	2	2	1	2	1	2	1	*d*	*d*
41		2	2	*d*	1	*d*	3	*d*	*d*	*d*	*d*
29		14	2	8	2	1	1	5	2	5	1

[a] 20/30 eV collision energy. [b] Relative ion abundances (%), normalised to the most abundant fragment ion. [c] The CID spectrum of **1c** is very low because of the low abundance of the $[MH - ROH]^+$ ions in the NH_3-CI mass spectrum of **1c**. [d] Abundances below 1%.

Table 3 CID[a] mass spectral data[b] of $[MH - EtOH]^+$ ions obtained from stereoisomeric 1-ethoxy-4-methoxycyclohexanes **1** upon CI

		NH_3-CI[c]		Bu^i-CI				CH_4-CI			
		1t		**1t**		**1c**		**1t**		**1c**	
B *m/z*	B Ion	20 eV	30 eV	20 eV	30 eV	20 eV	30 eV	20 eV	30 eV	20 eV	30 eV
113	Parent [P]	360	63	190	57	75	9	180	22	120	11
81	$[P - EtOH]^+$	100	100	100	100	100	100	100	100	100	100
79		*d*	*d*	*d*	2	*d*	1	*d*	2	*d*	1
71		14	17	12	13	3	3	7	9	4	5
55		*d*	10	2	7	*d*	3	*d*	5	1	2
53		*d*	*d*	*d*	1	*d*	1	*d*	1	*d*	*d*
45		11	28	8	19	3	9	9	15	7	11
41		*d*	6	*d*	5	1	9	*d*	6	1	6
29		*d*	1	*d*	1	*d*	*d*	*d*	1	*d*	*d*

[a] 20/30 eV collision energy. [b] Relative ion abundances (%), normalised to the most abundant fragment ion. [c] The CID spectrum of **1c** is very low because of the low abundance of the $[MH - ROH]^+$ ions in the NH_3-CI mass spectrum of **1c**. [d] Abundances below 1%.

Table 4 CID[a] mass spectral data[b] of $[MH - MeOH]^+$ ions obtained from stereoisomeric deuterium labelled 1-ethoxy-4-methoxycyclohexanes **3** and **4** upon Bu^i-CI

		30 eV				20 eV			
m/z	Ion	**3c**	**4c**	**3t**	**4t**	**3c**	**4c**	**3t**	**4t**
131	Parent [P]	12	10	47	26	140	91	210	200
103	$[P - C_2H_4]^+$	1	*c*	2	1	4	1	4	4
87		1	*c*	3	1	3	1	4	2
86		*c*	1	2	1	1	1	4	2
85	$[P - EtOH]^+$	49	100	100	100	53	100	100	100
84	$[P - EtOD]^+$	100	22	78	50	100	24	77	51
82		1	1	1	1	*c*	*c*	*c*	*c*
59		1	*c*	6	4	1	*c*	2	2
58		1	1	6	5	1	*c*	2	2
57		2	1	7	5	1	*c*	2	2
48		2	1	4	3	2	2	4	4
46		*c*	*c*	1	1	*c*	*c*	*c*	*c*
45		1	*c*	3	2	*c*	*c*	*c*	*c*
44		*c*	1	2	1	*c*	*c*	*c*	*c*
43		1	1	3	2	*c*	*c*	*c*	*c*
29		5	2	13	14	2	1	4	4

[a] 20 and 30 eV collision energy. [b] Relative ion abundances (%), normalised to the most abundant fragment ion. [c] Abundances below 1%.

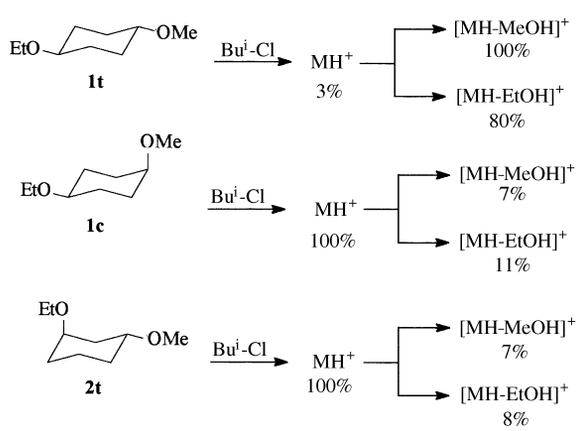
$MeOH]^+$ and $[MH - EtOH]^+$ ions, obtained from **1t** and **1c** under Bu^i-CI and CH_4-CI conditions, are listed in Tables 2 and 3. The comparison of the CID spectra clearly indicates different structures for each ion obtained from the two stereoisomeric diethers **1t** and **1c**. The difference between the CID data obtained from the *cis*- and *trans*-diethers is most pronounced when the $[MH - ROH]^+$ ions are formed upon Bu^i-CI. The less pronounced difference observed under CH_4-CI suggests formation of mixtures of isomeric $[MH - ROH]^+$ ions under these relatively higher energy conditions. The negligible abundance of the $[MH - ROH]^+$ ions in the NH_3-CI mass spectrum of **1c** did not allow measurement of the CID spectrum of this ion for comparison.

The results of CID measurements of the $[MH - MeOH]^+$ and $[MH - EtOH]^+$ ions, obtained from the deuterium labelled *trans*-1-ethoxy-4-methoxy[3,3,5,5]-$^2H_4$- and [2,2,6,6]-$^2H_4$-cyclo-

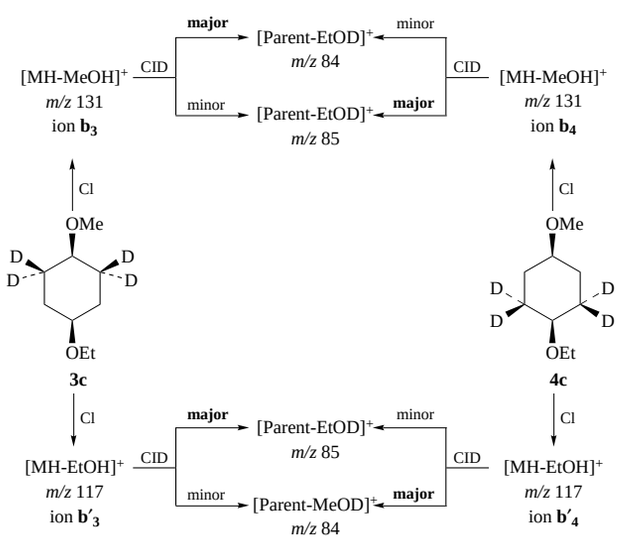
Table 5 CID[a] mass spectral data[b] of $[MH - EtOH]^+$ ions obtained from stereoisomeric deuterium labelled 1-ethoxy-4-methoxycyclohexanes **3** and **4** upon Bu^i-CI

		30 eV				20 eV			
m/z	Ion	**3c**	**4c**	**3t**	**4t**	**3c**	**4c**	**3t**	**4t**
117	Parent [P]	19	41	97	110	120	160	270	300
85	$[P - MeOH]^+$	100	53	100	100	100	53	100	100
84	$[P - MeOD]^+$	31	100	62	70	31	100	57	67
82		1	1	2	1	*c*	*c*	*c*	*c*
73		3	16	12	14	4	13	8	9
72		8	16	10	10	4	11	5	6
59		1	2	6	6	*c*	*c*	*c*	*c*
58		*c*	1	1	1	*c*	*c*	*c*	*c*
57		2	2	7	6	*c*	*c*	*c*	*c*
47		1	*c*	3	2	*c*	*c*	*c*	*c*
46		5	4	15	13	1	2	5	6
45		7	9	23	22	2	3	11	9
43		5	5	5	4	*c*	*c*	*c*	*c*
42		2	2	2	1	*c*	*c*	*c*	*c*

[a] 20 and 30 eV collision energy. [b] Relative ion abundances (%), normalised to the most abundant fragment ion. [c] Abundances below 1%.



Scheme 5



Scheme 6

hexanes **3t** and **4t**, and their comparison with those of the *cis*-isomers **3c** and **4c**, provide direct evidence for the bicyclic structures of the $[MH - ROH]^+$ ions **a** and **a′**. The results of the CID measurements are listed in Tables 4 and 5.

Deuterium labelled *cis*-diethers

The $[MH - ROH]^+$ ions of the *cis*-diethers **3c** and **4c** exhibit remarkably different CID spectra. The most pronounced difference appears in the extent of elimination of EtOH and EtOD.

Table 6 CID[a] mass spectral data[b] of $[MH - EtOH]^+$ ions obtained from stereoisomeric deuterium labelled 1-ethoxy-4-methoxycyclohexanes **5** and **6** upon Bu^i-CI

m/z	Ion	**5c**	**5t**	**6c**	**6t**
128	Parent [P]	22	86	34	88
100	$[P - C_2H_4]^+$	*c*	2	*c*	2
86		*c*	2	*c*	2
85		*c*	1	*c*	2
82	$[P - EtOH]^+$	100	100	100	100
81	$[P - EtOD]^+$	*c*	*c*	1	*c*
56		*c*	1	*c*	1
55		*c*	1	*c*	1
47		1	1	1	2
29		1	1	*c*	1

[a] 20 eV collision energy. [b] Relative ion abundances (%) normalised to the most abundant fragment ion. [c] Abundances below 1%.

The *m/z* 131 $[MH - MeOH]^+$ ion obtained from **3c** undergoes preferential elimination of EtOD, while that formed from the isotopomer **4c** exhibits a major loss of EtOH (see abundances of the *m/z* 84 and 85 ions in Table 4). On the other hand the major product ion formed from the *m/z* 117 $[MH - EtOH]^+$ ion of **3c** affords a major *m/z* 85 $[MH - EtOH\text{-}MeOH]^+$ ion, while preferential elimination of MeOD takes place in the case of **4c**, giving rise to a major *m/z* 84 product ion (see Table 5). These results, summarised in Scheme 6, suggest occurrence of preferential elimination of EtOH from $[MH - ROH]^+$ ions under CID conditions involving a hydrogen from position 3 or 5, which is adjacent to the original position of the first eliminated RO group.

The different behaviour under CID conditions of the $[MH - ROH]^+$ ions obtained from **3c** and **4c** clearly indicates different structures for these ions, excluding occurrence of cyclisation or rearrangement processes which would lead to a common structure from both isomers.

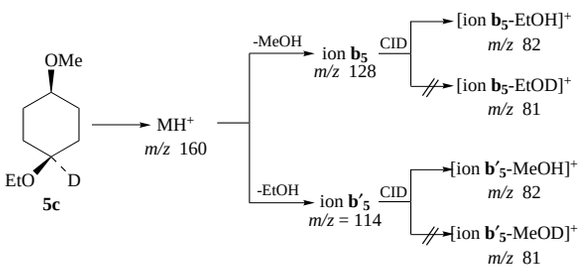
CID measurements were performed for the $[MH - MeOH]^+$ and $[MH - EtOH]^+$ ions obtained under Bu^i-CI from [1-$^2H_1$]- and [4-$^2H_1$]-*cis*-1-ethoxy-4-methoxycyclohexanes **5c** and **6c**. The data listed in Tables 6 and 7 show exclusive elimination of the unlabelled ethanol and methanol in both cases (see Scheme 7 for **5c**). These results exclude occurrence of 1,1- and 1,4-eliminations of alcohol upon CID conditions. They also eliminate the possibility of rearrangements involving hydrogen–deuterium exchange in the course of the CI-induced alcohol eliminations of the *cis*-1,4-diethers.

All the results of the CID measurements of the deuterium labelled **3c**, **4c**, **5c** and **6c** are consistent with the monocyclic *O*-protonated 4-alkoxycyclohexene structures **b** and **b′** for the

Table 7 CID[a] mass spectral data[b] of $[MH - EtOH]^+$ ions obtained from stereoisomeric deuterium labelled 1-ethoxy-4-methoxycyclohexanes **5** and **6** upon Bu^i-CI

m/z	Ion	**5c**	**5t**	**6c**	**6t**
114	Parent [P]	36	110	41	101
82	$[P - MeOH]^+$	100	100	100	100
81	$[P - MeOD]^+$	*c*	*c*	1	*c*
72		1	3	1	5
71		1	3	1	5
46		*c*	1	*c*	2
45		2	2	2	5

[a] 20 eV collision energy. [b] Relative ion abundances (%), normalised to the most abundant fragment ion. [c] Abundances below 1%.



Scheme 7

$[MH - ROH]^+$ ions, which are obtained by an anchimerically unassisted C–O bond cleavage in the MH^+ ions of the *cis*-1,4-diethers (Scheme 4). The mechanism of formation of these ions upon CI, which must involve migration of a hydrogen atom from the ring to the oxygen atom, will be dealt with later, in the section on *ab initio* calculations, and a detailed treatment will be reported elsewhere.[19]

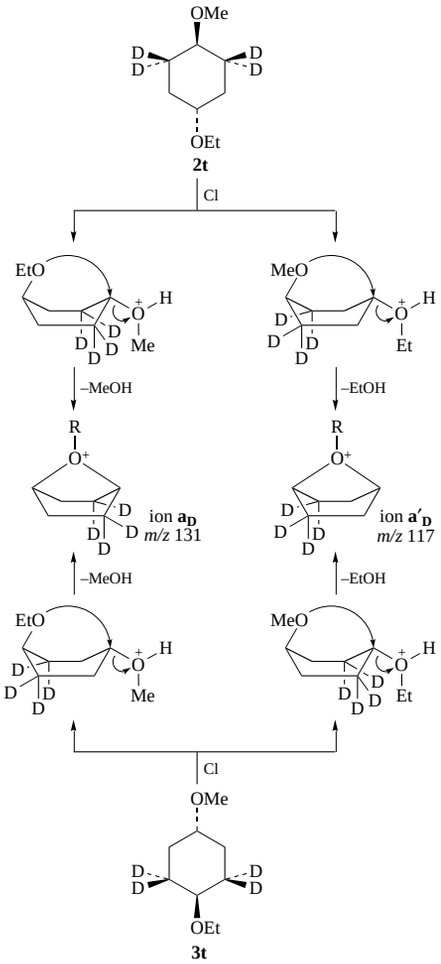
Deuterium labelled *trans*-diethers

In contrast to the behaviour of the *cis*-diethers, the $[MH - ROH]^+$ ions obtained from the *trans*-isomers **3t** and **4t**, deuterium labelled at positions 3 and 5 and 2 and 6 respectively, exhibit similar CID spectra (see Tables 4 and 5), which suggest common structures for these ions formed from the two isotopomers. The CID spectra are practically identical for the $[MH - ROH]^+$ ions obtained under low energy NH_3-CI conditions. They are quite similar under Bu^i-CI, and become considerably different under the more energetic CH_4-CI conditions (see Tables 4, 5, 8 and 9).

Rearrangements involving hydrogen-deuterium exchange are excluded on the basis of the CID spectra of the $[MH - ROH]^+$ ions obtained upon CI from **5t** and **6t**, labelled at positions 1 and 4 respectively. Both isotopomers afford similar CID spectra for both $[MH - EtOH]^+$ and $[MH - MeOH]^+$ ions (see Tables 6 and 7), all showing exclusive elimination of non-deuteriated EtOH. The fact that the hydrogen atoms at positions 1 and 4 are not involved in the process clearly eliminates the possibility of a hydrogen–deuterium exchange in the course of the ROH elimination.

The above experimental data obtained for the labelled and unlabelled *trans*-1,4-diethers are consistent with the formation of bicyclic methyl- and ethyl-oxonium ions **a** and **a′** respectively by an anchimerically assisted alcohol elimination, shown in Scheme 8. This is the only process occurring under low energy NH_3-CI conditions. It is also the major reaction taking place under the more energetic Bu^i-CI conditions, but in this case it is accompanied in part by formation of non-symmetrical ions, which may have monocyclic structures analogous to **b** and **b′**. The latter competing fragmentation is even more pronounced under the more energetic CH_4-CI conditions.

Additional evidence for the bicyclic *O*-alkyloxonium structure of ions **a** and **a′** may be derived from the CID spectra of

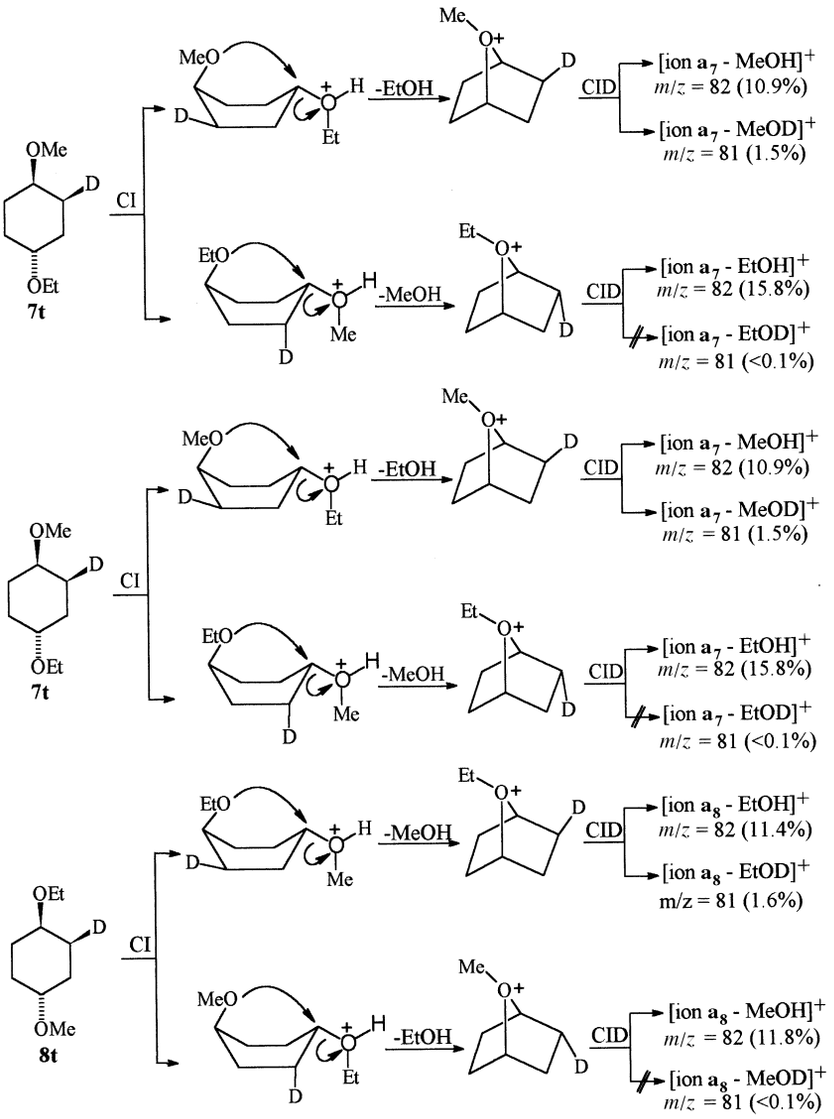


Scheme 8

the $[MH - ROH]^+$ ions obtained under Bu^i-CI from the stereospecifically deuterium labelled analogues **7t** and **8t**. The $[MH - ROH]^+$ ions, obtained from these two diethers by elimination involving the 4-alkoxy group (distant from the deuterium position), undergo elimination of both the deuteriated (minor) and the non-deuteriated (major) methanol and ethanol under CID conditions, while the isotopomeric $[MH - ROH]^+$ ions, obtained from **7t** and **8t** by CI-induced elimination involving the 1-alkoxy group (adjacent to the deuterium position), exhibit exclusive elimination of the non-deuteriated methanol and ethanol upon CID. This behaviour, shown in Scheme 9, is consistent with the formation of bicyclic *O*-alkyloxonium ions by a mechanism which retains the original configurational relationships of the neutral precursors.

Attempts have been made to obtain additional evidence for the bicyclic structure of the $[MH - EtOH]^+$ ions, formed from the *trans*-diethers, by comparison of their CID spectra with those of the corresponding $[M + CH_3]^+$ ions generated by iodomethane-CI of 7-oxabicyclo[2.2.1]heptane. The CID spectra of the non-deuteriated ions were similar. However, technical difficulties with the synthesis of specifically deuterium labelled 7-oxabicyclo[2.2.1]heptane did not allow conclusive evidence to be obtained by this route.

The established monocyclic *O*-protonated 4-alkoxycyclohexene structure of ions **b** and **b′**, obtained from the *cis*-1,4-diethers, clearly shows that these ions do not undergo spontaneous rearrangement to the bicyclic ions **a** and **a′**. Therefore the formation of the symmetrical bicyclic ions **a** and **a′** from the *trans*-1,4-diethers may be considered as direct evidence for the involvement of anchimeric assistance in the elimination of alcohol from the MH^+ ions of *trans*-1,4-dialkoxycyclohexanes upon CI, as shown in Scheme 8.



Scheme 9

Ab initio calculations

Computational results

Ab initio calculations[20] were carried out in order to assist the interpretation of the experimental results and to provide further information on the structures and energies of the various species and intermediates involved in the alcohol elimination processes. We focused our theoretical study on the formation of the bicyclic symmetrical ions **a** from the MH^+ ions of *trans*-1,4-dialkoxycyclohexanes **1t** *via* the anchimerically assisted elimination of ROH. The relatively large size of the experimentally investigated compounds dictated the use of smaller model systems in the computational study; we chose the cyclohexane-1,4-diols **9t** and **9c** as models for the experimentally studied 1,4-dialkoxycyclohexanes **1c** and **1t** respectively. The entire range of the species studied theoretically is shown in Scheme 10.

Even for the model systems our computational resources allow the use of only relatively simple theoretical methods. Thus, geometry optimisations were carried out at the HF level with both the split valence 3-21G basis set[21a] and the polarised 6-31G* basis set[21b] using standard gradient techniques as implemented in the GAUSSIAN92 series of programs.[22] With both basis sets frequency calculations were used to characterise stationary points as minima (no imaginary frequency) or as saddle points (one imaginary frequency) on the potential energy surface (PES).[20] Zero-point vibration energies (ZPVE) were scaled by a factor of 0.908[21c] for 3-21G and of 0.893[21c] for 6-31G* vibrations, to account for the deficiencies in the basis sets used and for anharmonicity.[20] Transition state structures, which were located (at both 3-21G and 6-31G*) using the TS routine of the GAUSSIAN program, were characterised as such by their Hessian matrices, and were connected to the corresponding minima using the intrinsic reaction coordinate (IRC) method.[23] For obtaining more reliable energetic comparisons the energies of the various species were calculated at the correlated MP3/6-31G*//3-21G and MP3/6-31G*//6-31G* levels of theory, *i.e.* using a polarised basis set and the Møller–Plesset perturbation theory of the third order[24] to account for dynamic electron correlation. The total energies of all species are given in the Supplementary Material,‡ and the relative energies of the protonated compounds at various levels of theory are compiled in Table 10. The calculated structures at HF/6-31G*, indicating the most interesting bond lengths and bond angles, are shown in Figs. 1 and 3. The full details of all calculated structures in the form of Z-matrices are given in the Supplementary Material.‡ The following discussion is based, unless stated otherwise, on the 6-31G* optimised geometries and the MP3/6-31G*//6-31G*+ZPVE energies.

‡ Z-matrices of all calculated structures including transition states and a table of the total energies of all species has been deposited as supplementary material (Suppl. Pub. 57220, 27 pp.). For details of the British Library Supplementary Publications scheme, see 'Instructions for Authors' *J. Chem. Soc., Perkin Trans. 2*, 1997, Issue 1.

Table 8 CID[a] mass spectral data[b] of $[MH - MeOH]^+$ ions obtained from stereoisomeric deuterium labelled 1-ethoxy-4-methoxycyclohexanes **3** and **4** upon NH_3-CI and CH_4-CI

		NH_3-CI[c]		CH_4-CI			
m/z	Ion	**3t**	**4t**	**3c**	**4c**	**3t**	**4t**
131	Parent [P]	77	92	24	9	34	15
103	$[P - C_2H_4]^+$	4	5	8	1	5	4
87		3	2	3	*d*	3	1
86		3	1	4	2	1	2
85	$[P - EtOH]^+$	100	100	58	100	95	100
84	$[P - EtOD]^+$	60	67	100	34	100	55
83		*d*	*d*	*d*	3	*d*	*d*
82		1	1	*d*	1	*d*	*d*
59		6	6	5	1	5	3
58		9	6	5	3	8	2
57		7	7	4	1	7	*d*
48		4	3	2	2	2	*d*
46		1	4	1	*d*	1	1
45		4	6	1	1	3	4
44		4	2	3	*d*	1	*d*
43		4	3	3	*d*	3	2
29		21	19	13	3	15	6

[a] 30 eV collision energy. [b] Relative ion abundances (%), normalised to the most abundant fragment ion. [c] The CID spectrum of **3c** and **4c** are very low because of the low abundance of the $[MH - ROH]^+$ ions in the NH_3-CI mass spectra of **3c** and **4c**. [d] Abundances below 1%.

Table 9 CID[a] mass spectral data[b] of $[MH - EtOH]^+$ ions obtained from stereoisomeric deuterium labelled 1-ethoxy-4-methoxycyclohexanes **3** and **4** upon NH_3-CI and CH_4-CI

		NH_3-CI[c]		CH_4-CI			
m/z	Ion	**3t**	**4t**	**3c**	**4c**	**3t**	**4t**
117	Parent [P]	140	98	20	34	37	39
85	$[P - MeOH]^+$	100	100	100	61	100	100
84	$[P - MeOD]^+$	68	64	54	100	68	78
82		1	1	1	*d*	1	1
73		14	13	3	27	5	10
72		13	12	13	31	5	8
71		*d*	*d*	5	*d*	*d*	*d*
59		7	*d*	2	2	3	2
58		1	1	*d*	2	*d*	1
57		8	7	2	2	3	3
55		*d*	*d*	*d*	2	*d*	*d*
47		4	3	2	1	2	1
46		18	18	6	4	9	8
45		29	28	6	18	11	18
44		1	1	1	1	2	1
43		5	4	3	4	3	4
42		3	2	2	2	2	3
15		2	1	*d*	*d*	*d*	1

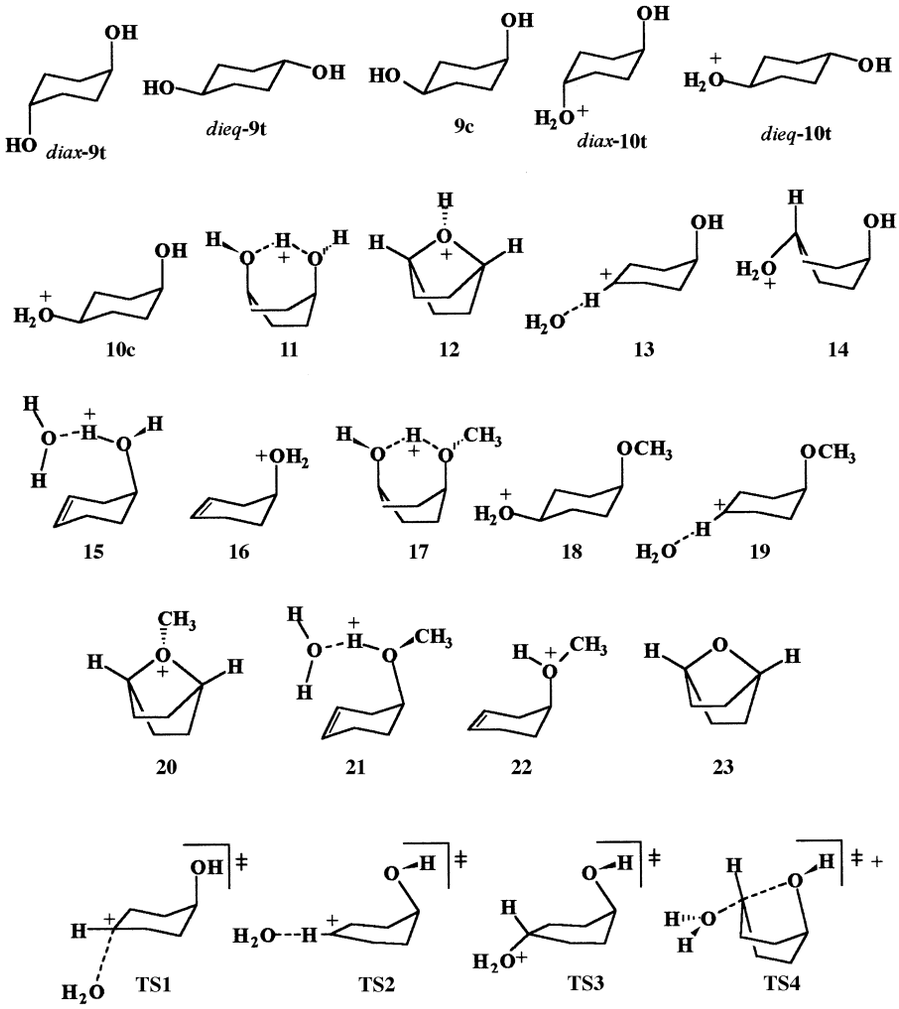
[a] 30 eV collision energy. [b] Relative ion abundances (%), normalised to the most abundant fragment ion. [c] The CID spectra of **3c** and **4c** are very low because of the low abundance of the $[MH - ROH]^+$ ions in the NH_3-CI mass spectra of **3c** and **4c**. [d] Abundances below 1%.

Calculated proton affinities

The two *trans*-cyclohexane-1,4-diol conformers, diax-**9t** and dieq-**9t**, have nearly the same energy, the former being more stable by 0.3 kcal mol^{-1} (1 cal = 4.184 J) (MP3/6-31G*//6-31G*+ZPVE; 2.5 kcal mol^{-1} at 6-31G*//6-31G*). Direct comparison with gas phase experimental data is not available,[25] but the preference in 1,4-substituted cyclohexanes bearing electronegative substituents X (X = Cl, Br, OH, OAc) of the diaxial chair-conformer over the diequatorial conformer was noted earlier and it has been rationalised by a more favourable electrostatic interaction between the two C–X dipoles in the diaxial than in the diequatorial conformation.[26,27] In agreement with this interpretation, the energy difference between the corresponding protonated diols, diax-**10t** and dieq-**10t**, increases further, diax-**10t** being more stable than dieq-**10t** by 5.3 kcal mol^{-1} (MP3/6-31G*//6-31G*+ZPVE). The larger steric bulk of alkoxy groups compared to the hydroxy group suggests, that the difference between the diaxial and the diequatorial conformers of the experimentally studied protonated 1,4-dialkoxycyclohexanes is smaller than for diax-**10t** and dieq-**10t**, but the calculated diax-**10t**–dieq-**10t** energy difference is sufficiently large to conclude that the diaxial conformer is the more stable also for the protonated *trans*-1,4-dialkoxycyclohexanes.

The calculated proton affinities of diax-**9t** and of dieq-**9t** are (at MP3/6-31G*//6-31G*+ZPVE) 195.3 and 190.3 kcal mol^{-1}, respectively (see Table 11). Protonation of *cis*-cyclohexane-1,4-diol **9c** produces either the open protonated diol **10c** or the hydrogen bridged ion **11** in which the cyclohexane ring adopts a twisted boat conformation. **11** is more stable than **10c** by 12.3 kcal mol^{-1} at MP3/6-31G*//6-31G*+ZPVE. The calculated proton affinity of **9c**, to yield the hydrogen bridged **11**, is 207.7 kcal mol^{-1} (MP3/6-31G*//6-31G*+ZPVE, see Table 11), *i.e.* 12.4 kcal mol^{-1} higher than that of diax-**9t**. The higher proton affinity of **9c** compared to **9t** is a consequence of the stabilisation of **11** by the intramolecular hydrogen bridge. Structural constraints prevent formation of a similar hydrogen-bridged species for protonated *trans*-cyclohexane-1,4-diol.

The calculated proton affinities are in reasonably good agreement with the available experimental data. The experimental values of proton affinity of *trans*-cyclohexane-1,4-diol measured by metastable ion (MI) and by collisional activation dissociation (CAD, under NH_3-CI conditions) are 199.2 and



Scheme 10

200.3 kcal mol^{-1}, respectively.[28] The experimental proton affinity of *cis*-cyclohexane-1,4-diol was determined to be 207.4 (MI) and 209.9 kcal mol^{-1} (CAD).[28] The higher measured proton affinity of *cis*-cyclohexane-1,4-diol is in excellent agreement with the calculated proton affinity of **9c** forming the bridged ion **11** (207.7 kcal mol^{-1}). We conclude that the observed high abundance of the MH^+ ions in the spectra of **1c** results from the formation of the hydrogen bridged structure **11**.

Calculated structures of the protonated diols

The lowest energy conformation for the three open monoprotonated diols: diax-**10t**, dieq-**10t** and **10c** is the regular chair conformation (see Fig. 1). Upon protonation, the protonated C^1–O bond of the diol is elongated considerably, *i.e.* by 0.177–0.206 Å, relative to the C–O bonds in the corresponding diols or of the non-protonated C–O bonds in the protonated diols. The hydrogen bridged protonated *cis*-diol **11** adopts a twist-boat conformation. The H–O distances in the non-symmetrical hydrogen bridge are 1.549 and 1.005 Å, significantly longer than regular O–H bond distances (*ca*. 0.95 Å at HF/6-31G*), and the OHO angle is 153.8°. The C^1–O and C^4–O bond lengths are 1.527 and 1.441 Å respectively, intermediate between the C–$^+OH_2$ and C–OH bond lengths in **10c** (1.586 and 1.406 Å, respectively).

Possible fragmentation reactions for protonated *trans*-cyclohexane-1,4-diols

There are two possible reaction paths to form the symmetrical oxonium ion **12** from the diax-**10t** (Scheme 11): (*i*) diax-**10t** eliminates water without anchimeric assistance *via* the 4-hydroxycyclohexyl ion–H_2O complex, **13**, which then loses H_2O to give **12**. (*ii*) A two step reaction, *via* the twist-boat conformer **14**, in which the H_2O molecule is eliminated with anchimeric assistance by the 4-hydroxy group.

To differentiate between these possibilities we have calculated various stationary points along the two reaction paths in Scheme 11, and the calculated relative energies for the two reaction pathways at both the MP3/6-31G*//6-31G*+ZPVE and at the HF/6-31G*//6-31G* (in parentheses) levels of theory are shown in Fig. 2.

The carbenium ion–water complex **13** is a minimum both at MP3/6-31G*//6-31G*+ZPVE and at HF/6-31G*, but the barriers for either its recombination reaction or for the forward reaction leading to **12** are very small (0.4 and 0.8 kcal mol^{-1} respectively at MP3/6-31G*//6-31G*+ZPVE). Thus **13** is predicted to be a very weakly bound complex, and therefore the transformation of diax-**10t** to **12** without anchimeric assistance proceeds effectively in one step *via* transition state **TS2** with an overall activation barrier of 12.3 kcal mol^{-1} (MP3/6-31G*//6-31G*+ZPVE). Most of this energy is required for the dissociation of the water molecule from diax-**10t**. The 4-hydroxycyclohexyl cation is not a stable species (or it exists in a very shallow energy well), and it undergoes a fast ring-closure to the bicyclic oxonium ions **12**.

The second dissociation path in Scheme 11 is calculated to be a two-step process. In the first step diax-**10t** undergoes a ring flip process to the twisted boat conformer **14** which is 4.2 kcal mol^{-1} higher in energy than diax-**10t**. The calculated barrier for the ring flip is 6.1 kcal mol^{-1} at MP3/6-31G*//6-31G*+ZPVE.[29] Conformer **14** eliminates water by an internal S_N2 process with anchimeric assistance by the 4-hydroxy group to form the bicyclic oxonium ion **12**. The calculated barrier for this second

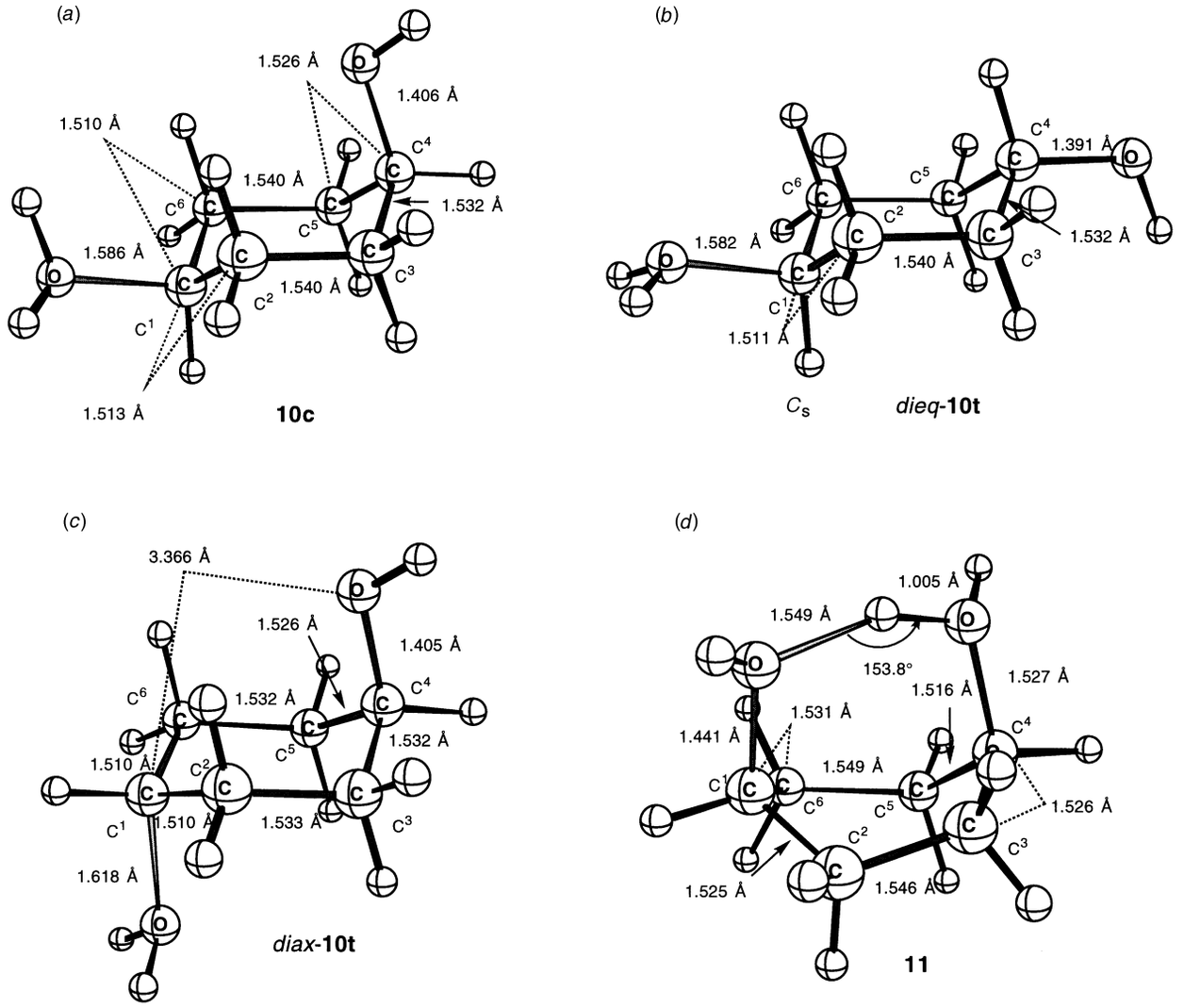


Fig. 1 Calculated structures (at HF/6-31G*) of: (*a*) **10c**; (*b*) diax-**10t**; (*c*) dieq-**10t**; and (*d*) **11**

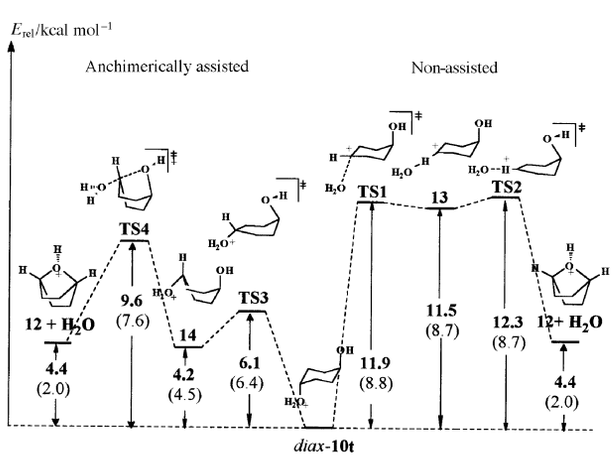
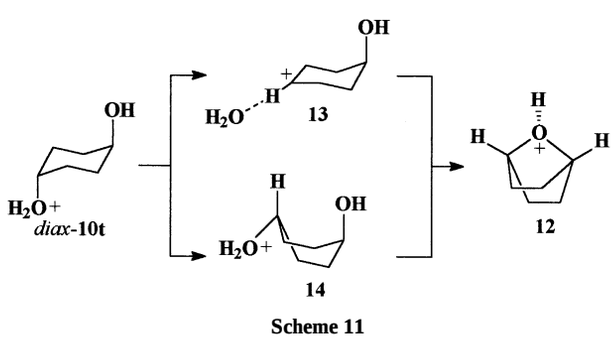


Fig. 2 Energy profile for the elimination of H_2O from the protonated diaxial conformer of *trans*-cyclohexane-1,4-diol (diax-**10t**) at MP3/6-31G*//6-31G*+ZPVE (HF/6-31G*//6-31G* values given in parentheses)

step is 5.4 kcal mol^{-1} (MP3/6-31G*//6-31G*+ZPVE), *i.e.* somewhat lower than for the first step. Thus, the overall barrier of the anchimerically assisted dehydration of diax-**10t** to the bicyclic ion **12** is 9.6 kcal mol^{-1}, by 2.7 kcal mol^{-1} more favourable than the non-assisted reaction channel *via* **TS2**. Although the calculated energy difference between the anchimerically assisted pathway and the competing non-assisted pathway is



Scheme 11

small, only 2.7 kcal mol^{-1}, it does corroborate our experimental findings and supports the conclusion that the elimination of ROH from *trans*-1,4-dialkoxycyclohexanes **1t** is anchimerically assisted and that it does not proceed *via* an open structure analogue to **13** or **TS2**. Actually, an important and somewhat surprising conclusion of the calculations is that the anchimerically assisted and the anchimerically non-assisted pathways are so close in energy.

Finally, it is interesting to note that the major conclusions and calculated energy differences are very similar whether one uses the 3-21G* or the 6-31G* optimised geometries (see Table 10), although the calculated 3-21G* and the 6-31G* geometries may differ considerably. On the other hand, the addition of electron correlation (using either the 3-21G* or the 6-31G* optimised geometries) lowers considerably the energy differ-

Table 10 Calculated relative energies and total zero point vibrational energies

Structure	HF/3-21G[a]/ kcal mol^{-1}	MP3/6-31G*+[a] ZPVE[b]	HF/6-31G*[c]/ kcal mol^{-1}	MP3/6-31G*+[c] ZPVE[b]	ZPVE[e]/kcal mol^{-1}
diax-**10t**	0.0	0.0	0.0	0.0	114.6
dieq-**10t**	7.5	4.4	4.9	5.3	114.7
10c	−0.3	−0.6	−0.4	−0.4	114.8
11	−21.6	−14.0	−9.4	−12.7	115.4
12 + H_2O	11.3	3.0	2.0	4.4	99.7
13	22.3	11.0	8.7	11.5	110.3
14	4.5	3.9	4.5	4.2	114.9
15	−11.8	−7.2	−2.5	−7.0	112.5
16 + H_2O	26.5	14.7	19.1	16.2	97.9
TS1	24.7	11.0	8.8	11.9	110.3
TS2	23.9	11.3	9.6	12.3	110.3
TS3	11.1	9.4	6.4	6.1	113.6
TS4	9.9	9.2	7.6	9.6	112.8
TS5	24.5	10.9	8.9	11.7	110.3
18	0.0	0.0	0.0	0.0	132.7
17	−24.3	−17.3	−14.1	−16.3	131.8
19	22.5	11.5	9.0	11.8	127.3
20 + H_2O	5.5	−1.8	0.9	−1.3	116.6
21	−14.0	−10.4	−6.6	−10.2	129.8
22 + H_2O	20.5	9.5	13.0	11.1	115.3

[a] Using optimised HF/3-21G geometries. [b] Scaled by a factor of 0.908. [c] Using optimised HF/6-31G* geometries. [d] Scaled by a factor of 0.893. [e] At 6-31G*.

Table 11 Calculated proton affinities of cyclohexane-1,4-diols

Structure	HF/6-31G*// 3-21G/ kcal mol^{-1}	MP3/6-31G*// 6-31G*/ kcal mol^{-1}	MP3/6-31G*// 6-31G*+ ZPVE/kcal mol^{-1}
diax-**9t**	203.6	201.3	195.3
dieq-**9t**	199.5	197.4	190.3
9c[a]	204.1	202.3	195.3
9c[b]	213.2	215.4	207.7

[a] Protonation to give **10c**. [b] Protonation to give **11**.

ences between the various species, making the entire potential surface significantly flatter.

Calculated structures of ions 12–14 and the transition states connecting them

The calculated structures of ions **12**–**14** and of the transition states connecting them are shown in Fig. 3. The bicyclic oxonium ion **12** adopts the symmetrical boat conformation. The C–O bonds in **12** are by 0.107 Å longer than the calculated C–O bond length in the neutral bicyclic ether **23** (1.414 Å), but it is by 0.076 Å shorter than the C^1–$^+OH_2$ distance in **14**. As expected the oxygen atom in **12** has a pyramidal geometry.

The open 4-hydroxycyclohexyl ion–H_2O complex, **13**, adopts a flattened chair conformation (the $C^1C^2C^3C^5$ dihedral angle is 8.8°) in which the distance between the O-atom of the 4-hydroxy group and the positively charged C^1 atom (3.122 Å) is shorter by 0.244 Å than in diax-**10t** (3.366 Å). In the transition state for the ring closure of **13** to the bicyclic ion **12**, **TS2**, this distance is further reduced to 2.760 Å and the ring adopts a half-chair conformation [$\theta(C^1C^2C^3C^5) = -3.4°$].

In **14**, the 4-hydroxy group has approached C^1 to a distance of 2.762 Å. However, the C^1–$^+OH_2$ distance in **14** (1.597 Å) is intermediate between that in diax-**10t** (1.618 Å) and in dieq-**10t** (1.582 Å), indicating that in **14** the water molecule is as strongly bound as in diax-**10t**.

In **TS4**, the transition state structure for anchimeric assistance, the molecule adopts a boat conformation, placing the attacking oxygen atom of the 4-hydroxy group, the attacked C^1 and the leaving H_2O molecule in a nearly ideal *anti* arrangement (the OC^1O-angle is 167.9°), as expected for an internal S_N2 process. The cleaving C^1–$^+OH_2$ bond is elongated to 2.055 Å and the remote 4-hydroxy O-atom approaches C^1 to a distance of 2.498 Å. The sum of the bond angles around C^1 is 357.1° pointing to a nearly perfect trigonal bipyramid structure at C^1—the ideal transition state geometry for an internal S_N2 process.

Possible fragmentation reactions for protonated *cis*-cyclohexane-1,4-diol and *cis*-4-methoxycyclohexanol

As pointed out above, for the fragmentation of protonated *cis*-1,4-dialkoxycyclohexanes, where anchimeric assistance is not geometrically possible, the experiments show that the bridged ion **a** is not the resulting ion. A detailed analysis of the dissociation of protonated *cis*-cyclohexane-1,4-diol, **9c**, will be dealt with elsewhere.[19]

As pointed out above, protonation of *cis*-cyclohexane-1,4-diol, **9c**, leads to the hydrogen-bridged ion **11**. Elimination of water from **11** may take place, as shown in Scheme 12, either *via* the open isomer **10c** after cleavage of the hydrogen bridge, or alternatively *via* the ion–neutral complex **15**.[19] **10c** will lead to the bicyclic ion **12** *via* the open ion **13**. To mimic more closely the experimentally studied compounds (see Scheme 4) we have studied computationally also the elimination of H_2O from the bridged protonated *cis*-4-methoxycyclohexanol **17**.[30] The results are presented in Table 10.

The calculations performed so far at the MP3/6-31G*//6-31G* level for the model *cis*-cyclohexane-1,4-diol (Table 10) show that the two possible fragmentation pathways shown in Scheme 12, one leading to the symmetrical bicyclic ion **12** and the other to the non-symmetrical ion **16**, are very close in energy and therefore, at the currently used level of theory, it is impossible to decide which path is energetically more favourable. Similar calculations for *cis*-4-methoxycyclohexanol lead to a similar conclusion. Further calculations involving 1,4-dimethoxycyclohexanes or higher level calculations of the simpler model systems will be required to resolve the current experimental–theoretical inconsistency. Such studies are in progress.

Conclusions

The experimental results obtained in this study demonstrate that under chemical ionisation conditions the elimination of alcohols (methanol and ethanol) from the MH^+ ions of *trans*-1,4-dialkoxycyclohexanes yields symmetrical bicyclic ions, while alcohol elimination from the *cis*-isomers leads to non-symmetrical species. The formation under identical experi-

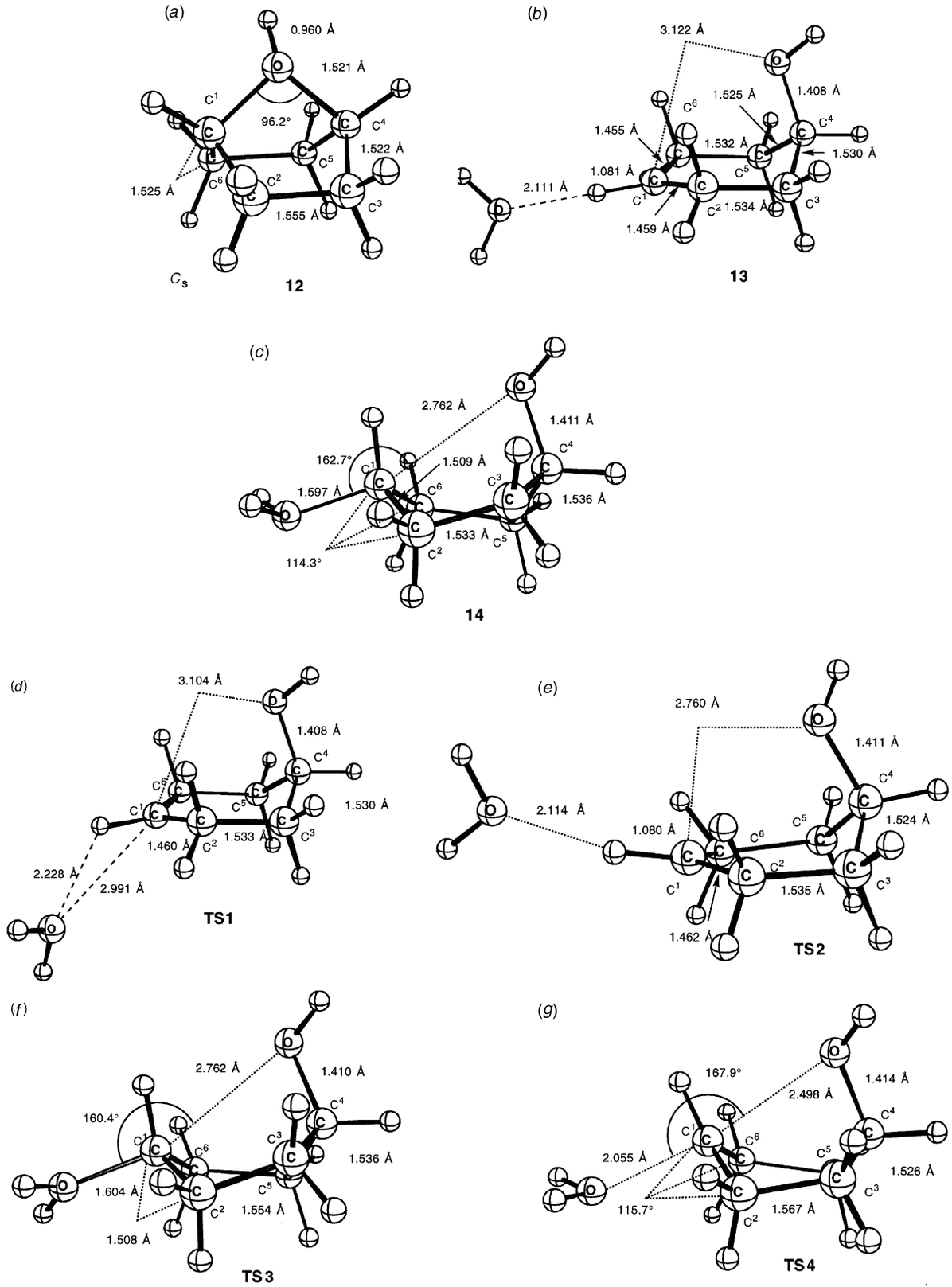
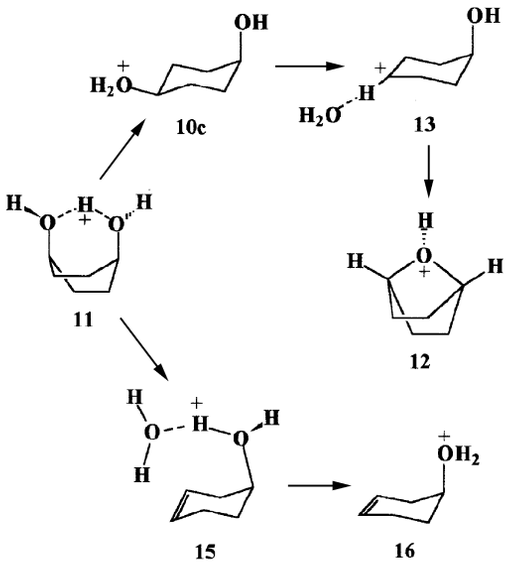


Fig. 3 Calculated structures of: (*a*) **12**; (*b*) **13**; (*c*) **14**; (*d*) **TS1**; (*e*) **TS2**; (*f*) **TS3**; and (*g*) **TS4**

mental conditions of different species from the two stereoisomers provides strong direct evidence for anchimeric assistance in gas-phase alcohol elimination from protonated *trans*-1,4-dialkoxycyclohexanes. *Ab initio* molecular orbital calculations at the MP3/6-31G*//6-31G* level, performed on cyclohexane-1,4-diols as models, support the anchimerically assisted elimination mechanism observed in *trans*-1,4-dialkoxycyclohexanes, but the energy difference between the assisted and the non-assisted elimination mechanisms is small (*ca*. 2–3 kcal mol^{-1}). The *ab initio* calculations identified also two possible mechanistic routes for the non-assisted elimination of water from the corresponding *cis*-diol (and of methanol from the corresponding 4-methoxycyclohexanol), one leading to the symmetrical bicyclic ion **12** and the other to the non-symmetrical protonated cyclohexenol **16**. However these two pathways are very close in energy and therefore, at the currently used level of theory, it is impossible to decide which path is energetically more favourable.



Scheme 12

Experimental

Mass spectrometry

CI–GC–MS analyses and CID measurements were carried out on a Finnigan TSQ-70B triple stage quadrupole mass spectrometer. The stereoisomeric pairs were introduced as mixtures, and separations were performed on a DB-5 (0.25 μm film) 30 m × 0.25 mm (i.d.) capillary column at 110 °C isotherm. The scan rate was 1 scan s^{-1}. The elution sequence for all compounds was: *trans*-diethers followed by *cis*-isomers. CI measurements were performed at 150 °C ion source temperature and 0.4 Torr (indicated) reagent gas pressure (isobutane, ammonia and methane). CID measurements were performed with argon as the target gas (0.3 mTorr, indicated) at 20 and 30 eV collision energy (indicated). All data presented in each table for the same protonation reagent were obtained on a single day under identical conditions in order to assure reliable comparisons.

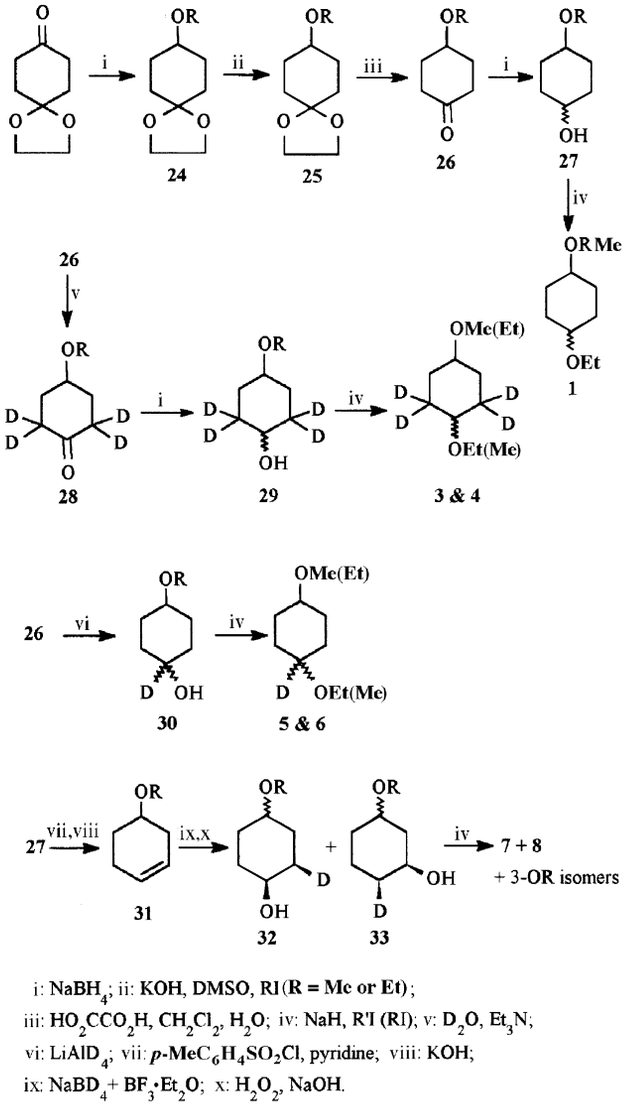
Materials

Stereoisomeric 1-ethoxy-4-methoxycyclohexanes **1** and their deuterium labelled analogues were prepared by routes outlined in Scheme 13 (R = Me or Et). NMR spectra were obtained with a Bruker EM-200 spectrometer. *J* Values in Hz.

Cyclohexane-1,4-dione ethylene ketal. A mixture of cyclohexane-1,4-dione (10.50 g, 94 mmol), ethylene glycol (5 ml, 90 mmol) and a few drops of conc. sulfuric acid in benzene was refluxed with a Dean–Stark apparatus overnight. The mixture was washed with brine, aq. $NaHCO_3$, and the organic layer was dried over $MgSO_4$, evaporated and separated by column chromatography on silica gel [hexane–acetone (7:1)] to give 4.84 g of pure product. $\delta_H(CDCl_3)$ 1.89 (t, *J* 6.9, 4 H), 2.39 (t, *J* 6.9, 4 H), 3.92 (s, 4 H).

4-Hydroxycyclohexanone ethylene ketal 24. $NaBH_4$ (7.28 g, 192.3 mmol) was added in portions to a mixture of cyclohexane-1,4-dione ethylene ketal (10.0 g, 64.1 mmol) in methanol (200 ml) in a water–ice bath with stirring. After 0.5 h stirring was continued at room temp. for 1 h, the solvent was evaporated under reduced pressure, 75 ml of brine were added and the solution was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to afford 98% of **24**. $\delta_H(CDCl_3)$ 1.55 (m, 4 H), 1.75 (m, 4 H), 3.73 (quintet, *J* 3.6, 1 H), 3.89 (s, 4 H).

4-Methoxycyclohexanone ethylene ketal 25 (R = Me). A mixture of **24** (2.0 g, 12.7 mmol), MeI (3.2 ml, 50.8 mmol) and KOH pellets (2.85 g, 50.8 mmol) in dimethyl sulfoxide (DMSO) (25 ml) was vigorously stirred at room temp. overnight. 75 ml of brine were added and the solution was extracted with diethyl ether. The organic layer was washed with brine, dried over $MgSO_4$ and the solvent evaporated under reduced pressure to afford 81% of **25** (R = Me). $\delta_H(CDCl_3)$, 1.65 (m, 8 H), 3.27 (m, 1 H), 3.29 (s, 3 H), 3.90 (s, 4 H).



i: $NaBH_4$; ii: KOH, DMSO, RI (R = Me or Et);
iii: HO_2CCO_2H, CH_2Cl_2, H_2O; iv: NaH, R'I (RI); v: D_2O, Et_3N;
vi: $LiAlD_4$; vii: *p*-$MeC_6H_4SO_2Cl$, pyridine; viii: KOH;
ix: $NaBD_4$ + BF_3·Et_2O; x: H_2O_2, NaOH.

Scheme 13

4-Ethoxycyclohexanone ethylene ketal 25 (R = Et). Compound **25** (R = Et) was prepared (83%) by the procedure described above for **25** (R = Me), but using EtI instead of MeI. $\delta_H(CDCl_3)$ 1.51 (t, *J* 7.0, 3 H), 1.65 (m, 8 H), 3.35 (m, 1 H), 3.44 (quart, *J* 7.0, 2 H), 3.90 (s, 4 H).

4-Methoxycyclohexanone 26 (R = Me). A mixture of **25** (R = Me) (2.25 g, 13.1 mmol) in 75 ml of CH_2Cl_2 and oxalic acid (4.7 g, 41.9 mmol) dissolved in 60 ml of water was vigorously stirred at room temp. overnight. The organic phase was separated and the aqueous phase extracted with chloroform. The combined organic phase was dried over $MgSO_4$ and the solvent evaporated under reduced pressure to give **26** (R = Me) (85%). $\delta_H(CDCl_3)$ 1.9–2.1 (m, 4 H), 2.25 (m, 2 H), 2.54 (m, 2 H), 3.38 (s, 3 H), 3.59 (m, 1 H).

4-Ethoxycyclohexanone 26 (R = Et). Compound **26** (R = Et) was prepared by the procedure described above for **26** (R = Me), but using **25** (R = Et). $\delta_H(CDCl_3)$ 1.20 (t, *J* 7.0, 3 H), 1.9–2.1 (m, 4 H), 2.25 (m, 2 H), 2.54 (m, 2 H), 3.51 (quart, *J* 7.0, 2 H), 3.69 (m, 1 H).

1-Ethoxy-4-methoxycyclohexane 1. 4-Methoxycyclohexanol **27** (R = Me) [65 mg, 0.5 mmol, obtained from **26** (R = Me) by the procedure described above for the reduction of cyclohexanedione ethylene ketal] dissolved in tetrahydrofuran (THF)

was added to a suspension of NaH (65%) (75 mg, 2 mmol, prewashed with hexane) in THF at 60 °C with stirring under nitrogen atmosphere. After 0.5 h EtI (0.16 ml, 2 mmol) was added. After 2 h the flask was cooled in an ice bath and 10 ml of brine were added slowly. The organic phase was separated and the aqueous phase extracted with ethyl acetate. The combined organic phase was dried over $MgSO_4$ and the solvent evaporated under reduced pressure. $\delta_H(CDCl_3)$ 1.16 and 1.18 (t, *J* 7.0, 3 H total), 1.61 (m, 4 H), 1.75 (m, 2 H), 1.99 (m, 2 H), 3.25 (m, 1 H), 3.29 and 3.31 (s, 3 H total), 3.45 and 3.46 (quart, *J* 7.0, 2 H total). Compound **1** was also prepared from 4-ethoxycyclohexanol **27** (R = Et) (72 mg, 0.5 mmol) by the procedure described above, using MeI (0.12 ml, 2 mmol) instead of EtI. The **1c**:**1t** concentration ratio was 1.2:1 (GC–MS).

4-Methoxy- and 4-ethoxy[2,2,6,6-$^2H_4$]-cyclohexanone 28 (R = Me) and 28 (R = Et). A suspension of **26** (R = Me) (2.6 g, 20 mmol) in D_2O (10 ml) and Et_3N (0.2 ml) was stirred overnight at room temp. The reaction mixture was extracted with ethyl acetate, the organic phase was dried over $MgSO_4$ and the solvent evaporated under reduced pressure.[31] [$^2H_4$] > 97%, [$^2H_3$] < 3%. **28** (R = Et) was prepared by a similar route starting with **26** (Et). [$^2H_4$] > 97%, [$^2H_3$] < 3%.

1-Ethoxy-4-methoxy[$^2H_4$]-cyclohexanes 3 and 4. These isotopomers were prepared from **28** (R = Me) and **28** (R = Et) by the procedure described above for the preparation of **1** from **26**. [$^2H_4$ > 95%, [$^2H_3$] < 5%.

[1-$^2H_1$]- and [4-$^2H_1$]-1-Ethoxy-4-methoxycyclohexane 5 and 6. $LiAlD_4$(33 mg, 0.78 mmol) was added to the mixture of 4-methoxycyclohexanone **26** (R = Me) (50 mg, 0.39 mmol) in ether in water–ice bath with stirring under nitrogen atmosphere. After 15 min the bath was removed and stirring continued at room temp. for 1 h. More diethyl ether was added followed by several drops of water while stirring until the solid became white. The suspension was dried with $MgSO_4$, filtered, and the solvent evaporated under reduced pressure to afford 1-[$^2H_1$]-4-methoxycyclohexanol **30** (R = Me) (95%). **30** (R = Et) was prepared from **26** (R = Et) by an analogous procedure. **5** and **6** were prepared from **30** (R = Me) and **30** (R = Et) respectively by the procedure described above for the preparation of **1** from **26**. [$^2H_4$] > 95%, [$^2H_3$] < 5%. The concentration ratio was 2.5:1, and that of **6c**:**6t** was 2.9:1 (GC–MS).

4-Methoxycyclohexene 31 (R = Me). A solution of toluene-*p*-sulfonyl chloride (2.52 g, 13.23 mmol) in $CHCl_3$ (50 ml) was added slowly to a solution of 4-methoxycyclohexanol **27** (R = Me) (1.72 g, 13.23 mmol) in pyridine (15 ml) at 0 °C. After stirring overnight at 0 °C, the solution was washed with water, 5% HCl, saturated $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$ and the solvent evaporated under reduced pressure affording 94% of 4-methoxycyclohexyl tosylate. $\delta_H(CDCl_3)$ d: 1.66 (m, 4 H), 1.85 (m, 4 H), 2.42 (s, 3 H), 3.21 (m, 1 H), 3.27 (s, 3 H), 4.57 (m, 1 H), 7.30 (d, *J* 8, 2 H), 7.77 (d, *J* 8, 2 H). The foregoing tosylate (3.55 g, 12.5 mmol) and 75 ml of 12% KOH were placed in a distillation apparatus at 110 °C. More 12% KOH was added during the distillation. The distillate (collected for 7–8 h of heating) was extracted with diethyl ether, the organic phase was dried over $MgSO_4$ and the solvent evaporated under reduced pressure in a cold bath affording 35% of **31** (R = Me). $\delta_H(CDCl_3)$ 1.9–2.1 (m, 5 H), 2.35 (dd, 1 H), 3.33 (s, 3 H), 3.44 (m, 1 H), 5.61 (m, 2 H).

4-Ethoxycyclohexene 31 (R = Et). This compound was prepared by the procedure described above for **31** (R = Me), but using **28** (R = Et) (3.52 g, 11.8 mmol) and heating at 130 °C (60%). $\delta_H(CDCl_3)$ 1.19 (t, *J* 7, 3 H), 1.91–2.1 (m, 5 H), 2.36 (m, 1 H), 3.52 (quart, *J* 7, 2 H), 5.59 (m, 2 H).

***cis*-2-[2-$^2H_1$]-4-Methoxycyclohexanol 32 (R = Me).** A solution of 4-methoxycyclohexene **31** (Me) (0.14 g, 1.25 mmol) in 5 ml of diglyme was added to $NaBD_4$ (0.03 g, 0.71 mmol) in diglyme (2 ml) at room temp. A solution of BF_3–Et_2O (0.2 ml, 1.57 mmol) in diglyme (3 ml) was added slowly (foaming occurs during the addition). After stirring at room temp. for another 1 h water (1 ml), 3 M NaOH (0.5 ml) and 30% H_2O_2 (2 ml) were added slowly in an ice bath. The mixture was extracted with ethyl acetate, the organic phase was washed several times with water, dried over $MgSO_4$ and the solvent evaporated under reduced pressure to give a mixture of deuteriated 4- and 3-methoxycyclohexanol in diglyme,[32] which were identified by GC–MS (standard 3-methoxycyclohexanol for comparison was prepared independently).[33] [$^2H_1$] > 98%, [$^2H_0$] < 2%. The 3-:4-methoxycyclohexanol isomers concentration ratio was 3:2, based on a GC–MS analysis of the diethers. *cis*-[2-$^2H_1$]-4-Ethoxycyclohexanol **32** (R = Et) was prepared by the procedure described above for **32** (R = Me), starting from **31** (R = Et). [$^2H_1$] > 98%, [$^2H_0$] < 2%.

***cis*-[2-$^2H_1$]-1-Methoxy-4-ethoxycyclohexane 7.** Etherification of **32** (R = Et) with MeI to **7** was carried out by the procedure described above for the preparation of **1** from **27**. **7** was obtained as a mixture of deuteriated 1,4- and 1,3-dialkoxycyclohexane in diglyme, which was used for the GC–MS analyses without further purification (standard 1-ethoxy-3-methoxycyclohexane for comparison was prepared independently).[33] [$^2H_1$] > 98%, [$^2H_0$] < 2%. The **7c**:**7t** concentration ratio was 1:2 (GC–MS).

***cis*-[2-$^2H_1$]-1-Ethoxy-4-methoxycyclohexane 8.** This compound was prepared from **32** (R = Me) by the procedure described above for **7**, but using EtI instead of MeI. [$^2H_1$] > 98%, [$^2H_1$] < 2%. The **8c**:**8t** concentration ratio was 1.4:1 (GC–MS).

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References

1 A. Mandelbaum, in *Stereochemistry*, ed. H. Kagan, Thieme, Stuttgart, 1977, vol. 1, p. 138, and references cited therein.
2 A. Mandelbaum, *Mass Spectrom. Rev.*, 1983, **2**, 223.
3 (*a*) F. Turecek, *Collect. Czech. Chem. Commun.*, 1987, **52**, 1928; (*b*) F. Turecek, *Int. J. Mass Spectrom. Ion Processes*, 1991, **108**, 137.
4 A. G. Harrison, *Chemical Ionisation Mass Spectrometry*, 2nd edn., CRC Press, Boca Raton, Florida, 1992, p. 108 and references cited therein.
5 R. D. Bowen, M. J. Harrison, D. Neill and S. E. Susan, *J. Chem. Soc., Chem. Commun.*, **1991**, 1346.
6 M. Vairamani, M. Saraswathi and K. V. Siva Kumar, *Org. Mass Spectrom.*, 1992, **27**, 27.
7 J. March, *Advanced Organic Chemistry*, 4th edn., Wiley, New York, 1992, pp. 308–320 and references cited therein.
8 C. C. Van de Sande, S. Z. Ahmad, F. Borchers and K. Levsen, *Org. Mass Spectrom.*, 1978, **13**, 666.
9 Related anchimerically assisted bimolecular substitution reactions in gas-phase ions have been reported under radiolytic conditions: (*a*) G. Angelini and M. Speranza, *J. Am. Chem. Soc.*, 1981, **81**, 3792; (*b*) G. Angelini and M. Speranza, *J. Am. Chem. Soc.*, 1981, **81**, 3800.
10 (*a*) C. C. Van de Sande, *Tetrahedron*, 1976, **32**, 1741; (*b*) Van de Sande, *Org. Mass Spectrom.*, 1976, **11**, 121.
11 C. C. Van de Sande, *Org. Mass Spectrom.*, 1976, **11**, 130.
12 C. C. Van de Sande and F. W. McLafferty, *J. Am. Chem. Soc.*, 1974, **97**, 2298.
13 F. W. McLafferty and F. Turecek, *Interpretation of Mass Spectra*, 4th edn., University Science Books, Mill Valley, California, 1993, sections 8.3 and 8.11.
14 C. M. Orlando, M. George and M. L. Gross, *Org. Mass Spectrom.*, 1993, **28**, 1184.

15 (*a*) P. Ashkenazi, B. Domon, A. L. Gutman, A. Mandelbaum, D. Mueller, W. J. Richter and D. Ginsburg, *Isr. J. Chem*., 1989, **29**, 131; (*b*) A. Mandelbaum, *Adv. Mass Spectrom*., 1995, **13**, 227.
16 (*a*) M. Attina, F. Cacace and A. Marzio, *J. Am. Chem. Soc*., 1989, **111**, 6004 and references cited therein; (*b*) P. M. Viruela-Martin, I. Nebot, R. Viruela-Martin and J. Planelles, *J. Chem. Soc*., *Perkin Trans. 2*, **1986**, 49.
17 J. S. Splitter and F. Turecek, *Applications of Mass Spectrometry to Organic Stereochemistry*, VCH Publishers, New York, 1993, pp. 144, 437, 443, 448, 450, and references cited therein.
18 (*a*) D. S. Noyce and B. R. Thomas, *J. Am. Chem. Soc*., 1957, **79**, 755; (*b*) N. Mori, *J. Chem. Soc. Jpn*., 1960, **33**, 1332.
19 R. Shvily, T. Müller, Y. Apeloig and A. Mandelbaum, in preparation.
20 For a description of the computational methods used see: W. J. Hehre, L. Radom, P. v. R. Schleyer and J. A. Pople, *Ab initio Molecular Orbital Theory*, Wiley-Interscience, New York, 1986.
21 (*a*) P. C. Hariharan and J. A. Pople, *Chem. Phys. Lett*., 1972, **66**, 217; (*b*) M. M. Francl, W. J. Pietro, W. J. Hehre, J. S. Binkley, M. S. Gordon, D. J. DeFrees and J. A. Pople *J. Chem. Phys*., 1982, **77**, 3654; (*c*) J. B. Foresman and A. Frisch, *Exploring Chemistry with Electronic Structure Methods*, Gaussian Inc., Pittsburgh, PA, 2nd edn. 1996.
22 GAUSSIAN 92, Revision B.3, M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Patterson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Otiz, J. B. Foresma, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Repogle, J. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. DeFrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Pittsburgh PA, 1995.
23 (*a*) C. Gonzalez and H. B. Schlegel, *J. Phys. Chem*., 1989, **90**, 2154; (*b*) C. Gonzalez and H. B. Schlegel, *J. Phys. Chem*., 1990, **94**, 5523.
24 C. Møller and M. S. Plesset, *Phys. Rev*., 1934, **46**, 618.
25 An NMR study showed that in solution the diaxial : diequatorial conformers concentration ratio was 15 : 85 in pyridine and 2 : 98 in water: W. F. Trager, B. J. Nist and A. C. Huitric, *J. Pharm. Sci*., 1967, **56**, 698.
26 (*a*) For a review see: F. R. Jensen and C. H. Bushweller, *Adv. Alicyclic Chem*., 1971, **3**, 139; (*b*) R. J. Abraham and Z. L. Rossetti, *J. Chem. Soc*., *Perkin Trans. 2*, 1973, 582.
27 Early extended Hückel MO calculations suggested that the diequatorial conformer is more stable than the diaxial conformer by 1.0 kcal mol^{-1}: Yu. A. Zhdanov and E. N. Malysheva, *Carbohydr. Res*., 1972, **24**, 87.
28 C. Guenat, R. Houriet, D. Stahl and F. J. Winkler, *Helv. Chim. Acta*, 1985, **68**, 1647.
29 Dixon and Komornicki (D. A. Dixon and A. Komornicki, *J. Phys. Chem*., 1990, **94**, 5630) found at the MP2/tzp level of theory a somewhat higher barrier (12 kcal mol^{-1}) for the conversion of the chair conformation of cyclohexane to the twisted boat conformation than we calculated for the conversion of diax-**10t** to **14**. We believe that this is due to the stabilisation of **TS3** relative to diax-**10t** by the more favourable electrostatic interaction between the positively charged carbon and the 4-hydroxy group in the developing twist-boat conformation of **TS3**.
30 **17** serves as a model for estimating more accurately the effects operating in these protonated 4-methoxycyclohexanols. In the CIMS experiment preferential protonation will occur at the methoxy group, which has a higher proton affinity.
31 G. S. Hammond and J. Warkentin, *J. Am. Chem. Soc*., 1961, **83**, 2554.
32 H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc*., 1959, **81**, 6423.
33 O. Averin and A. Mandelbaum, unpublished results.

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