Available online at www.sciencedirect.com
SCIENCE DIRECT
ELSEVIER
International Journal of Mass Spectrometry 249–250 (2006) 433–445
International Journal of Mass Spectrometry
www.elsevier.com/locate/ijms

The effect of steric hindrance on the relative rates of anchimerically assisted alcohol eliminations from MH^+ ions of 2-substituted 1,4-dialkoxybutanes upon CI and CID Experiment and theory

Julius Ben Ari, Ilana Navon, Asher Mandelbaum *

Department of Chemistry, Technion – Israel Institute of Technology, Haifa, Israel

Received 11 October 2005; received in revised form 6 November 2005; accepted 10 November 2005
Available online 27 December 2005

Dedicated to the memory of Chava Lifshitz. Her personality and scientific achievements will be always remembered by her many friends all over the world.

Abstract

1,4-Dialkoxybutanes afford very abundant $[MH–ROH]^+$ ions upon isobutane chemical ionization (CI) and collision induced dissociation (CID), in contrast to other primary mono-ethers or 1,ω-diethers of long chain diols. This behavior suggests involvement of anchimeric assistance in the mechanism of alcohol elimination from the MH^+ ions of 1,4-dialkoxybutanes. This concerted mechanistic pathway finds support in the CI and CID behavior of the $[MH–ROH]^+$ ions, obtained from isomeric mixed 1,4-dialkoxybutanes (1-ethoxy-4-methoxy- and 1-methoxy-4-ethoxy) substituted at position 2 with alkyl groups or with deuterium atoms. Density functional (DFT) calculations at B3LYP/6-31G** level of theory also support the anchimerically assisted elimination mechanism. The isomeric mixed 1,4-dialkoxybutanes, substituted at position 2 with alkyl groups of variable bulkiness, exhibit preferential elimination of alcohol from position C-4 rather than from C-1, and this tendency increases with the size of the substituents. This steric effect is explained by a more hindered transition state involved in the anchimerically assisted elimination of alcohol from C-1 due to interaction of the substituent(s) at position 2 with the protonated alkoxy group at position 1. Calculations show the energies of transition states resulting in 4-elimination products are lower than those leading to the elimination of alcohol from position 1, and the difference significantly increases with the increase of the bulkiness of the 2-substituents.

Keywords: Anchimeric assistance; Steric effects in mass spectrometry; Density functional (DFT) calculations; Diethers; Chemical ionization (CI); CID; Deuterium labeling

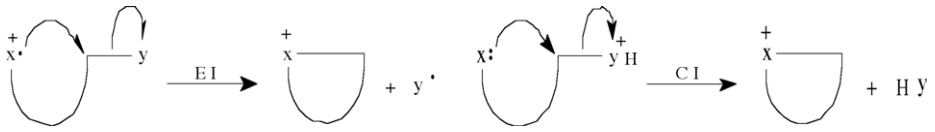
1. Introduction

Anchimeric assistance has been suggested to play an important role in the mechanisms of numerous fragmentation processes of gas-phase cations obtained under electron ionization (EI) and chemical ionization (CI) conditions. Such intramolecular backside nucleophilic attacks (Scheme 1), which have strict configurational requirements, provide explanations for the variations in ion abundances, often observed in the mass spectra of stereoisomers [1–11].

Anchimerically assisted eliminations result in cyclic product ions. In many cases where anchimeric assistance has been proposed, the cyclic structures of the resulting ions have not been supported by experimental evidence. We have shown by an experimental and computational study involving specific deuterium labeling and CID measurements, that under chemical ionization conditions the elimination of alcohol (methanol or ethanol) from the MH^+ ions of *trans*-1-ethoxy-4-methoxycyclohexane gives rise to symmetrical bicyclic ions, while alcohol elimination from the *cis*-isomer leads to non-symmetrical mono-cyclic species [7]. The formation under identical experimental conditions of different species from the two stereoisomers provides a strong direct evidence for anchimeric assistance in the gas-phase alcohol elimination from protonated *trans*-1,4-dialkoxycyclohexanes [7–8].

* Corresponding author at: 4a Kanfei Nesharim Street, Jerusalem 95464, Israel. Tel.: +97 22 651 6339; fax: +97 24 829 5703.
E-mail address: chr17am@tx.technion.ac.il (A. Mandelbaum).

1387-3806/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijms.2005.11.011



Scheme 1.

We have recently observed that the elimination of methanol or ethanol from the MH^+ ions of 1,4-dimethoxy- and diethoxybutane upon isobutane-CI gives rise to $[MH–ROH]^+$ ions which are much more abundant than those obtained from primary monoethers. This finding suggests operation of an anchimerically assisted mechanistic pathway in the alcohol elimination from 1,4-dialkoxybutanes.

We have previously shown that *t*-butyl substitution at position 2 in maleates and succinates has a pronounced effect on the relative efficiencies of elimination of alcohol from the two ester moieties upon CI and CID [12–14]. The preferential elimination from the 1-alkoxycarbonyl group of the MH^+ ions of 2-*t*-butylmaleates and 2-*t*-butylsuccinates, has been explained by a site specific gas-phase protonation at the less sterically hindered 4-alkoxycarbonyl group [12,13].

The objective of the present work was (i) to explore the question whether the efficient alcohol elimination from gas phase protonated dialkoxybutanes upon CI and CID indeed involves anchimeric assistance, and (ii) to examine the effect of steric hindrance on the relative efficiencies of alcohol elimination from the two positions 1 and 4 of 1,4-dialkoxybutanes substituted at position 2 with alkyl groups of variable bulkiness.

2. Experimental

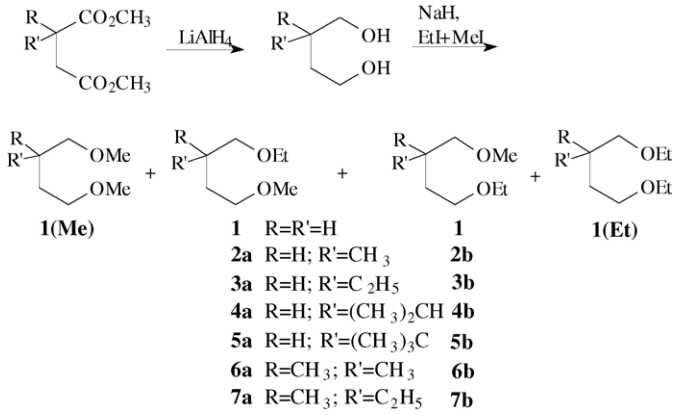
2.1. Mass spectrometry

The 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 thickness) capillary column (30 m × 0.25 mm i.d.) under isothermal conditions. The temperature was programmed from 60 to 200 °C at 5–10 °C/min. The scan rate was 1 scan/s. The elution sequence of the 2-alkyl-1,4-diethers was: 2-alkyl-1-ethoxy-4-methoxybutanes were followed by the isomeric 2-alkyl-1-methoxy-4-ethoxybutanes: **2a** was followed by **2b**; **3a** by **3b**; **4a** by **4b**; **5a** by **5b**; **6a** by **6b, and 7a** was followed by **7b**.

CI measurements were performed at 150 °C ion source temperature and 0.4 Torr (indicated) reagent gas pressure. Isobutane was used as protonation reagent. CID measurements were performed with argon as a target gas (0.3 mTorr indicated) at 25 eV collision energy (indicated).

2.2. Materials

Mixtures of the isomeric mixed ethyl methyl diethers **2a**–**7a** and **2b**–**7b** were prepared by Williamson etherification of the corresponding substituted butanediols (Scheme 2) with a mixture of ethyl and methyl iodides [7,10,11]. The resulting



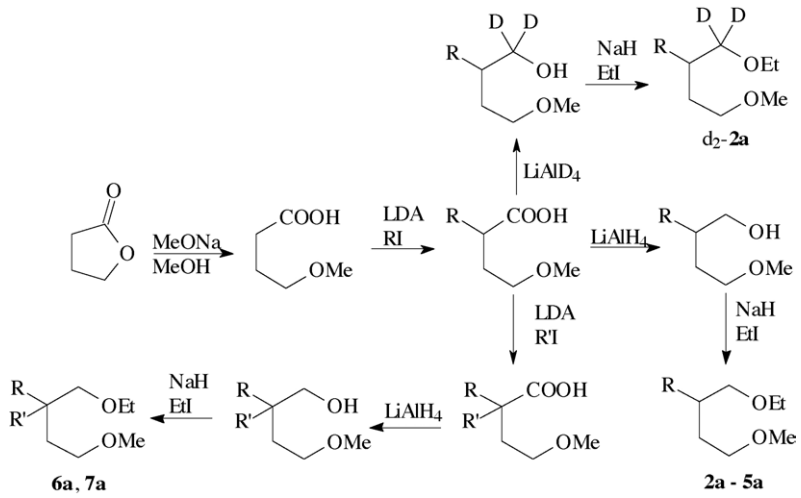
Scheme 2.

mixtures, which also contained the corresponding diethyl and dimethyl ethers, were easily analyzed by GCMS.

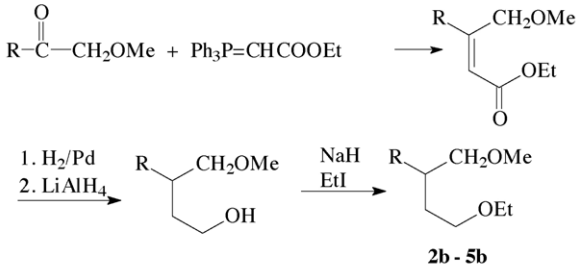
The structural assignment of the isomeric mixed diethers has been made by unequivocal syntheses of **2a**–**5a** and **2b**–**5b** (the synthetic routes are shown in Schemes 3a and 3b). Methanolysis of butyrolactone with sodium methoxide in boiling methanol resulted in 4-methoxybutanoic acid [15], which was readily transformed to the diethers **2a**–**5a** by α-substitution followed by $LiAlH_4$ reduction and Williamson etherification with iodoethane. The deuterium labeled analog d_2-**2a** was prepared by the reduction of 2-methyl-4-methoxybutanoic acid (Scheme 3a, R=CH_3) with $LiAlD_4$ followed by Williamson etherification with iodoethane.

3. Computational details

The GAUSSIAN 98 series of programs [16] was used for all calculations. The geometries of all molecules were optimized using the hybrid B3LYP [17] density functional method [18] with the 6-31G(d,p) basis set [16]. Vibrational frequencies were calculated at this level of theory for all stationary points, in order to differentiate them as minima or transition states. Real vibrational frequencies confirmed the presence of minima on the potential energy surface. Transition states were identified as stationary points with one imaginary frequency. Additionally, the IRC (intrinsic reaction coordinate) calculations were performed in one case (for transition state **TS-11**, see below, Fig. 6), in order to test its validity. Other anchimerically assisted transition states were not explored by IRC calculations because of their great similarity. The conformational analysis of transition and ground states were performed and only conformers of the lowest energy are presented in this work. All energies discussed in this work were calculated at the B3LYP/6-31G(d,p)+ZPVE level of theory.



(a)



(b)

Scheme 3.

4. Results and Discussion

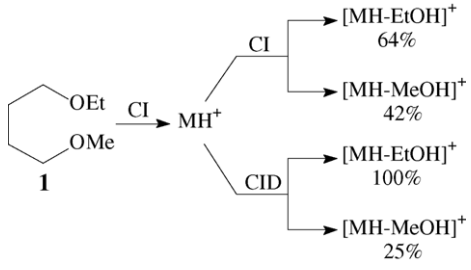
4.1. Anchimerically assisted alcohol elimination

The elimination of alcohol from the MH^+ ions of primary ethers upon isobutane-CI is a highly energetic process affording non-abundant $[MH–ROH]^+$ ions (e.g. 7% $[MH–EtOH]^+$ ion in the case of ethyl hexyl ether, see Table 1). The elimination of alcohol is even less efficient in long-chain 1,ω-dialkoxyalkanes (3–4% $[MH–ROH]^+$ ion in the isobutane-CI mass spectra of 1,10-diethoxy-, 1,10-dimethoxy- and 1-ethoxy-10-methoxydecanes, see Table 1), where the MH^+ ions may be stabilized by proton bridging between the two basic sites. On the other hand, alcohol elimination from the MH^+ ion of 1-ethoxy-4-methoxybutane **1** is an efficient process upon isobutane-CI, giving rise to abundant $[MH–MeOH]^+$ and $[MH–EtOH]^+$ ions (42 and 64%, respectively, Scheme 4).

We have previously shown that *trans*-1,4-dialkoxycyclohexanes exhibit a highly stereospecific efficient alcohol elimination upon CI. The stereospecificity of this elimination suggested a mechanistic pathway involving anchimeric assistance for that process, which was strongly supported by a detailed mechanistic study and by ab initio calculations [7]. The high

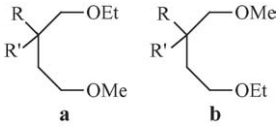
Table 1
Relative abundances of $[MH–alcohol]^+$ ions in the isobutane-CI mass spectra of primary ethers

	$[MH–MeOH]^+$ (%)	$[MH–EtOH]^+$ (%)	MH^+ (%)
n-C_6H_{13}—OEt	–	7	100
MeO—$(CH_2)_4$—OEt	42	64	100
MeO—$(CH_2)_4$—OMe	72	–	100
MeO—$(CH_2)_5$—OMe	51	–	100
MeO—$(CH_2)_6$—OMe	29	–	100
MeO—$(CH_2)_7$—OMe	10	–	100
MeO—$(CH_2)_{10}$—OMe	5	–	100
EtO—$(CH_2)_{10}$—OEt	–	4	100
MeO—$(CH_2)_{10}$—OEt	1	4	100
MeO—$(CH_2)_{12}$—OMe	6	–	100



Scheme 4.

Table 2
Relative abundances of [MH–alcohol]$^+$ ions in the isobutane-CI mass spectra of diethers **1**–**7**



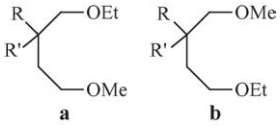
	[MH–MeOH]$^+$ (%)	[MH–EtOH]$^+$ (%)	[MH–MeOH]$^+$/[MH–EtOH]$^+$
1. R=R′=H	42	64	0.66
2a. R=H; R′=CH_3	55	36	1.5
2b. R=H; R′=CH_3	20	56	0.36
3a. R=H; R′=C_2H_5	54	47	1.15
3b. R=H; R′=C_2H_5	6	100	0.06
4a. R=H; R′=$(CH_3)_2CH$	39	8	4.9
4b. R=H; R′=$(CH_3)_2CH$	15	98	0.15
5a. R=H; R′=$(CH_3)_3C$	68	2	34
5b. R=H; R′=$(CH_3)_3C$	2	26	0.08
6a. R=CH_3; R′=CH_3	23	5	4.6
6b. R=CH_3; R′=CH_3	3	44	0.07
7a. R=CH_3; R′=C_2H_5	46	0.1	460
7b. R=CH_3; R′=C_2H_5	4	45	0.09

efficiency of the alcohol elimination from the MH$^+$ ion of **1** upon CI and CID suggested an anchimerically assisted pathway also in this case. 2-Alkyl-substituted isomeric 1-ethoxy-4-methoxy- (series **a**) and 1-methoxy-4-ethoxybutanes (series **b**) **2**–**7** were prepared and their isobutane-CI and CID mass spectra were measured, in order to investigate the question whether the [MH–alcohol]$^+$ ions have cyclic structures. The relative abundances of the [MH–Alcohol]$^+$ ions in the isobutane-CI and CID mass spectra of diethers **1**–**7** are listed in Tables 2 and 3. Anchimerically assisted elimination of methanol or ethanol from the isomeric 2-alkyl-1-ethoxy-4-methoxybutanes (series **a**) and 2-alkyl-1-methoxy-4-ethoxybutanes (series **b**) is expected to give rise to identical cyclic [MH–MeOH]$^+$ and [MH–EtOH]$^+$ ions **a**($\mathbf{R_a}$) and **a**($\mathbf{R_b}$) shown in Scheme 5. On the other hand an unassisted elimination (i.e. a simple cleavage of C–O bonds) should give rise, at least in the first stage, to isomeric acyclic structures.

4.2. Cyclic structures of [MH-alcohol]$^+$ ions

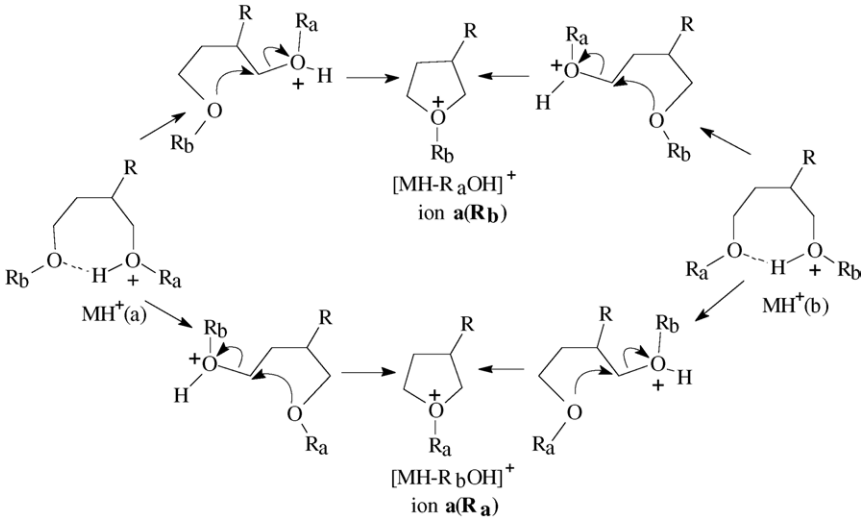
The *m*/*z* 115 [MH–MeOH]$^+$ ions, obtained from 2-methyl-1-ethoxy-4-methoxybutane **2a** and from 2-methyl-1-methoxy-4-ethoxybutane **2b** upon isobutane-CI, exhibit identical CID spectra (see Fig. 1a and b; correlation coefficient 0.9992). The same is also true for the *m*/*z* 101 [MH–EtOH]$^+$ ions obtained from the two isomeric diethers **2a** and **2b** (Fig. 1c and d; correlation coefficient 0.9976). Similar behavior was observed for 2-ethyl and 2-*t*-butyl analogous isomeric pairs **3a** and **3b** and **5a** and **5b**. The correlation coefficients were 0.9965 and 0.9983 for the [MH–MeOH]$^+$ ions and 0.9988 and 0.9940 for the [MH–EtOH]$^+$

Table 3
Relative abundances of [MH–alcohol]$^+$ ions in the CID mass spectra[a] of the MH$^+$ ions[b] of diethers **1**–**7**



	[MH–MeOH]$^+$ (%)	[MH–EtOH]$^+$ (%)	[MH–MeOH]$^+$/[MH–EtOH]$^+$
1. R=R′=H	25	100	0.25
2a. R=H; R′=CH_3	63	77	0.82
2b. R=H; R′=CH_3	7	100	0.07
3a. R=H; R′=C_2H_5	100	65	1.5
3b. R=H; R′=C_2H_5	6	100	0.06
4a. R=H; R′=$(CH_3)_2CH$	100	30	3.3
4b. R=H; R′=$(CH_3)_2CH$	2	100	0.02
5a. R=H; R′=$(CH_3)_3C$	47	1	47
5b. R=H; R′=$(CH_3)_3C$	<0.1	57	<0.002
6a. R=CH_3; R′=CH_3	25	6	4.2
6b. R=CH_3; R′=CH_3	1	37	0.03
7a. R=CH_3; R′=C_2H_5	67	11	6.1
7b. R=CH_3; R′=C_2H_5	1	100	0.01

[a] Collision energy 25 eV.
[b] Obtained upon isobutane-CI.



Scheme 5.

ions, respectively. All these findings are consistent with the cyclic tetrahydrofuran structures of the $[MH–ROH]^+$ ions $\mathbf{a_1}$ and $\mathbf{a_2}$, and thus support the proposed mechanistic pathway for the alcohol elimination involving anchimeric assistance.

Additional evidence for the cyclic structure of the $[MH–ROH]^+$ ions was derived from the CID behavior of the specifically deuterium labeled 1,1-d_2-2-methyl-1-ethoxy-4-methoxybutane d_2-**2a** and 1,1-d_2-2-methyl-1-methoxy-4-ethoxybutane d_2-**2b**. The *m*/*z* 103 ions, obtained by the elimination of ethanol from both d_2-**2a** and d_2-**2b**, give rise to identical abundance ratios of the *m*/*z* 45 and 47 $CH_2{=}O^+Me$ and $CD_2{=}O^+Me$ ions (94:6, respectively, for both isomers, see Scheme 6), indicating an identical tetrahydrofuran structure for the elimination product ion **a**(Me). A similar CID behavior has been observed for the *m*/*z* 117 products of the elimination of methanol from the MH^+ ions of d_2-**2a** and d_2-**2b**. The identical abundance ratios (95:5 in both cases) of the *m*/*z* 59 and 61 $CH_2{=}O^+Et$ and $CD_2{=}O^+Et$ ions are also consistent with the cyclic structure of ion **a**(Et) obtained by the anchimerically assisted pathway (Scheme 6).

The preferential cleavage of the C4–C5 bond in ions **a**(Me) and **a**(Et) giving rise to the predominant unlabeled *m*/*z* 45 and

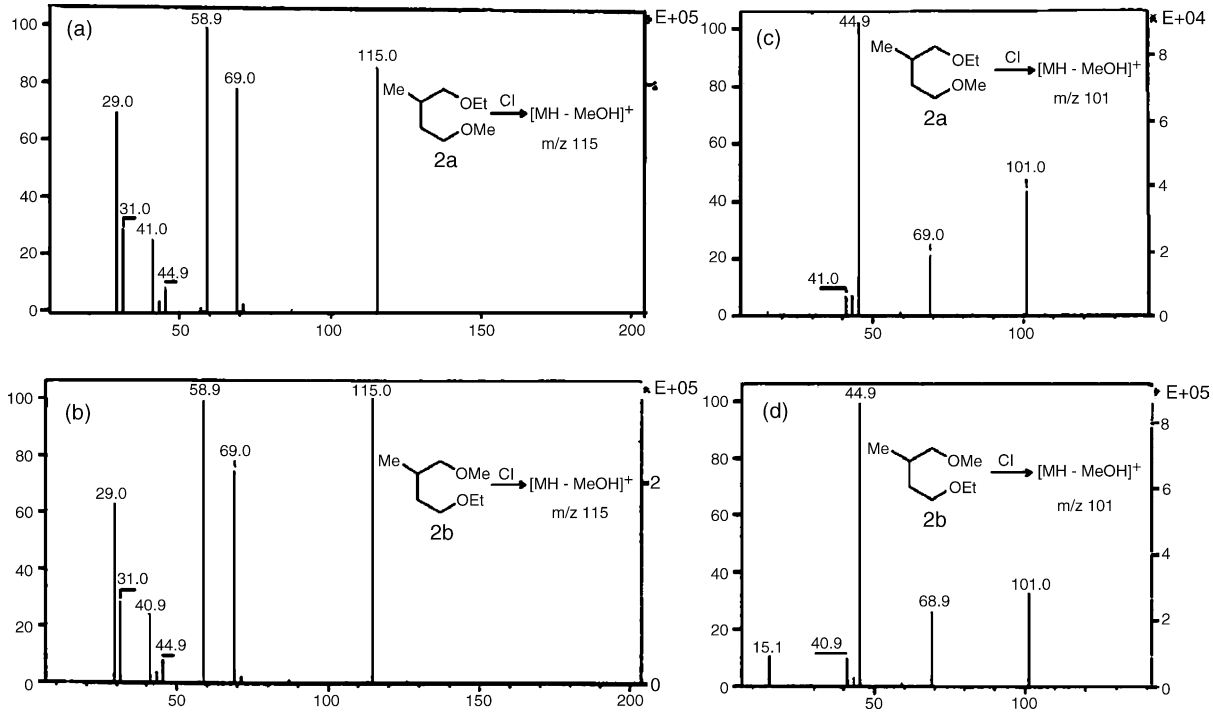
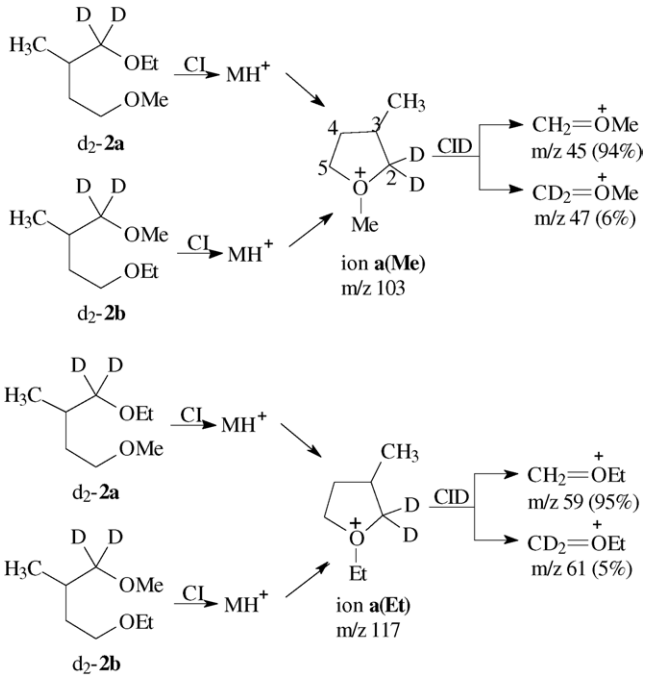


Fig. 1. CID spectra (30 eV collision energy) of $[MH–MeOH]^+$ ions, obtained upon isobutane-CI (a) from 2-methyl-1-ethoxy-4-methoxybutane **2a**, and (b) from 2-methyl-1-methoxy-4-ethoxybutane **2b**, and of $[MH–EtOH]^+$ ions, obtained upon isobutane-CI (c) from 2-methyl-1-ethoxy-4-methoxybutane **2a**, and (d) from 2-methyl-1-methoxy-4-ethoxybutane **2b**.



Scheme 6.

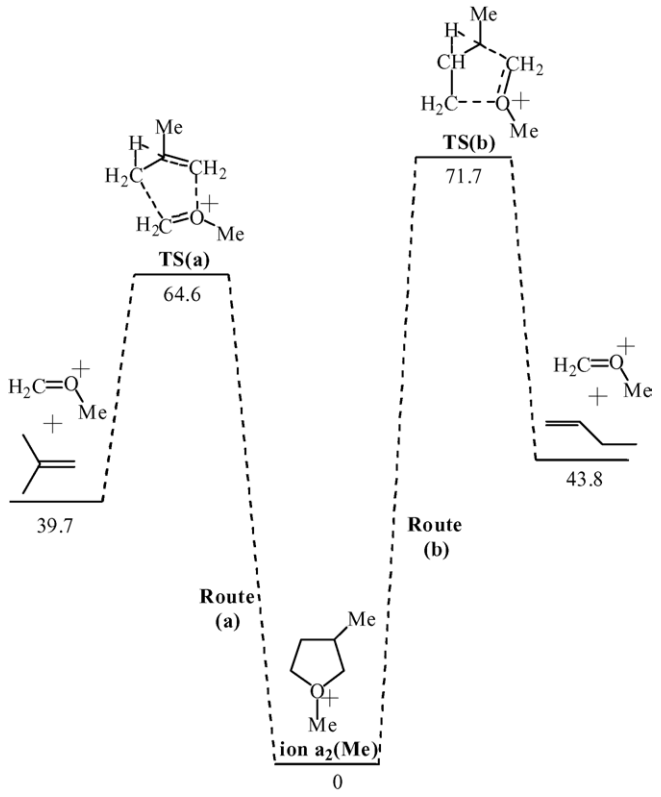


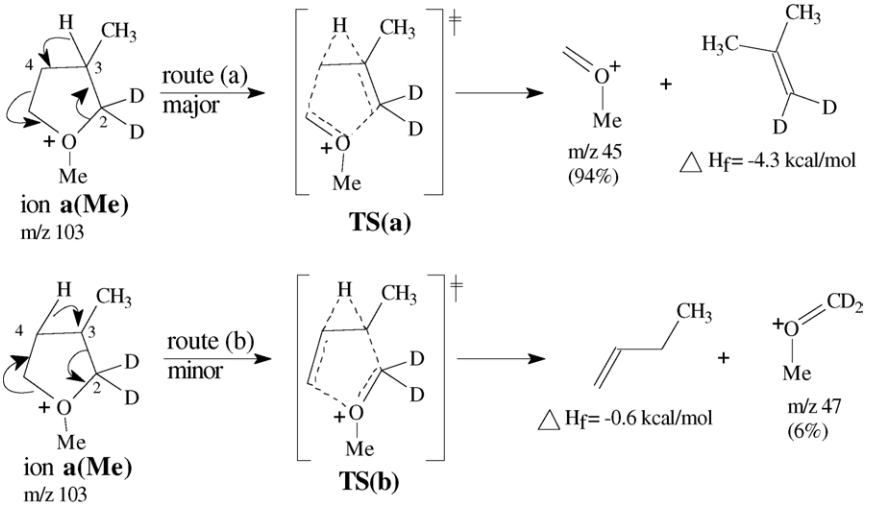
Fig. 2. Calculated potential energy profile of the fragmentation of ion **a(Me)** upon CID (outlined in Scheme 7).

59 ions, respectively, may be explained by the mechanistic pathway proposed in Scheme 7. A hydrogen transfer from the tertiary position 3 to 4 in the course of the cleavage of bonds 1–2 and 4–5 gives rise to the *m/z* 45 ion (94%) and to neutral d_2-isobutene (route (a)). Hydrogen migration from the secondary position 4 to 3 is proposed to occur in the course of the cleavage of bonds 1–4 and 2–3 affording the labeled *m/z* 47 ion (6%) and unlabeled 1-butene (minor route (b)). The greater stability of neutral isobutene (its enthalpy of formation is lower by 3.7 kcal/mol than that of 1-butene [18], see Scheme 7 and Fig. 2) is in keeping with the higher efficiency of route (a).

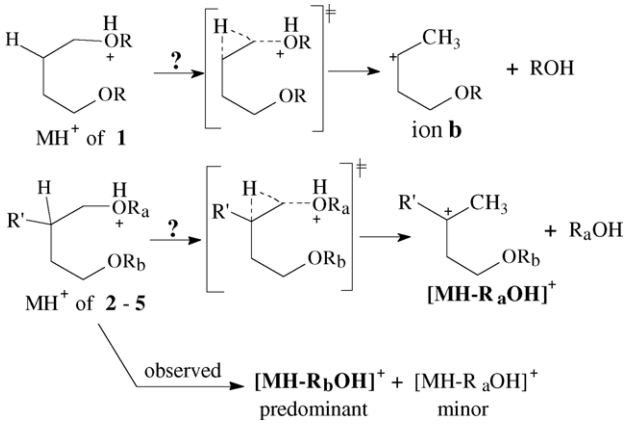
DFT calculations have been performed for the energies related to the two routes (a) and (b), and the resulting energy profile is shown in Fig. 2. The energy of transition state **TS(a)** involved in route (a) is lower than that of **TS(b)** of route (b) by 7 kcal/mol, which is consistent with the preferential occurrence of route (a) upon CID of ion **a(Me)**.

4.3. Hydride transfer versus anchimeric assistance

A possible alternative pathway, that would explain the high efficiency of alcohol elimination from the MH^+ ions of 1,4-dialkoxybutane, might involve a hydride transfer from position



Scheme 7.



Scheme 8.

2 to 1, resulting in a secondary carbocation structure **b** shown in Scheme 8. An analogous 1,2-H-migration from the β- to α-position, leading to tertiary carbocation structures, has been previously shown to play a role in the stereospecific alcohol elimination from the MH^+ ions of *cis*-2-methyl-1-methoxycyclohexane and *cis*-1-methoxy-*trans*-decalin [10,20,21]. This proposed pathway disagrees with the behavior of the isomeric 2-alkyl-1-ethoxy-4-methoxy- and -1-methoxy-4-ethoxybutanes **2a** and **b**, **3a** and **b**, **4a** and **b** and **5a** and **b**, upon CI and CID, shown in Tables 1 and 2. If the alcohol elimination were assisted by a 1,2-hydride transfer, the elimination of alcohol involving position 1 would be expected to afford the more abundant $[MH–R_aOH]^+$ tertiary product ion (see Scheme 8). However, in all the examined isomeric pairs, preferential elimination of the alcohol from position 4, giving rise to the more abundant $[MH–R_bOH]^+$ ions, has been observed. This finding provides further support for the mechanistic pathway involving anchimeric assistance.

The energies related to the two possible mechanistic pathways of methanol elimination from protonated 1,4-dimethoxybutane **1**, namely those involving anchimeric assistance and 1,2-hydride shift, have been calculated using the hybrid density functional theory (B3LYP). The results of the calculations are given in the energy profile shown in Fig. 3. The cyclic proton bridged MH^+ ion is the most stable species in this system, 22.6 kcal/mol below the ring-open conformer that is suitable for the anchimerically assisted elimination of methanol. The energy of formation of the cyclic *O*-methyl tetrahydrofuran oxonium structure **a** plus methanol is much lower than that of the carbocation **b** (25.5 kcal/mol versus 48.0 kcal/mol), and very much lower than that of the primary 4-methoxybutyl carbocation (64.5 kcal/mol), that would result from a simple cleavage of the C–O bond. Furthermore, the energy of the transition

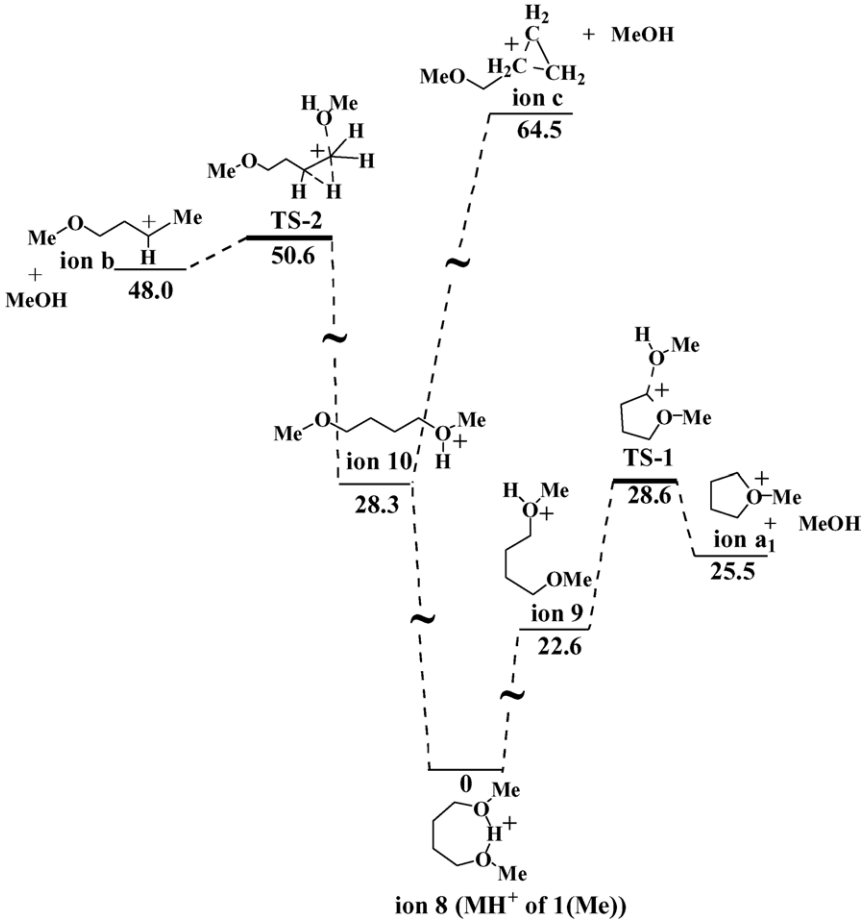


Fig. 3. Calculated potential energy profile of the fragmentation of the MH^+ ion of 1,4-dimethoxybutane (ion **8**) upon CID (comparison of mechanistic pathways involving anchimeric assistance and simple bond cleavage).

structure **TS-1** in the anchimerically assisted pathway is considerably lower than that of **TS-2** in the mechanism involving 1,2-hydride transfer (28.6 kcal/mol versus 50.6 kcal/mol). This result is an additional strong support for the anchimerically assisted pathway of the alcohol elimination from protonated 1,4-dialkoxybutanes.

DFT calculations were also performed for the two mechanistic pathways of the elimination of ethanol from the protonated isomeric 1-ethoxy-4-methoxy- and 1-methoxy-4-ethoxy-2-*t*-butylbutanes **5a** and **5b** (the IUPAC names are 1-methoxy-3-ethoxymethyl- and 1-ethoxy-3-methoxymethyl-4,4-dimethylpentanes, respectively). It has been shown before in this section (Scheme 8), that the MH^+ ions of 2-alkyl-1,4-dialkoxybutanes exhibit preferential elimination of alcohol originating from position 4 as compared with that from C-1. The elimination involving a 1,2-hydride transfer has been claimed above to prefer loss of alcohol from position 1, which would result in a tertiary carbocation, while the elimination from position 4 would lead (at least in the initial step) to a secondary ion structure. The calculated energies of the transition structures (see Fig. 4) support this conclusion. The energy of **TS-3** involved in the elimination of alcohol from position 1 (34.6 kcal/mol) is lower by 8.5 kcal/mol than that of **TS-4** involving position 4 (43.1 kcal/mol), which is in contrast with the experimental data. On the other hand the energies of the transition structures involved in the anchimerically assisted mechanistic pathway are in agreement with the experiment: the energy of **TS-6** involved in the elimination from position 1 (27.9 kcal/mol) is significantly higher than that of **TS-7** (24.7 kcal/mol) involving position 4. These results, as well as the lower energies of **TS-6** and **TS-7**, as compared with those of transition structures **TS-3** and **TS-4**, exclude the 1,2-hydride shift mechanism, and thus strongly support the anchimerically assisted pathway.

4.4. Preferential elimination of ethanol from protonated 1-ethoxy-4-methoxybutane 1

We have previously shown that protonated 1-ethoxy-4-methoxybutane **1** undergoes preferential elimination of ethanol both under CI and CID conditions (see Scheme 4 and Tables 1–3). This finding has to be taken in account when drawing quantitative conclusions concerning mechanistic pathways from comparative studies of substituted mixed dialkoxybutanes. DFT calculations were performed for the two competing alcohol eliminations from the MH^+ ion of **1**, and the resulting energy profile for the anchimerically assisted processes is shown in Fig. 5.

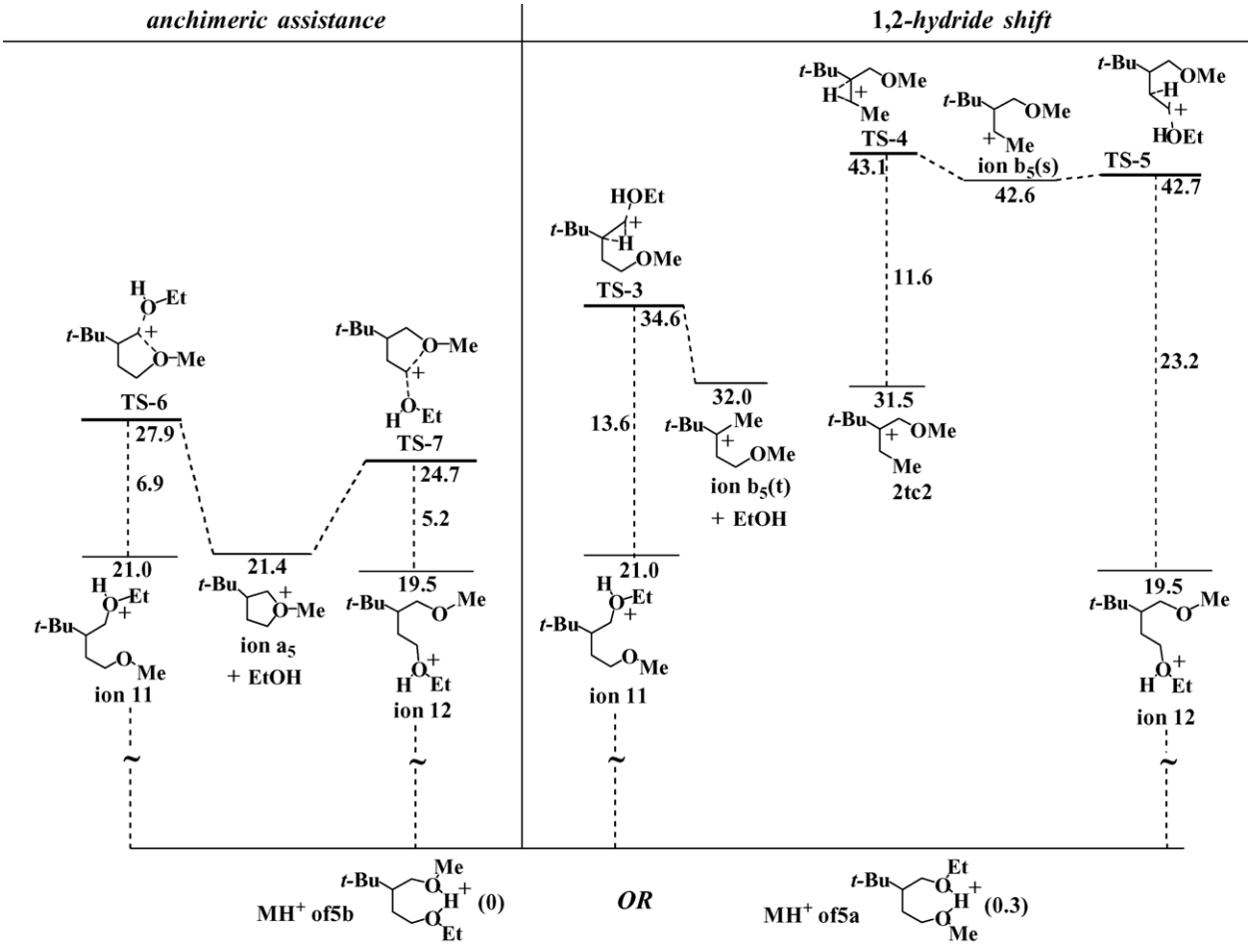


Fig. 4. Calculated potential energy profile of the fragmentation of the MH^+ ions of isomeric 1-ethoxy-4-methoxy- and 1-methoxy-4-ethoxy-2-*t*-butyl-butanes **5a** and **5b** upon CID (comparison of mechanistic pathways involving anchimeric assistance and 1,2-hydride shift).

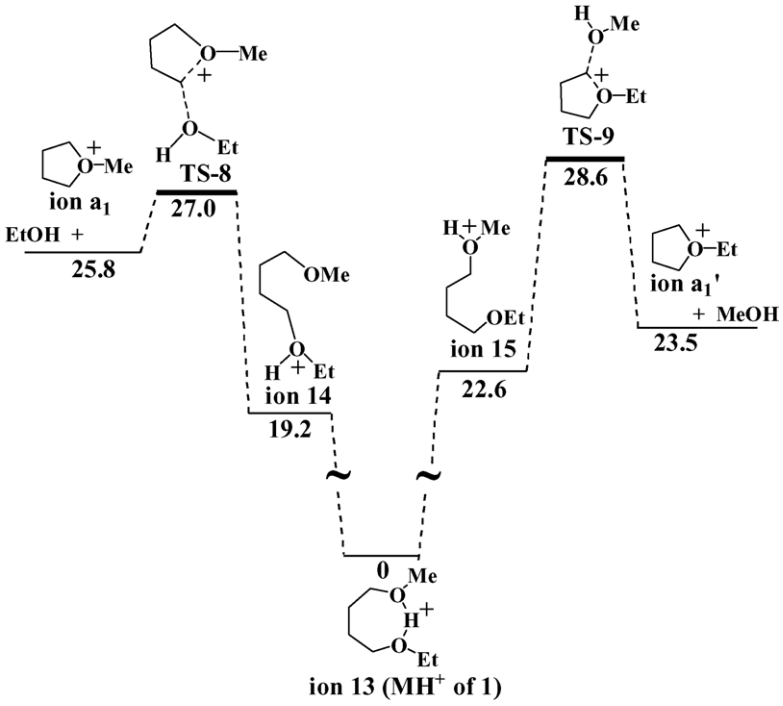
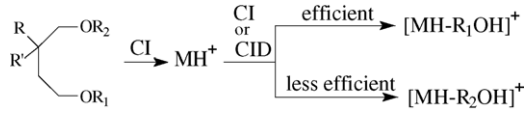
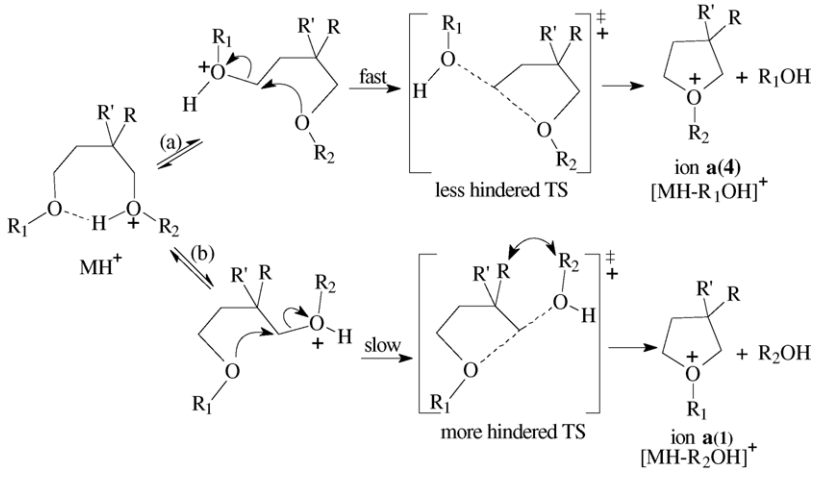


Fig. 5. Calculated potential energy profile of the fragmentation of the MH^+ ions of 1-ethoxy-4-methoxybutane **1** (ion **13**) upon CID (comparison of the energy barriers of the competing elimination of methanol and ethanol).

Ring opening of the stabilized cyclic proton-bridged MH^+ ion **13** gives rise to the isomeric ethoxy- and methoxy-protonated ethers **14** and **15**, respectively. The considerably lower energy of the ethoxy-protonated **14** (19.2 kcal/mol versus 22.6 kcal/mol) is in agreement with the higher proton affinities (PA) and gas phase basicities (GB) of ethyl ethers, as compared with methoxy analogs (e.g. PA's of diethyl ether and methyl propyl ether are 198.0 and 194.8 kcal/mol, respectively [19]). The energy of the transition structure **TS-8**, leading to the elimination of ethanol from ion **14** and formation of ion $\mathbf{a}_1$(Me), is lower by 1.6 kcal/mol than that of **TS-9**, which is involved in the elimination of methanol (27.0 kcal/mol versus 28.6 kcal/mol). This result explains the observed higher efficiency of ethanol elimination from protonated 1-ethoxy-4-methoxybutane. It should be noted that the thermochemistry of the two eliminations shows a different pattern: the summed energy of the products of ethanol elimination (ion $\mathbf{a}_1$(Me) plus ethanol) is higher than that of the elimination of methanol (ion $\mathbf{a}_1$(Et) plus methanol).



Scheme 9.



Scheme 10.

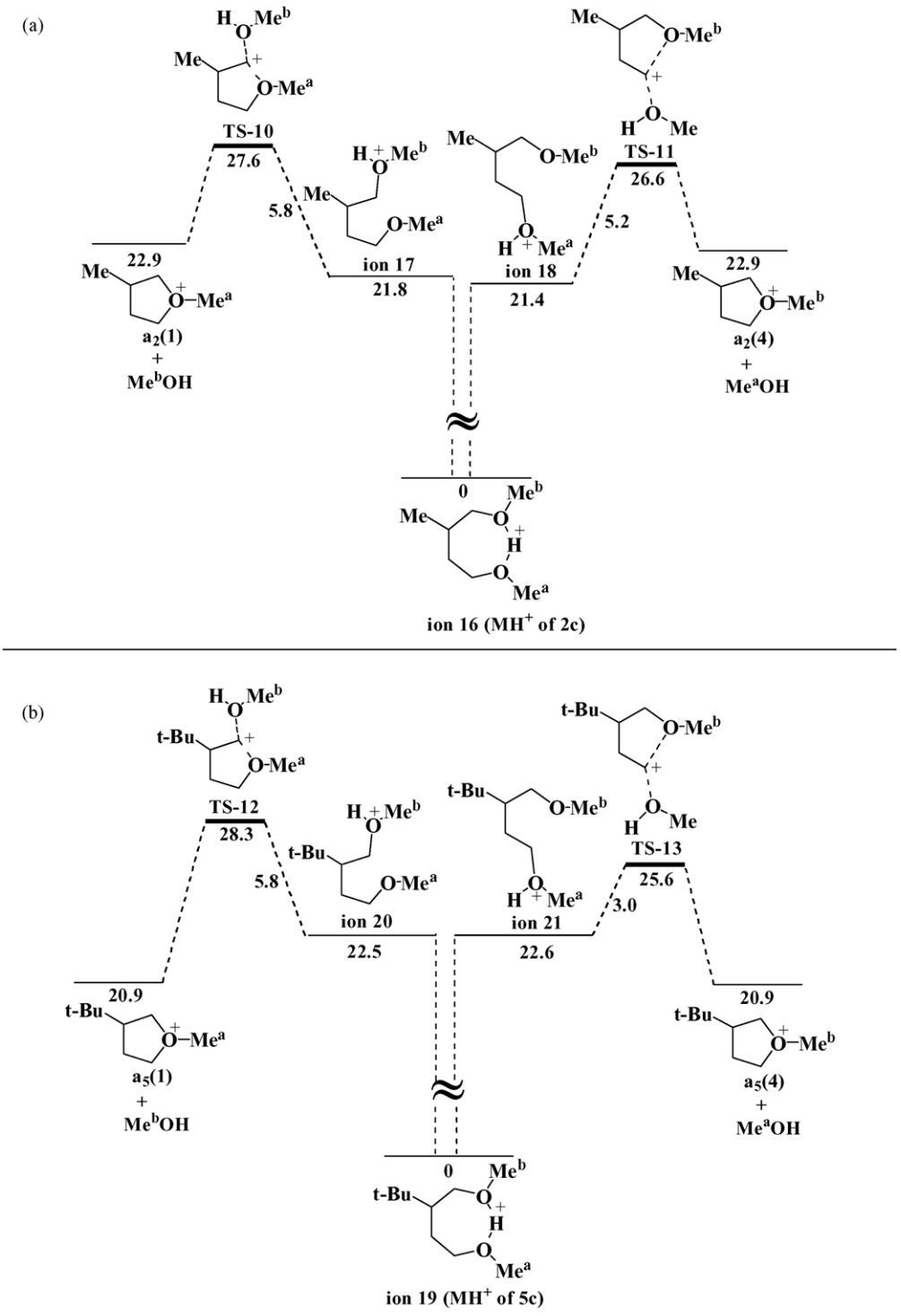


Fig. 6. Calculated potential energy profiles of the fragmentation of the MH^+ ions of: (a) 1,4-dimethoxy-2-methyl-butane **2c** (ion **16**) and (b) 1,4-dimethoxy-2-*t*-butyl-butane **5c** (ion **19**) upon CID.

4.5. Steric effect of 2-substituents

The mass spectral data listed in Tables 2 and 3 show a pronounced steric effect of the substituents at position 2 on the relative efficiencies of elimination of the alcohols originating at the two positions 1 and 4 of 2-alkyl-1,4-dialkoxybutanes **2**–**7** upon CI and CID. Preferential elimination of the alcohol from position 4 has been observed in all the examined isomeric pairs (Scheme 9), and this trend increases with the size of the 2-substituent and with the number of the substituents at position 2. The abundance ratio $[MH–R_1OH]^+/[MH–R_2OH]^+$ is significantly large in the case of 2-*t*-butyl-, 2,2-dimethyl- and 2-ethyl-2-methyl-1,4-dialkoxybutanes **5**, **6**, and **7**, and much smaller in the CI and CID spectra of 2-methyl- and 2-ethyl-analogs **2** and **3**.

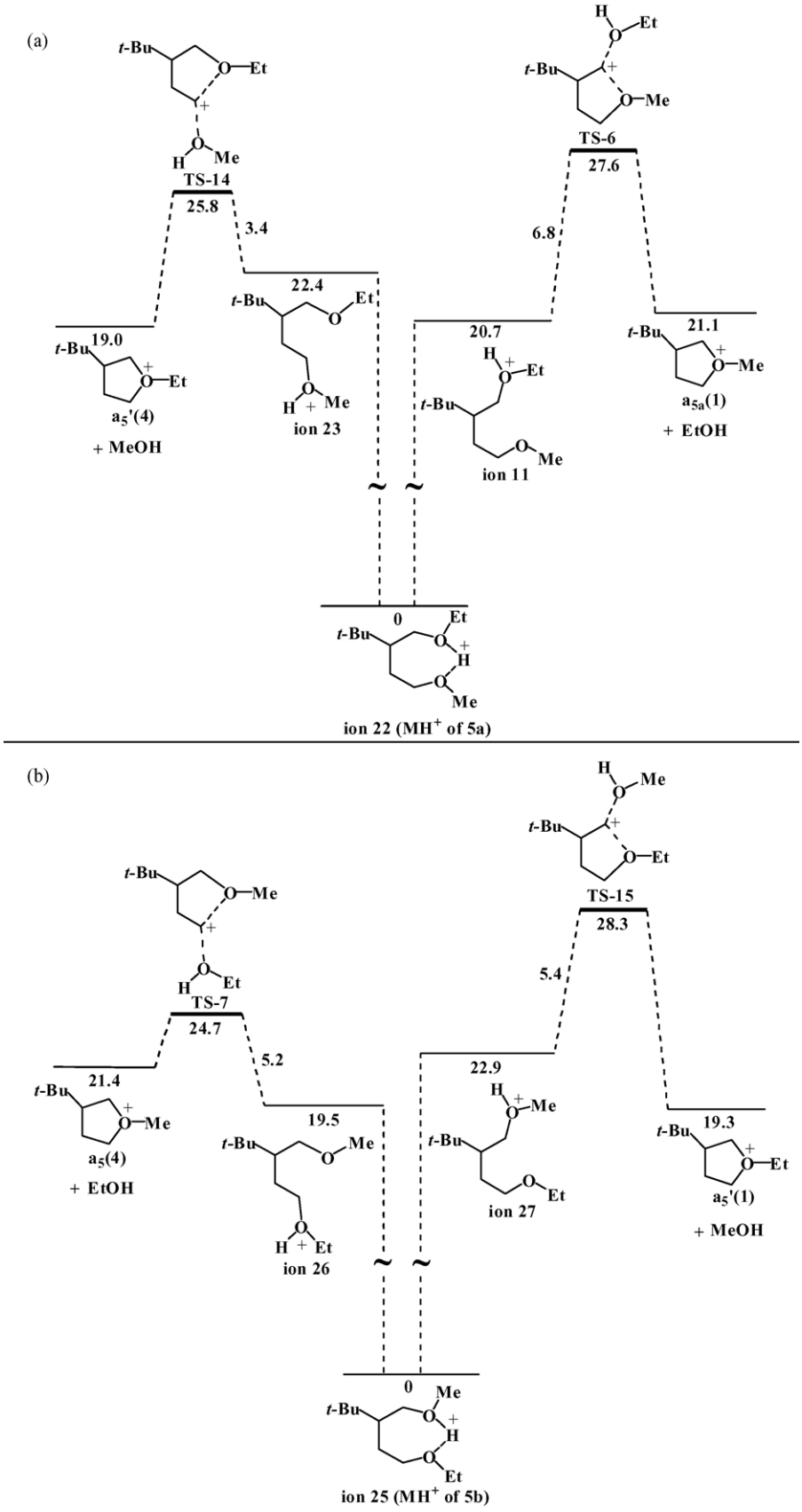


Fig. 7. Calculated potential energy profile of ethanol and methanol elimination upon CID from (a) protonated 1-methoxy-4-ethoxy-2-*tert*-butylbutane **5a** (ion **22**) and (b) 1-ethoxy-4-methoxy-2-*tert*-butylbutane **5b** (ion **25**).

A qualitative inspection of models suggests a more hindered transition structure for the anchimerically assisted elimination of alcohol R_2OH (route (b) in Scheme 10) due to interaction of the substituent(s) at position 2 with the OR_2 group at position 1. This highly specific behavior is an additional support for the anchimerically assisted mechanistic pathway of alcohol elimination from protonated dialkoxybutanes upon CI and CID. Calculations have been performed for 2-methyl- and 2-*t*-butyl-1,4-dialkoxybutanes **2** and **5** in order to obtain a quantitative measure for the steric effect. The mass spectral measurements were performed using isomeric methoxy-ethoxy derivatives (series **a** and **b**), because this is the easiest unequivocal way to determine the origin of the eliminated alcohols. The DFT calculations were performed on both dimethoxy- and mixed ethoxy-methoxy-butanes, the first in order to eliminate the effect of the different thermochemical properties (such as basicities and proton affinities) of the methoxy and ethoxy groups (see previous section and Fig. 5), and the latter in order to enable semi-quantitative comparison of the theoretical predictions with the experimental results.

4.6. Computational studies of the steric effect

The calculated potential energy profiles of the anchimerically assisted methanol elimination from protonated 1,4-dimethoxy-2-methylbutane and 1,4-dimethoxy-2-*tert*-butylbutane **2c** and **5c** are shown in Fig. 6. The energy of the transition structure **TS-11**, involved in the elimination of methanol from position 4 of **2c** leading to ion **a-4(Me)** (26.6 kcal/mol, relative to the proton bridged MH^+ ion of **2c**, ion **16**), is slightly lower (by 1 kcal/mol) than **TS-10**, which is involved in the alternative elimination from position 1 affording ion **a-1(Me)**. This small difference in barrier energies suggests small preference for the elimination of methanol from position 4 of the protonated 2-methyl diether **2c**. The difference between the energies of the corresponding transition structures **TS-12** and **TS-13**, involved in the elimination of methanol from positions 1 and 4 of the *t*-butyl substituted analog **5c** (28.3 and 25.6 kcal/mol, respectively), is significantly larger than that of **2c** (by 2.7 kcal/mol). This computational result is in agreement with the experimentally observed more pronounced preferential elimination involving position 4 of the diether with the bulky 2-substituent, giving rise to ion **a-4(tBu)**.

The calculated energy profile of the anchimerically assisted methanol and ethanol elimination pathways from protonated 1-ethoxy-4-methoxy- and 1-methoxy-4-ethoxy- 2-*tert*-butylbutanes **5a** and **5b** are shown in Fig. 7. In overall, the results are qualitatively similar to those obtained for the dimethyl ether **5c** (Fig. 6). There is, however, a difference between the energies of the transition structures leading to the elimination of ethanol and methanol from the two protonated isomeric diethers. The energy of **TS-14**, involved in the elimination of methanol from position 4 of **5a** (25.8 kcal/mol), is lower by 1.8 kcal/mol than that of **TS-15**, leading to the elimination of ethanol from position 1 (27.6 kcal/mol). This difference between the energy barriers of the two competing channels is enhanced by a factor of two in **5b**: the energy of **TS-7**, involved in the elimination of ethanol from position 4 of **5b** (24.7 kcal/mol), is lower by 3.6 kcal/mol than that of **TS-15**, leading to the elimination of methanol from position 1 (28.3 kcal/mol). This difference between the two isomers stems from the intrinsic relatively small preference, observed and calculated above (1.6 kcal/mol, Fig. 5) for the elimination of ethanol, as compared to methanol, from protonated 1-ethoxy-4-methoxybutane **1**.

5. Conclusion

We have shown in this work, both by experiment and by hybrid DFT calculations, that the elimination of alcohol from gas-phase protonated 1,4-dialkoxybutane and from analogs substituted at C-2, takes place by a concerted anchimerically assisted mechanism. Of particular interest is the effect of steric crowding on the relative efficiencies of the anchimerically assisted alcohol eliminations from the MH^+ ions of 1,4-dialkoxybutanes substituted at position 2 with alkyl groups of variable bulkiness. Such effects have not been observed in many cases. We have previously reported on the effect of steric hindrance on the site of protonation in certain aminoethers and aminoalcohols upon isobutane-CI, resulting in different mass spectral behavior of analogous compounds with substituent of varying bulkiness [22,23]. In this work, we have been able to show the dependence of the barrier energies on the steric crowdedness of the 2-substituents in 1,4-dialkoxybutanes, and thus to explain the different mass spectral behavior upon CI and CID.

Acknowledgment

This work was supported by the Fund for Promotion of Research at the Technion.

References

[1] A.G. Harrison, Chemical Ionization Mass Spectrometry, second ed., CRC Press, Boca Raton, Florida, 1992, p. 176 and references cited therein.
[2] J. Respondek, H. Schwarz, F. Van Gaever, C.C. Van de Sande, Org. Mass Spectrom. 13 (1978) 618.
[3] (a) L. D'Haenens, C.C. Van de Sande, F. Vangaever, Org. Mass Spectrom. 14 (1979) 145;
(b) L. D'Haenens, C.C. Van de Sande, M. Schelfaut, M. Vandewalle, Org. Mass Spectrom. 22 (1987) 330.
[4] R.D. Bowen, M.J. Harrison, D. Neill, S.E. Susan, J. Chem. Soc. Chem. Commun. (1991) 1346.
[5] M. Vairamani, M. Saraswathi, K.V. Siva Kumar, Org. Mass Spectrom. 27 (1992) 27.
[6] (a) M. Speranza, A. Filippi, Chem. Eur. J. 5 (1999) 834;
(b) M. Speranza, A. Filippi, Chem. Eur. J. 5 (1999) 845.
[7] R. Shvily, T. Mueller, Y. Apeloig, A. Mandelbaum, J. Chem. Soc. Perkin Trans. 2 (1997).1221.
[8] A. Mandelbaum, Adv. Mass Spectrom. 13 (1995) 227.
[9] I. Kuzmenkov, A. Etinger, A. Mandelbaum, J. Mass Spectrom. 34 (1999) 797.
[10] N. Morlender-Vais, A. Mandelbaum, J. Mass Spectrom. 32 (1997) 1124.
[11] N. Morlender-Vais, A. Mandelbaum, J. Mass Spectrom. 34 (1999) 637.
[12] A. Weisz, M. Cojocaru, A. Mandelbaum, J. Chem. Soc. Chem. Commun. (1989) 331.

[13] A. Mandelbaum, D.R. Mueller, W.J. Richter, I. Vidavsky, A. Weisz, J. Mass Spectrom. 24 (1989) 857.
[14] For leading references concerning stereochemical effects in mass spectrometry see: J.S. Splitter, F. Turecek, Applications of Mass Spectrometry to Stereochemistry, VCH Publishers, New York, 1993.
[15] W. Reppe, Ann. 596 (1955) 169;
W. Reppe, Ann. 596 (1955) 191.
[16] Gaussian 98, Revision A.11.3, M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, V.G. Zakrzewski, J.A. Montgomery Jr., R.E. Stratmann, J.C. Burant, S.Dapprich, J.M. Millam, A.D. Daniels, K.N. Kudin, M.C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G.A. Petersson, P.Y. Ayala, Q. Cui, K. Morokuma, N. Rega, P. Salvador, J.J. Dannenberg, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J. Cioslowski, J.V. Ortiz, A.G. Baboul, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, Komaromi, R. Gomperts, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, J.L. Andres, C. Gonzalez, M. Head-Gordon, E.S. Replogle, J.A. Pople, Gaussian Inc., Pittsburgh PA, 2002.
[17] (a) C.T. Lee, W.T. Yang, R.G. Parr, Phys. Rev. B 37 (1988) 785;
(b) A.D. Becke, J. Chem. Phys. 98 (1993) 5648.
[18] (a) R.G. Parr, W. Yang, Density-functional Theory of Atoms and Molecules, Oxford University Press, Oxford, 1989;
(b) W. Koch, M.C. Holthausen, A Chemist's Guide to Density Functional Theory, Wiley-VCH, Weinheim, 2000.
[19] NIST Chemistry Webbook, NIST Standard Reference Data Program. August 2003 (http://webbook.nist.gov./chemistry/).
[20] N. Morlender-Vais, A. Mandelbaum, Interanat. J. Mass Spectrom. Ion Processes 167–168 (1997) 13.
[21] J. Ben Ari, M. Karni, Y. Apeloig, A. Mandelbaum, Internat. J. Mass Spectrom. 228 (2003) 297.
[22] V. Vais, A. Etinger, A. Mandelbaum, Eur. Mass Spectrom. 5 (1999) 449.
[23] A. Mandelbaum, V. Vais, A. Etinger, Adv. Mass Spectrom. 15 (2001) 346.