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The role of hydride migration in the mechanism of alcohol elimination from protonated ethers upon chemical ionization Experiment and theory

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Dedicated to Helmut Schwarz, a great scientist and a wonderful human being, "a cemented cistern that does not lose a drop" [Pirkey Avoth (Ethics of Fathers), chapter 2, mishnah 8], on the occasion of his 60th birthday.

Abstract

An enhanced elimination of methanol under isobutane-chemical ionization (CI) conditions, resulting in highly abundant $[MH–CH_3OH]^+$ ions, has been observed in several primary and secondary methyl ethers having a tertiary β-position (methine), as compared with those with β-methylene. This elimination is stereospecific in stereoisomeric 2-methyl-1-methoxycyclohexanes and in other ethers affording significantly more abundant $[MH–CH_3OH]^+$ ions in the *cis*-isomers than in their *trans*-counterparts. These findings suggest involvement of a 1,2-hydride migration from the β- to α-position in the course of the alcohol elimination from the MH^+ ions of the above *cis*-ethers, resulting in stabilized tertiary carbocation structures. The possible pathways of methanol elimination from protonated *cis*-2-methyl-1-methoxycyclohexane were explored by density functional calculations at the B3LYP/6-31+G(d,p) level of theory. The transition states for MeOH elimination involving 1,2-hydride migration were located and the activation energy of the process was evaluated. The activation barrier of the alcohol elimination assisted by 1,2-hydride migration is lower by ∼10 kcal/mol than the simple bond cleavage (9.6 kcal/mol vs. 20.5 kcal/mol). These computational results support the mechanistic pathway involving the 1,2-hydride transfer. A step-wise mechanistic pathway is proposed for the less efficient elimination of methanol from protonated *trans*-2-methyl-1-methoxycyclohexane.

Keywords: Hydrogen transfer; Density functional calculations; Stereospecific fragmentation; Chemical ionization (CI); Mechanism of alcohol elimination; Ethers

1. Introduction

The isobutane-chemical ionization (CI) mass spectra of primary and secondary ethers are known to exhibit abundant MH^+ ions, and they undergo elimination of alcohol affording relatively less abundant $[MH–ROH]^+$ ions [1]. For example, the MH^+ ion is the most abundant one (RA 100%) in the *i*-C_4H_{10}-CI mass spectrum of methoxycyclohexane, while the relative abundance of the $[MH–MeOH]^+$ ion is merely ∼20% [2]. On the other hand, tertiary ethers give

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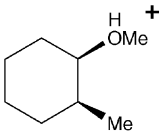
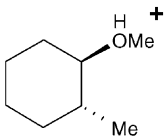
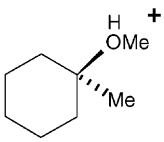
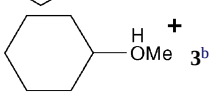
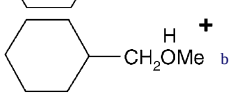
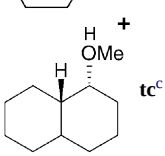
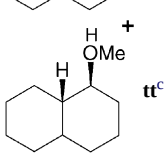
Table 1
Isobutane-CI mass spectral data of selected alicyclic methyl ethers

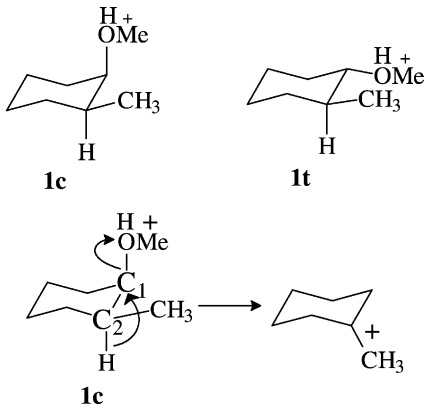
	RA (%) MH^+	RA (%) $[MH–ROH]^+$	$[MH–ROH]^+/MH^+$
 **1c**[a]	26	100	3.9
 **1t**[a]	100	59	0.6
 **2**[b]	0	100	≫100
 **3**[b]	100	21	0.2
 [b]	85	100	1.2
 **tc**[c]	7	100	14
 **tt**[c]	49	100	2

[a] Current study and Ref. [8].
[b] Ref. [2].
[c] Ref. [8].

rise to very abundant $[MH–ROH]^+$ ions, while MH^+ ions are often absent in their CI mass spectra [2] (see Table 1). This behavior results from the relatively high energy required for the cleavage of the RHO^+–C bond in protonated primary and secondary ethers in contrast to the tertiary analogs.

Primary and secondary carbocations are known to be unstable species. Consequently, it has been established that the elimination of H_2O and ROH from the MH^+ ions of primary and secondary alcohols and ethers affords rearranged tertiary product ions under CI conditions [3,4]. For example, the $C_6H_{11}^+$ ion obtained from cyclohexanol or other cyclohexyl derivatives, has been shown to have the stabilized tertiary methylcyclopentyl carbocation structure [3–7]. This rearrangement preceding the dissociation of the RHO^+–C bond lowers the energy of the elimination process.

In the course of our previous studies of the stereochemistry of organic gas phase ions, we have observed that the elimination of methanol from the MH^+ ion of *cis*-2-methyl-1-methoxycyclohexane **1c**



Scheme 1.

upon isobutane-CI is much more efficient than that of the *trans*-isomer **1t** [8,9]. The $[MH–MeOH]^+/MH^+$ ion abundance ratio of **1c** is ca. 6 times greater than that observed for **1t**. A similar stereospecific course has also been found in stereoisomeric 1-methoxydecalins (**tc** vs. **tt** see Table 1) [8] and in other systems. On the other hand, the elimination of methanol from protonated stereoisomeric 3- and 4-methyl-1-methoxycyclohexanes has been shown to be non-stereospecific [8].

The above behavior suggested a mechanistic pathway involving a hydride transfer in the course of the alcohol elimination from **1c**, leading to a stabilized tertiary $[MH–MeOH]^+$ ion which has the 1-methylcyclohexyl structure. The stereospecificity of this elimination is consistent with a concerted C–O bond cleavage and migration of the hydride from C2 to C1 (see Scheme 1). Such concerted migration is possible only in the *cis*-isomer **1c** with the antiperiplanar orientation of the H-atom and the protonated methoxy group. The proposed mechanism was supported by a considerable deuterium isotope effect detected in β-deuterium labeled *cis*-2,6,6-d_3-2-methyl-1-methoxycyclohexane, and by a collision-induced dissociation (CID) study of the structures of $[MH–ROH]^+$ ions obtained from *cis*- and *trans*-1,2-dialkoxycyclohexanes [8].

In the present work, the proposed mechanistic pathway of alcohol elimination assisted by a 1,2-hydride migration was explored both experimentally as well as by means of density functional computations.

2. Experimental

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.). The *cis*/*trans* pairs of **1c** and **1t** were measured under isothermal conditions. For the measurements of all other stereoisomers, the temperature was programmed from 60 to 200 °C at 5–10 °C/min. The scan rate was 1 scan/s.

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 50 eV collision energy (indicated).

3. Calculation details

The GAUSSIAN 98 series [10] of programs was used for all calculations. The geometries of all molecules were optimized using the hybrid B3LYP [11] density functional method [12] with the 6-31+G(d,p) basis set [10]. Vibrational frequencies were calculated at this level of theory for all stationary points, in order to differentiate them as minima or transition states. All the energies discussed in this work are at B3LYP/6-31+G(d,p)+ZPVE (zero-point vibration energies).

4. Results and discussion

Protonated *cis*- and *trans*-2-methyl-1-methoxycyclohexanes **1c** and **1t** were tested for the occurrence of 1,2-hydride shift. The stereoelectronic condition for hydrogen to migrate from the β- to the α-position

Table 2
Calculated[a] total energies, zero-point vibrational energies (ZPVEs) and relative energies of stationary points on possible pathways for the elimination of methanol from protonated alicyclic methyl ethers

Structure	Total energies (Hartrees)	ZPVE energies (kcal/mol)	Relative energies (kcal/mol)[b]
TRANS			
1t-ee	−390.07834	152.5	0.0
TS-2	−390.05071	148.7	13.6
Ion b	−274.29839	116.0	20.5[c]
Ion c	−390.06874	152.3	5.8
Ion e	−274.30162	115.9	16.0[c]
TS-3	−390.04550	147.0	15.2
Ion d	−274.31759	152.3	10.3[c]
6	−390.06981	151.3	4.2
CIS			
1c	−390.07703	152.5	0.9
TS-1	−390.05372	147.6	10.5
Ion a	−274.32313	116.1	8.5[c]
2	−390.08154	152.2	−2.3
CH_3OH	−115.73487	32.2	
Protonated methoxycyclohexane (**3**)	−350.75824	135.0	0.0
Cyclohexyl cation (**4**)	−234.97800	97.0	21.3[d]
1-Methylcyclopentyl cation (**5**)	−234.99798	96.5	9.6[d]

[a] At B3LYP/6-31+G(d,p).
[b] Including ZPVE.
[c] The energy of methanol is included.
[d] Relative to **3**.

in the course of alcohol elimination is fulfilled when the hydrogen and the leaving alkoxy group are antiperiplanar. *cis*-2-Methyl-1-methoxycyclohexane **1c** satisfies this condition, while in the *trans*-isomer **1t** the methyl group is antiperiplanar to the leaving protonated alkoxy group. The significantly different efficiencies of methanol elimination from the MH^+ ions of **1c** and **1t** (Table 1) suggest different mechanistic pathways for the two isomers.

The calculated energies of the species dealt with in this work are listed in Table 2, and the relative energies of species involved in the proposed pathways for the elimination of methanol from protonated ethers are shown in Fig. 1. Structural parameters of important stationary points on the potential energy surfaces are shown in Fig. 2.

The two possible pathways for the efficient elimination of methanol from protonated *cis*-2-methyl-1-methoxycyclohexane **1c** are shown in Scheme 2 and Fig. 1 (CIS): (a) the hydride transfer assisted mechanism via transition state **TS-1** leading directly to the $[MH–MeOH]^+$ methylcyclohexyl (**ion a**), and (b) a simple C–O bond cleavage (without an intermediacy of a transition state) followed by the rearrangement of the resulting unstable secondary 2-methylcyclohexyl (**ion b**) to the more stable (by 12.0 kcal/mol) tertiary 1-methylcyclohexyl cation (**ion a**) via a 1,2-hydride transfer.

The computed structures of all species involved in mechanistic pathways (a) and (b) are shown in Fig. 2a. The calculated bond lengths of the C1–O and C2–H bonds in protonated **1c** are 1.577 and 1.101 Å, respectively. As expected, protonation of the 2-methyl-1-methoxycyclohexanes causes a significant elongation (by 0.15 Å) of the C–O bond. In the transition state for the hydride assisted methanol elimination (**TS-1**), the C1–O and C2–H bonds are significantly elongated to 2.640 and 1.238 Å, respectively, and the new C1–H bond (1.465 Å) is

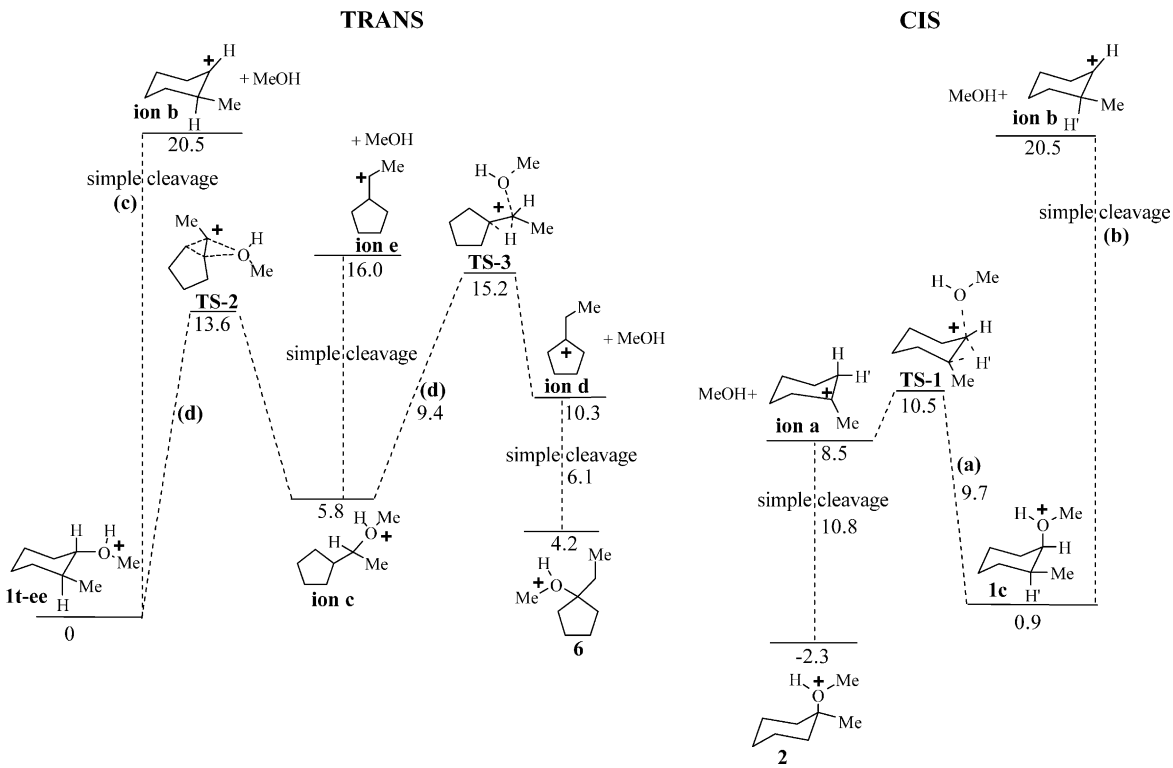
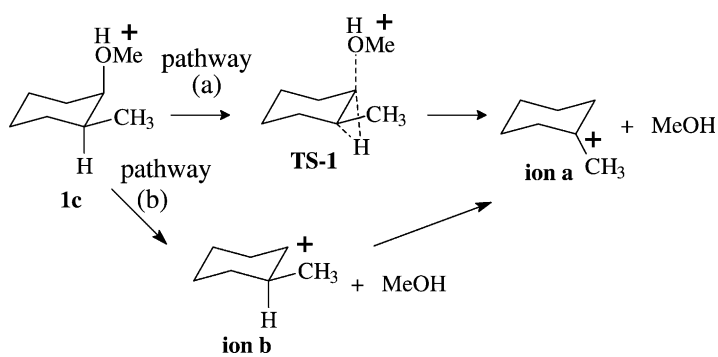


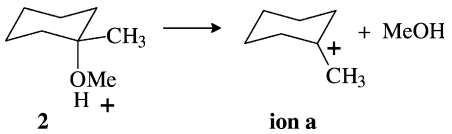
Fig. 1. Calculated (at B3LYP/6-31+G(d,p)//B3LYP/6-31+G(d,p)+ZPVE) energy profiles for possible pathways of methanol elimination from protonated stereoisomeric 2-methyl-1-methoxycyclohohexanes **1c** and **1t-ee** and 1-methyl-1-methoxycyclohexane **2** (energies in kcal/mol, relative to **1t-ee**).

partially formed. All these geometrical parameters point to a concerted but asynchronous mechanism in pathway (a).

The computed energy barrier for methanol elimination from protonated **1c** via pathway (a) is 9.6 kcal/mol. For comparison, the energy of methanol elimination from protonated 1-methyl-1-methoxy-cyclohexane, **2**, resulting in the same products (methanol and 1-methylcyclohexyl cation (**ion a**, Scheme 3)), was computed to be 10.8 kcal/mol (Table 2).



Scheme 2.



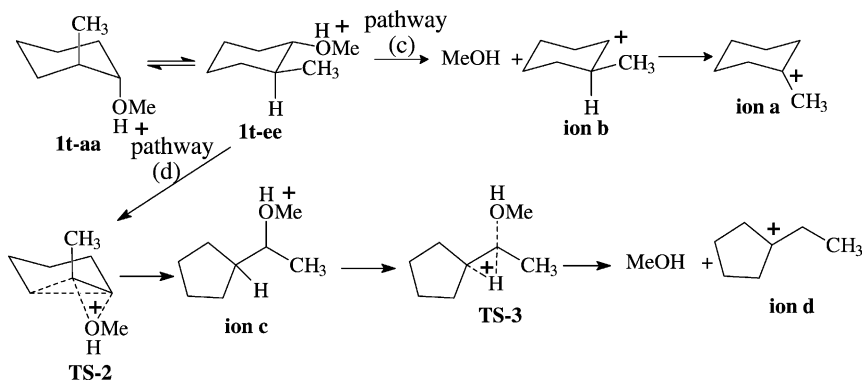
Scheme 3.

The calculated energy required for the elimination of methanol by a simple C–O bond cleavage from **1c** (pathway (b)) is 19.6 kcal/mol, 10 kcal/mol higher than that of pathway (a) (see footnote 1). This finding clearly supports a concerted one-step elimination of methanol from **1c** via pathway (a) in full agreement with the experimental evidence. The agostic participation of the 1,2-hydride shift in the elimination of methanol from **1c** is also supported by a measured isotope effect of 1.3.

Methanol elimination from protonated *trans*-2-methyl-1-methoxycyclohexane **1t** is less efficient than that from the *cis*-isomer **1c**, but considerably more efficient than that from methoxycyclohexane (Table 1). Two mechanistic pathways were explored for this process: a simple C–O bond cleavage followed by the rearrangement of the resulting unstable secondary 2-methylcyclohexyl cation (**ion b**) to the stabilized tertiary 1-methylcyclohexyl cation (**ion a**) via a 1,2-hydride transfer (pathway (c) in Scheme 4), and a stepwise skeletal rearrangement, via an intermediate **ion c** and two transition states **TS-2** and **TS-3**, leading to the stabilized tertiary ethylcyclopentyl cation (**ion d**) (pathway (d) in Scheme 4). The calculated energy profiles for these two pathways are shown in Fig. 1 (TRANS).

The initial step in pathway (c), namely simple cleavage of the C–O bond in protonated **1t**, requires 20.5 kcal/mol (see footnote 1). This value is similar to the computed energy of 21.3 kcal/mol for the C–O bond cleavage in protonated methoxycyclohexane, **3** producing an unstable cyclohexyl cation **4** and methanol (Scheme 5). Previous studies [3–7] suggested the occurrence of ring contraction in the course of this process, producing the methylcyclopentyl tertiary carbocation, **5**. According to our calculations, **5** is more stable than **4** by 11.7 kcal/mol (see Scheme 5), thus, lowering the energy required for alcohol elimination.

The calculated relative energies of the two transition states along pathway (d), **TS-2** and **TS-3**, are 13.6 and 15.2 kcal/mol above **1t-ee**, respectively, and the energy of the resulting ethylcyclopentyl **ion d** + methanol is 10.3 kcal/mol higher than that of **1t-ee**. The energy required for the simple cleavage, via pathway (c), forming the secondary cation **ion b** is 20.5 kcal/mol, by 5.3 kcal/mol higher than along pathway (d). **Ion b** collapses to the more stable tertiary **ion a** which is by 8.5 kcal/mol above **1t-ee**. The energy of the secondary cyclopentyl-1-ethyl cation, **ion e** (+ methanol), which results from a simple cleavage of methanol from **ion**



Scheme 4.

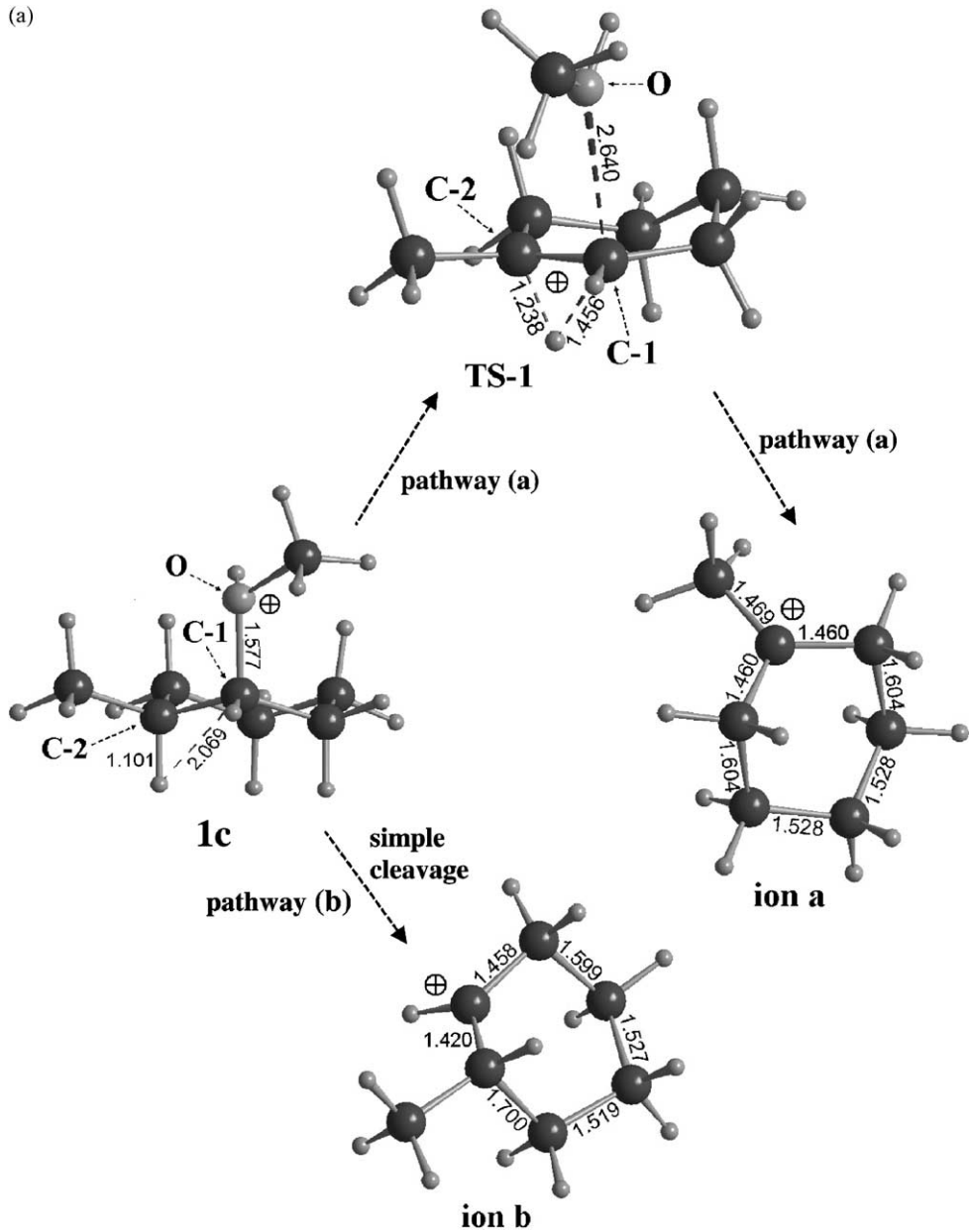


Fig. 2. Calculated (B3LYP/6-31+G(d,p)) bond lengths (in Å) of stationary points: (a) for the elimination of methanol from cation **1c** along pathways (a) and (b) shown in Scheme 2; (b) for the elimination of methanol from cation **1t-ee** along pathways (c) and (d) shown in Scheme 4.

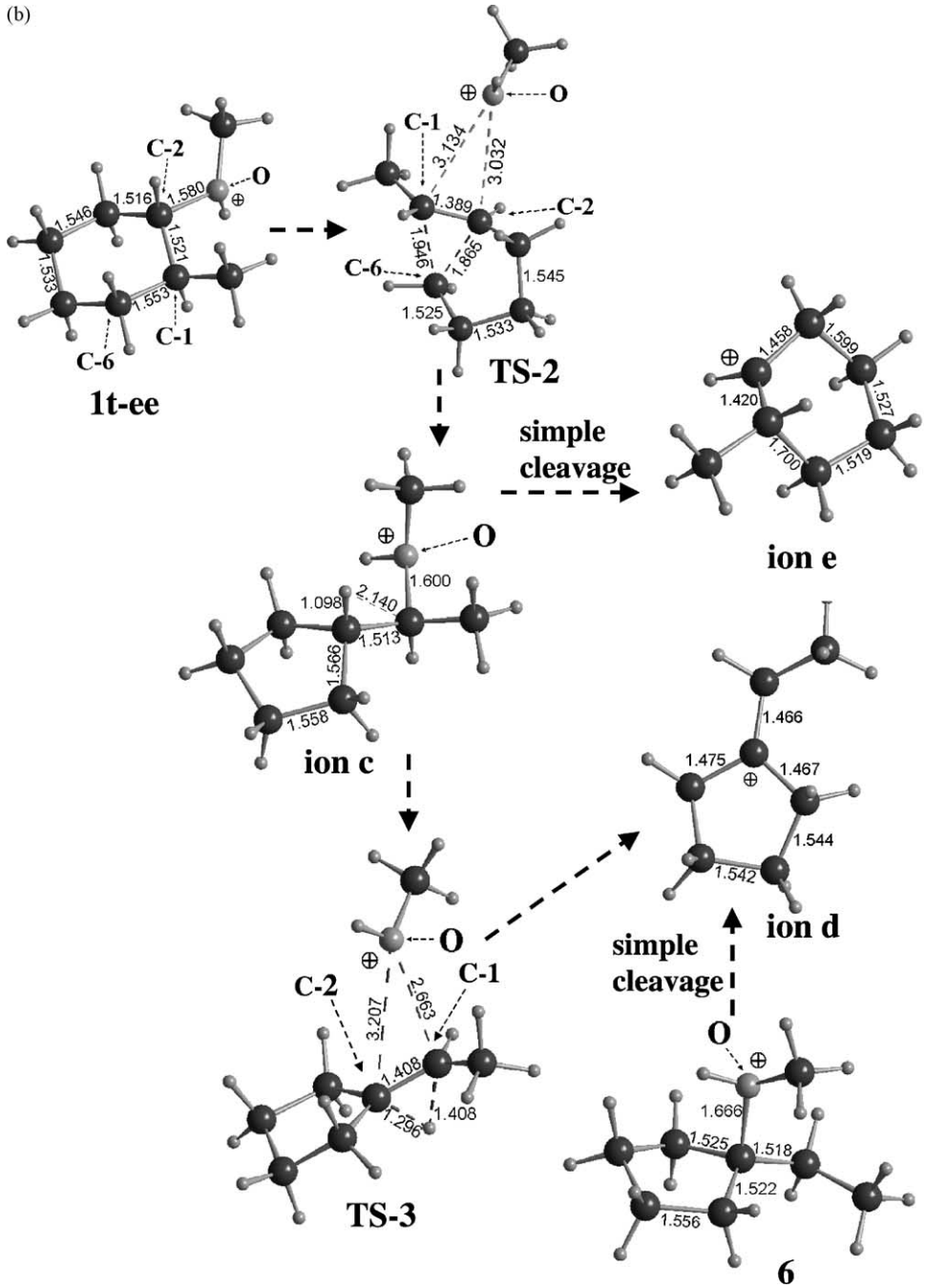
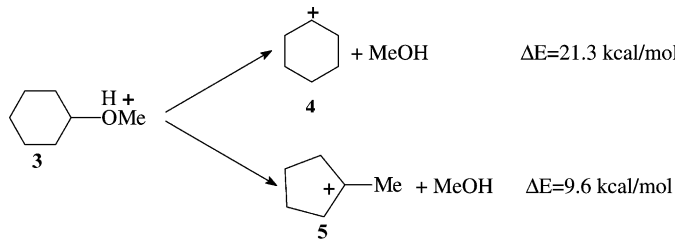


Fig. 2. (*Continued*).



Scheme 5.

c is by 16 kcal/mol higher in energy than **1t-ee**.[1] In contrast, a simple cleavage of methanol from the protonated 1-methoxy-1-ethyl cyclopentane, **6**, to yield **ion d** (Fig. 1 (TRANS)), requires only 6.1 kcal/mol. However, our attempts to locate a TS that leads in a one step reaction from **1t-ee** to **6** (i.e., involving a simultaneous ring contraction and a 1,2-hydrogen shift) have failed. Instead all these attempts led to the higher lying secondary **ion e**.

In conclusion, the calculations show clearly that the stepwise pathway (d) is energetically preferred over pathway (c) and over the path that involves a simple C–O cleavage in **ion c** but it is energetically *more demanding* than pathway (a) for methanol elimination from **1c**.

The computed geometries of the intermediate **ion c** and of the two transition structures **TS-2** and **TS-3** are shown in Fig. 2b and their total and relative energies are listed in Table 2. Interestingly, in **TS-3**, simultaneously with the dissociation of the methanol molecule from the secondary **ion c**, the α-hydrogen moves towards the secondary cationic center, forming a tertiary ion (**ion d**) which is by 5.7 kcal/mol more stable than the secondary **ion e**. Similarly to the structure of transition state for the elimination of methanol from **1c** (**TS-1**), also in **TS-3** the C1–O and C2–H bonds are significantly elongated to, i.e., to 2.663 and 1.296 Å, respectively, indicating also here a concerted but asynchronous rearrangement mechanism. The structure of **TS-2**, connecting **1t-ee** and **ion c** is also of interest, showing a concerted, almost synchronous migration of methanol from C2 to C1 and of C6 in the opposite direction from C1 to C2. The structure of **ion e** is interesting, having one long C–C bond of 1.72 Å in the 5-membered ring (Fig. 2b).

5. Conclusions

The computational study of alcohol elimination from acyclic protonated ethers support the previously proposed mechanism [8]. The transition state of alcohol elimination indicates that the C–O bond cleavage and the 1,2-hydride shift are concerted when the migrating β-H and the alkoxyl can achieve an antiperiplanar relationship like in the *cis*-ether **1c**. The elimination of alcohol from *trans*-substituted ethers having a tertiary β-hydrogen which is not antiperiplanar to the methoxy group, was found to proceed via a stepwise mechanism, that involves contraction of the cyclohexyl ring followed by a C–O cleavage that is assisted by a 1,2-hydride transfer. The computed barriers of the concerted methanol elimination process from the *cis*-isomer **1c** and the *trans*-isomer **1t-ee**, of 9.6 kcal/mol vs. 15.2 kcal/mol, respectively, provide a good explanation for the pronounced different efficiencies of these dissociations in the stereoisomeric ethers. The results of this study indicate the important role of the 1,2-hydride assistance and shifts in the mechanism of alcohol elimination from the MH^+ ions generated using isobutane-CI protonation,

[1] The endothermicity of the simple cleavage reactions leading to the elimination of methanol from **1c**, **1t-ee** and **ion c** is the lower energy limit for the C–O(H)CH_3 bond cleavage. In all cases, these energies are higher than the barriers for the competing pathways (Fig. 1), making the simple cleavage pathways less favorable. A variational transition state would further slow down the simple cleavage relative to the other pathways.

from primary and secondary ethers having a tertiary β-hydrogen.

Acknowledgements

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