Gas-phase intramolecular benzyl–benzyl interactions in protonated dibenzyl derivatives containing benzyl–oxygen, –sulfur and –nitrogen bonds

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Protonated molecules of a variety of benzyl diethers, diesters and ether-esters, produced by chemical ionization (CI), undergo a unique rearrangement yielding relatively abundant *m*/*z* 181 $C_{14}H_{13}^+$ ions, both in the ion source and under collision-induced dissociation (CID) conditions. This highly general rearrangement involves an intramolecular C–C bond formation between the two benzyl groups, and the resulting $C_{14}H_{13}^+$ ions have been shown by the analysis of their CID spectra to be an almost equimolar mixture of isomeric α-*o*-tolylbenzyl, α-*p*-tolylbenzyl and *p*-benzylbenzyl cation structures in all cases. This structural information suggests that this process may be viewed as gas-phase aromatic substitution of the non-charged benzoxy group by the benzyl cation originating from the protonated ether function involving a series of π- (and/or ion–neutral) and σ-complexes. The extent of this rearrangement process strongly depends on the nature of the benzyl bond heteroatoms. It is dramatically suppressed in the MH^+ ions of benzyl disulfides and absent in diamines, diamides and amino-amides. The different behaviour of the O-derivatives *vs*. S- and N-analogues is explained in terms of the energies of the benzyl–XH^+ bond heterolytic cleavages, which have been shown to increase in the order: O < S < N.

Introduction

The study of the rearrangements of organic cations in the gas phase has continued to be an active field of research for more than five decades.[1–4] These processes are not only of interest in gas-phase ion chemistry, but also play an important role in the application of mass spectrometry in the solution of structural problems.[5] While the appearance of rearrangement ions in mass spectra can provide considerable structural information when their formation is understood, it may lead to confusion when their origin is unclear. Meaningful correlations were often observed between the rearrangements of ionic species obtained under chemical ionization (CI) conditions and in solution.[6–8] The study of rearrangements of the gaseous protonated molecules (MH^+) can thus provide an important extension to our understanding of solution ion chemistry. Furthermore, the investigation of gas-phase reactions constitutes an invaluable tool for the study of structure–reactivity correlations, since the solvation effects are absent and the results are thus related to intrinsic reactivities.[9]

The most frequently occurring protonation sites of organic compounds are the lone-pair electrons of heteroatoms.[10] Therefore, the rearrangement processes of the ions under chemical ionization conditions usually involve heterolysis of the carbon–heteroatom bonds,[1–5] as shown in eqn. (1) (R is alkyl, X is

$$R\text{–}X^+H \longrightarrow R^+ + XH \qquad (1)$$

heteroatom-containing moiety). The propensity of these bonds to undergo heterolytic cleavage strongly influences the facility of the rearrangements in the protonated molecules.

Field has predicted that the extent of the R–XH^+ bond heterolysis under standard conditions (same reagent gas, same temperature, same residue R) should be approximately inversely proportional to the proton affinity of the neutral HX molecules.[11] The critical energy in the reverse reaction of eqn. (1) was shown to be negligible at least in some cases.[12] Thus, the leaving abilities of the heteroatom-containing molecules are expected to be dependent on their proton affinities. A variety of work has been reported on the examination of the validity of this qualitative prediction. It has been shown that the gas-phase affinities of many neutral species towards cyclohexyl, *n*-butyl, methoxymethyl and other cations are indeed proportional to their basicities.[13–19] On the other hand, it has been demonstrated that the rule can be misleading in some cases. Thus the affinities of morpholine, thiomorpholine and 1,4-thioxane towards methyl/ethyl cations follow the nucleophilicity scale (S > N > O) rather than proton affinities (N > S > O).[20]

We have recently reported a novel highly efficient rearrangement process occurring in a large number of gas-phase protonated benzyl diesters and diethers under isobutane-CI and CID conditions.[21,22] This rearrangement involves an intramolecular C–C bond formation between the two benzyl groups giving rise to abundant *m*/*z* 181 $C_{14}H_{13}^+$ ions. A CID study of the $C_{14}H_{13}^+$ ions has shown that they are an almost equimolar mixture of isomeric α-*o*-tolylbenzyl, α-*p*-tolylbenzyl and *p*-benzylbenzyl cation structures in all cases. The proposed mechanistic pathway for this rearrangement process is shown in Scheme 1.

The initial step in this pathway is the cleavage of the benzylic C–O bond of the protonated ether or ester function to form an ion–neutral complex, followed by the formation of a π-complex of the benzyl cation with the other benzyl group. The next step is the generation of two σ-complexes with *ortho* and *para* oriented benzyl substituents, followed by a proton transfer from the benzenium moieties to the adjacent oxygen atom and heterolytic fission of the second benzyl–oxygen bond.[21–23] This multi-step mechanism occurring in gas-phase ions is analogous to aromatic electrophilic substitution chemistry in the condensed phase.

In the present work we have explored the question of whether an analogous rearrangement occurs in protonated molecules of benzyl disulfides, diamines, amino-amides and diamides. The formation of the $C_{14}H_{13}^+$ ions *via* benzyl–benzyl interaction from the MH^+ ions of these dibenzyl derivatives should involve heterolysis of the benzyl C–SH^+ and C–NH_2^+ bonds. The energies of the heterolytic cleavages of the C–SH^+ and C–NH_2^+ bonds are expected to be higher than that of C–OH^+. It is,

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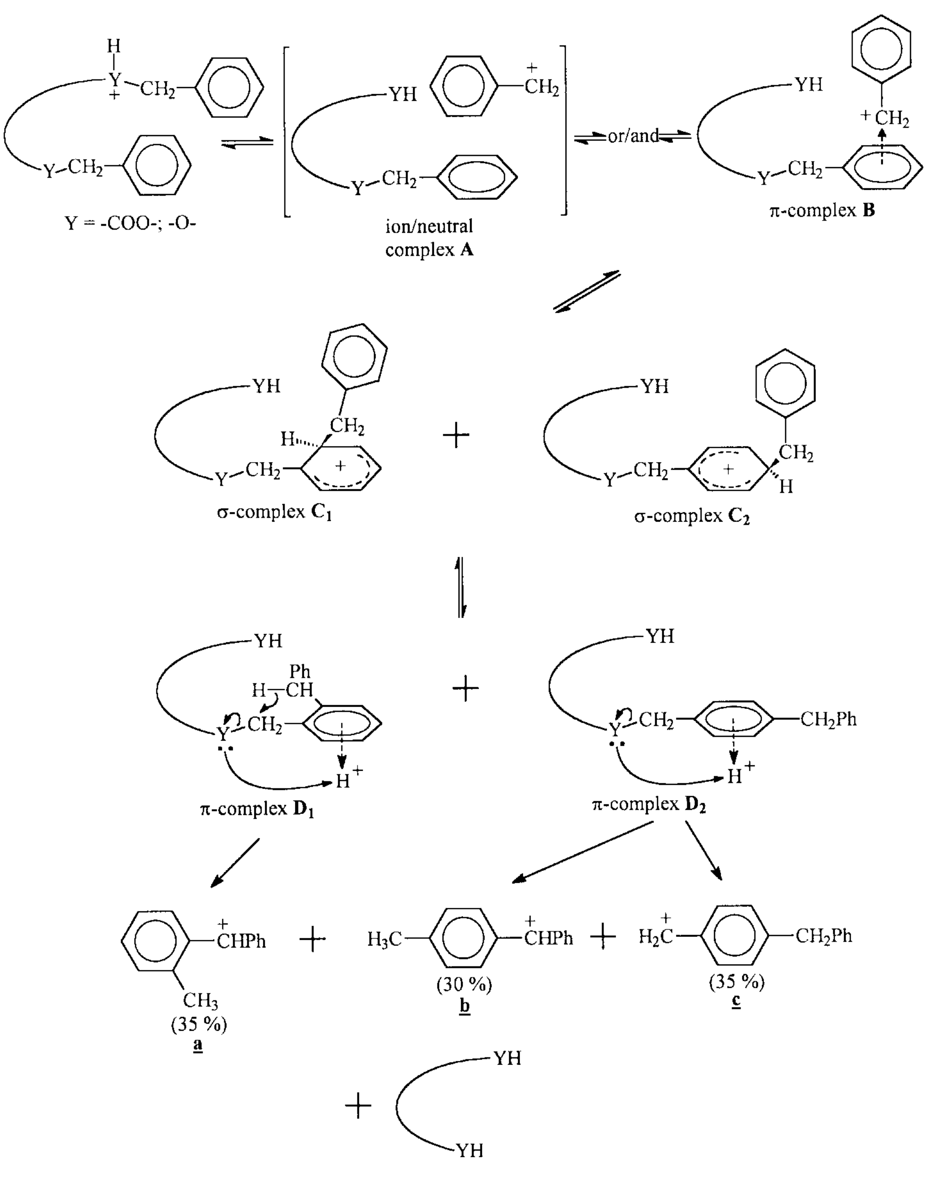
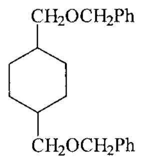


Scheme 1

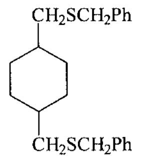
however, difficult to predict the relative efficiencies of the multistep rearrangement process in the above classes of compounds. Moreover, the comparison of the efficiencies of the rearrangement in the dibenzyl derivatives containing C–SH$^+$ and C–NH$^+$ benzyl bonds is of particular interest. The study of this aspect may be a useful test of the validity of Field's prediction for these bond cleavages.

Results and discussion

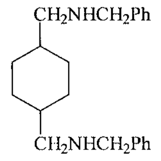
The series of dibenzyl derivatives **1**–**7** has been chosen for the study. The isobutane-CI mass spectral data of the compounds are summarized in Table 1. The results reveal a great difference in the behaviour of the O-derivatives as compared with the S- and N-analogues: while the protonated dibenzyl derivatives of the stereoisomeric diethers **1**, ether-esters **6** and diesters **7** give rise to the most abundant *m*/*z* 181 $C_{14}H_{13}^+$ ions, these ions are of extremely low abundance in the CI-mass spectra of the benzyl dithioethers **2**, and absent in those of the protonated diamines **3**, amino-amides **4** and diamides **5**. The *m*/*z* 181 $C_{14}H_{13}^+$ ions were not formed from the MH$^+$ ions of **3**–**5** even upon methane chemical ionization conditions.[24] A similar distinctive behaviour of the protonated dibenzyl derivatives is observed under collision-induced dissociation conditions, as shown in Table 2 and Scheme 2.



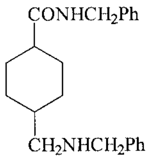
cis; *trans*
1



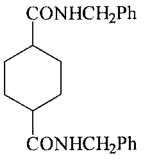
cis; *trans*
2



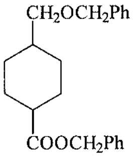
cis; *trans*
3



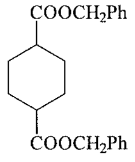
cis; *trans*
4



cis; *trans*
5



cis; *trans*
6



cis; *trans*
7

As mentioned in the Introduction, we have previously shown that the $C_{14}H_{13}^+$ ions produced by the rearrangement process from a variety of benzyl diesters and diethers are an almost equimolar mixture of α-*o*-tolylbenzyl, α-*p*-tolylbenzyl and *p*-benzylbenzyl cations **a**, **b** and **c** (bottom of Scheme 1).[21,22] The close similarity of the CID mass spectra of the *m*/*z* 181 $C_{14}H_{13}^+$ ions obtained from **1**, **6** and **7** (Fig. 1) indicates that their structures are identical and that they are formed by a common

Table 1 Selected isobutane-CI mass spectral data[a] (relative abundances,%) of the dibenzyl derivatives **1**–**7**

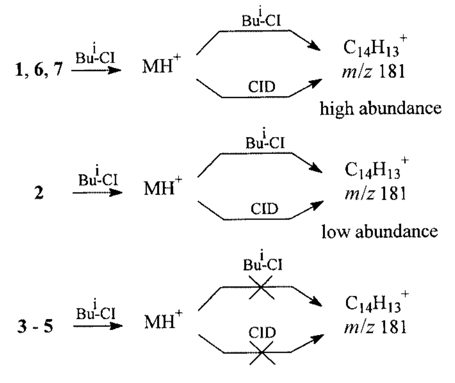
	Ion						
Compound	Y	MH^+	$C_{14}H_{13}^+$ *m*/*z* 181	$C_7H_7^+$ *m*/*z* 91	$[MH - C_{14}H_{12}]^+$	$[MH - BnXH]^+$ X = O, S or NH	$[MH - BnXBn]^+$ X = O,[b] S or NH
cis-**1**	O	27	100	4	7	2	12
trans-**1**	O	9	100	5	—	—	8
cis-**6**	O	43	100	4	9	5	20
trans-**6**	O	21	100	7	9	2	11
cis-**7**	O	56	100	5	5	7	28
trans-**7**	O	11	100	4	9	—	6
cis-**2**	S	100	0.1	1	—	1	—
trans-**2**	S	100	0.1	1	—	1	—
3(*cis*;*trans*)[c]	NH	100	—	0.2	—	0.1	—
4(*cis*;*trans*)[c]	NH	100	—	0.1	—	0.1	—
5(*cis*;*trans*)[c]	NH	100	—	0.1	—	1	—

[a] The data are the average of at least three separate runs. [b] The *m*/*z* values of the $[MH - BnOBn]^+$ fragment ions coincide with those of the possible $[MH - C_{14}H_{12} - H_2O]^+$ fragments. [c] The data are given for mixtures of the *cis*- and *trans*-epimers.

Table 2 The abundances[a] of the $C_{14}H_{13}^+$ ions in the CID mass spectra[b] of the protonated dibenzyl derivatives **1**–**7** obtained upon Bu^i-CI

Compound	$\%\Sigma C_{14}H_{13}^+$
cis-**1**	69.2
trans-**1**	44.1
cis-**2**	9.5
trans-**2**	6.2
cis-**6**	53.4
trans-**6**	64.1
cis-**7**	57.5
trans-**7**	66.4
3(*cis*;*trans*)	—
4(*cis*;*trans*)	—
5(*cis*;*trans*)	—

[a] The ion abundances are listed as percentages of the total product ion current (%Σ). [b] 30 eV collision energy.



Scheme 2

mechanistic pathway shown in Scheme 1. We had difficulties in obtaining reliable CID mass spectra of the extremely low abundance *m*/*z* 181 $C_{14}H_{13}^+$ ions from the protonated benzyl dithioethers **2**. We assume these ions are also formed by the mechanistic route proposed in Scheme 1.

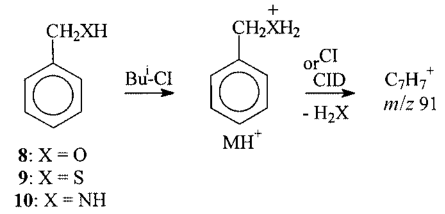
The distinctive extents of the formation of the *m*/*z* 181 $C_{14}H_{13}^+$ ions from the protonated dibenzyl derivatives **1**–**7** (Tables 1 and 2) result from different rates of the rearrangement in these compounds. On the basis of the mechanistic pathway of the rearrangement process proposed in Scheme 1, it is reasonable to assume that this distinctive behaviour results from the different facilities of the benzyl C–XH$^+$ heterolytic bond cleavages, which appear to decrease in the order O > S > N. The energies of the benzyl–XH$^+$ heterolytic bond fissions in the examined series of protonated dibenzyl derivatives **1**–**7** should be mainly governed by the affinities of the heteroatom-containing moieties for benzyl cations.[5,10,26,27]

Table 3 Isobutane-CI mass spectral data of $PhCH_2XH$ **8**–**10** (X = O, S and NH) with the respective proton affinities[25] of H_2X molecules

$PhCH_2XH$	$C_7H_7^+/MH^+$	Proton affinity of H_2X/kcal mol^{-1}[d]
X = O[a]	76	166.5
X = S[b]	3	170.2
X = NH[c]	0.1	204.0

[a] Additional fragment ions in the CI mass spectrum (the abundances are expressed relative to the base peak): $C_6H_7^+$ (1%), $[M - H]^+$ (3%). [b] $[M - H]^+$ (1%). [c] $[M - H]^+$ (3%). [d] 1 cal = 4.184 J.

In order to explore the relative affinities of the heteroatoms for the benzyl cation the relative extent of the *m*/*z* 91 $C_7H_7^+$ ion formation has been measured in the corresponding protonated monobenzyl derivatives, benzyl alcohol **8**, benzyl mercaptan **9** and benzylamine **10** (Scheme 3). The isobutane chemical ionization and collision induced dissociation mass spectral data of **8**–**10** are presented in Table 3. These results show that the propensity of the monobenzyl derivatives to lose the H_2X (X = heteroatom) molecules is inversely related to the proton affinity of the neutrals (Table 3 lists the proton affinities of the respective H_2X molecules).



Scheme 3

An energy-resolved CID study[28] of the protonated derivatives **1**–**3** has been performed in order to get a better insight into the different behaviour of the dibenzyl derivatives with benzyl–oxygen, –sulfur and –nitrogen bonds. The results of these measurements are presented in Figs. 2 and 3 in the form of breakdown graphs expressing the efficiencies of the fragmentation pathways of the protonated dibenzyl derivatives as a function of the collision energy. These results indicate that the rearrangement process leading to the formation of the *m*/*z* 181 $C_{14}H_{13}^+$ ions represents the major fragmentation channel of the protonated diethers **1** at all the applied collision energies. On the other hand, the data demonstrate that the rearrangement of the protonated benzyl disulfides **2** is relatively slow over the

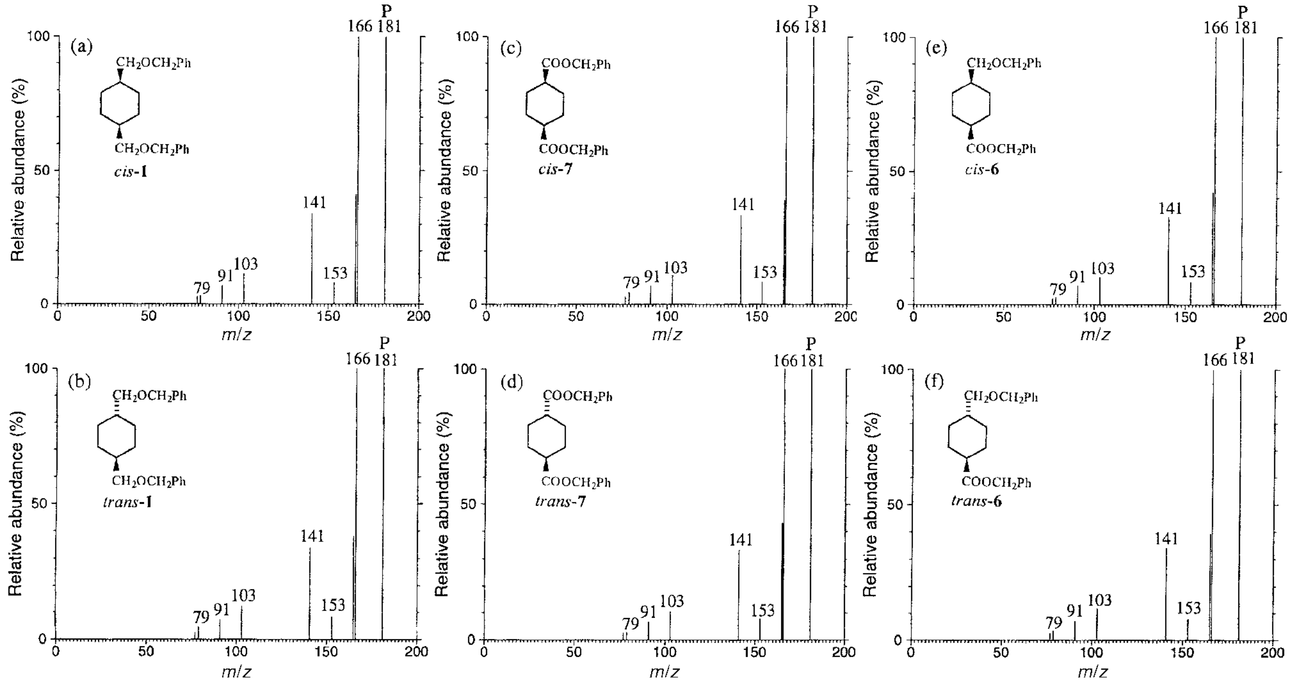


Fig. 1 CID spectra (50 eV collision energy, the relative ion abundances normalized to the most abundant product ion) of the *m/z* 181 ions obtained upon isobutane-CI from diethers **1** and ether-esters **6**: (a) *cis*-**1**; (b) *trans*-**1**; (c) *cis*-**7**; (d) *trans*-**7**; (e) *cis*-**6**; (f) *trans*-**6**.

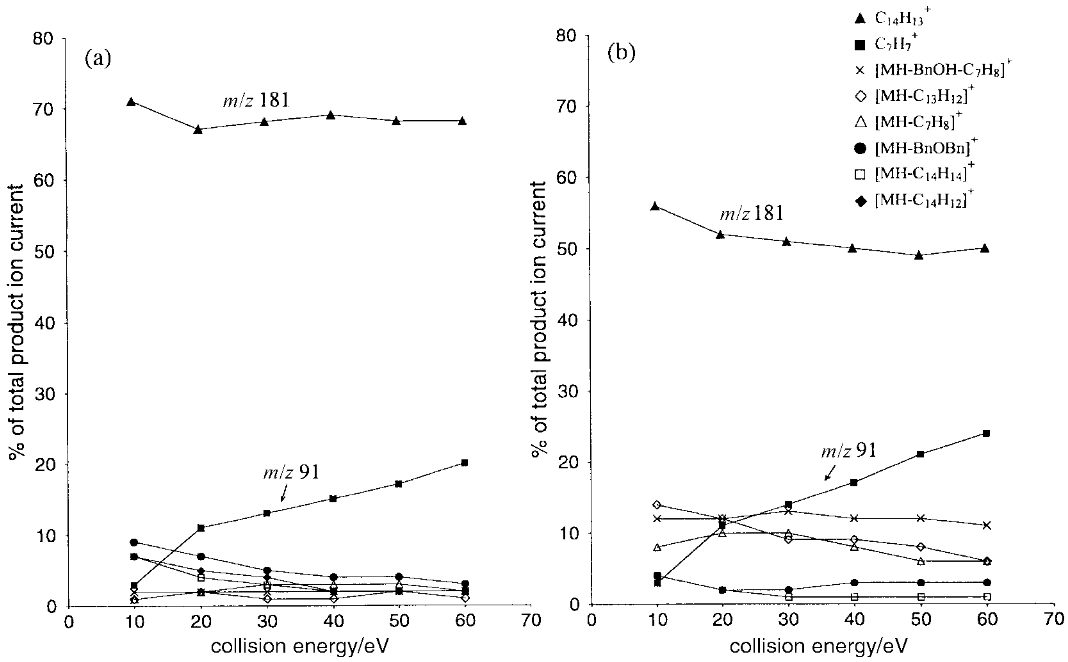


Fig. 2 Breakdown graphs for protonated (a) *cis*- and (b) *trans*-1,4-bis(benzyloxymethyl)cyclohexanes (*cis*-**1** and *trans*-**1**).

whole range of collision energies, and is not observed in the CID spectra of the MH^+ ions of diamines **3** even at 60 eV.

The results of the energy-resolved CID measurements (ERMS) show opposite trends in the energy dependence of the formation of the *m/z* 91 $C_7H_7^+$ and *m/z* 181 $C_{14}H_{13}^+$ ions from the diethers and disulfides. The abundances of the *m/z* 181 $C_{14}H_{13}^+$ ions decrease in the CID spectra of **1** but increase in those of **2** with the increase in the collision energy (see Figs. 2 and 3). In contrast, the abundance of the *m/z* 91 $C_7H_7^+$ product ion increases with the increase of the collision energies for the dibenzyl diethers **1**, but decreases for the disulfides **2**. It is well established that at low internal energies the relative rates of competing processes are determined by the relative activation energies.[5,29,30] From the results of the ERMS measurements it can be concluded that the simple benzyl bond cleavage affording the *m/z* 91 $C_7H_7^+$ ion rearrangement process of the C–O-containing derivatives has a higher critical energy than the rearrangement process leading to the *m/z* 181 ion formation, while the energy barrier for the latter process in the species with benzyl–S bonds is considerably higher than that of the former one. The absence of the *m/z* 181 ions in diamines **3** suggests that the energy barriers of the rearrangement in these benzyl derivatives are even higher (see Fig. 3c).

It should be noted that the decrease in the abundance of the *m/z* 181 ion and the increase of the *m/z* 91 ion at higher collision energies (Fig. 2) indicate different dependencies of the rate constants of these two processes on the internal energy of the dissociating diethers **1** (different *k versus E* curves).[5,30a] The increase of the rate constant of the simple bond cleavage with the internal energy is considerably steeper than that of the multi-step rearrangement, which is consistent with the expected

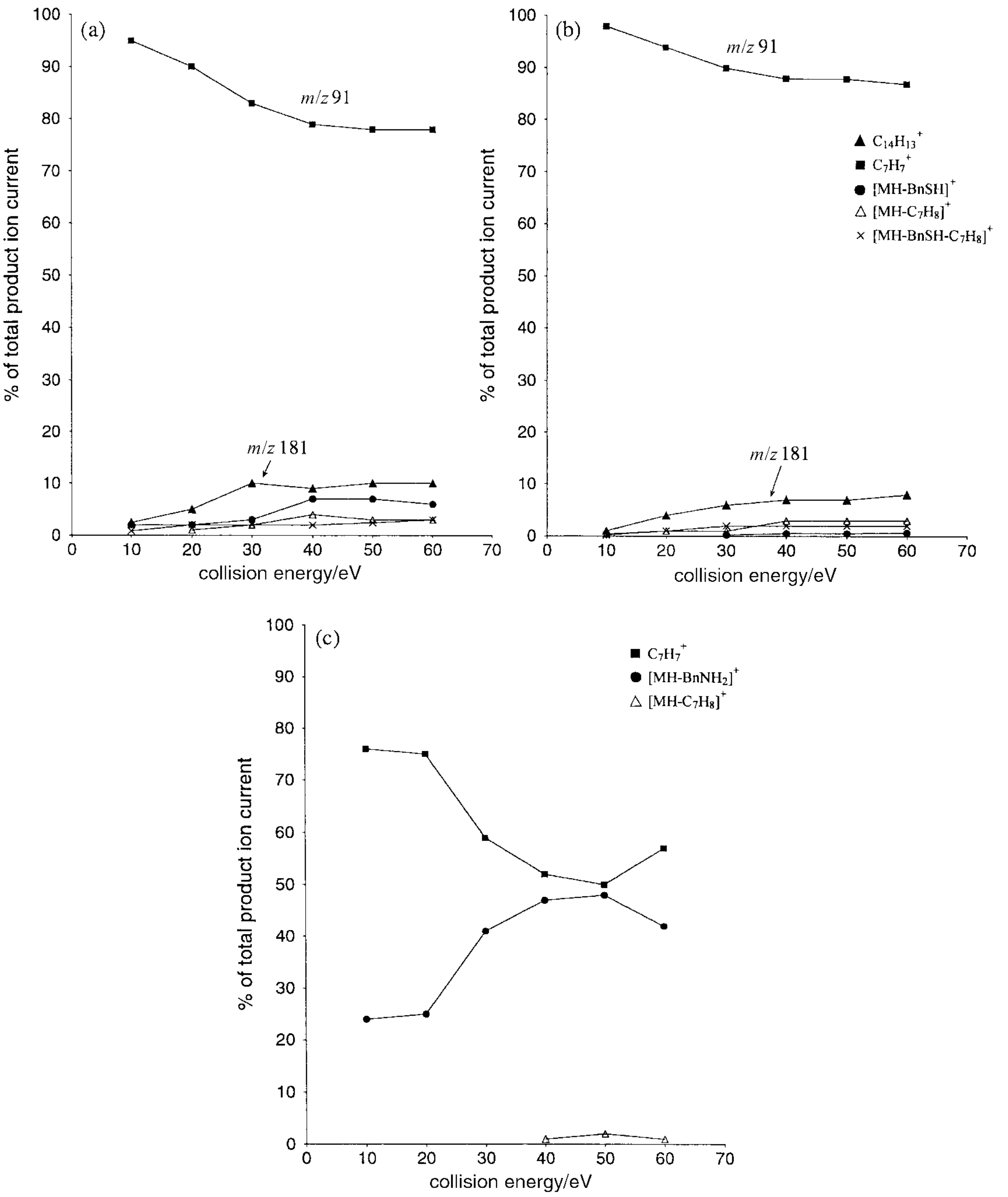


Fig. 3 Breakdown graphs for protonated (a) *cis*- and (b) *trans*-1,4-bis(benzylthiomethyl)cyclohexanes (*cis*-**2** and *trans*-**2**); (c) 1,4-bis(benzylaminomethyl)cyclohexanes **3** (mixture of *cis*- and *trans*-isomers).

entropy requirements of the latter process (tight activated complexes in each rearrangement step).

Partial potential energy surfaces of the competing decomposition processes resulting in the *m/z* 181 $C_{14}H_{13}^+$ and *m/z* 91 $C_7H_7^+$ ions have been constructed for the *trans*-isomers of **1**, **2** and **3** to get a more detailed insight into the origin of the different behaviour of these materials (Fig. 4). The enthalpies of formation of the starting materials, σ-complexes, π-complexes and the products were calculated by the AM1 semi-empirical method.[31] Transition state energies were not computed, and therefore are not included in these profiles. The ion–neutral complexes of the benzyl cation and the neutral monobenzyl derivatives (complexes **A** in Scheme 1) were also omitted.

The computations suggest small differences (*ca.* 1 kcal mol^{-1}) (1 cal = 4.184 J) between the enthalpies of formation of the isomeric σ-complexes $\mathbf{C_1}$ and $\mathbf{C_2}$ in the three systems *trans*-**1**, -**2** and -**3**. Considerably larger differences have been found between the ΔH_f values of the following π-complexes $\mathbf{D_1}$ and $\mathbf{D_2}$ (4–7 kcal mol^{-1}). Even more pronounced differences have been obtained between the three product ions **a**, **b** and **c** (up to 14 kcal mol^{-1}).

The computations show that the rearrangement process of *trans*-1,4-bis(benzyloxymethyl)cyclohexane (*trans*-**1**) is exothermic for the three product ions **a**, **b**, and **c** (by *ca.* 11, 17 and 3 kcal mol^{-1}, respectively), while that of *trans*-1,4-bis(benzylthiomethyl)cyclohexane (*trans*-**2**) is endothermic (by *ca.* 28, 23 and 37 kcal mol^{-1}), and the enthalpy of the hypothetical rearrangement from the MH^+ ion of *trans*-1,4-bis(benzylaminomethyl)cyclohexane (*trans*-**3**) is also positive (*ca.* 29, 23 and 37 kcal mol^{-1}). The calculated enthalpies of formation of the π-complexes of type **B** (see Scheme 1) are highest in each of the rearrangement reaction profiles (see Fig. 4). These results suggest that genesis of the π-complex **B**, involving benzyl–heteroatom bond cleavage, is the rate determining step in the generation of the *m/z* 181 $C_{14}H_{13}^+$ ions from the protonated dibenzyl derivatives. The calculations show that the π-complexes **B** obtained from *trans*-**2** and *trans*-**3** are much higher in energy than MH^+ ions of the analogous complex of the diether

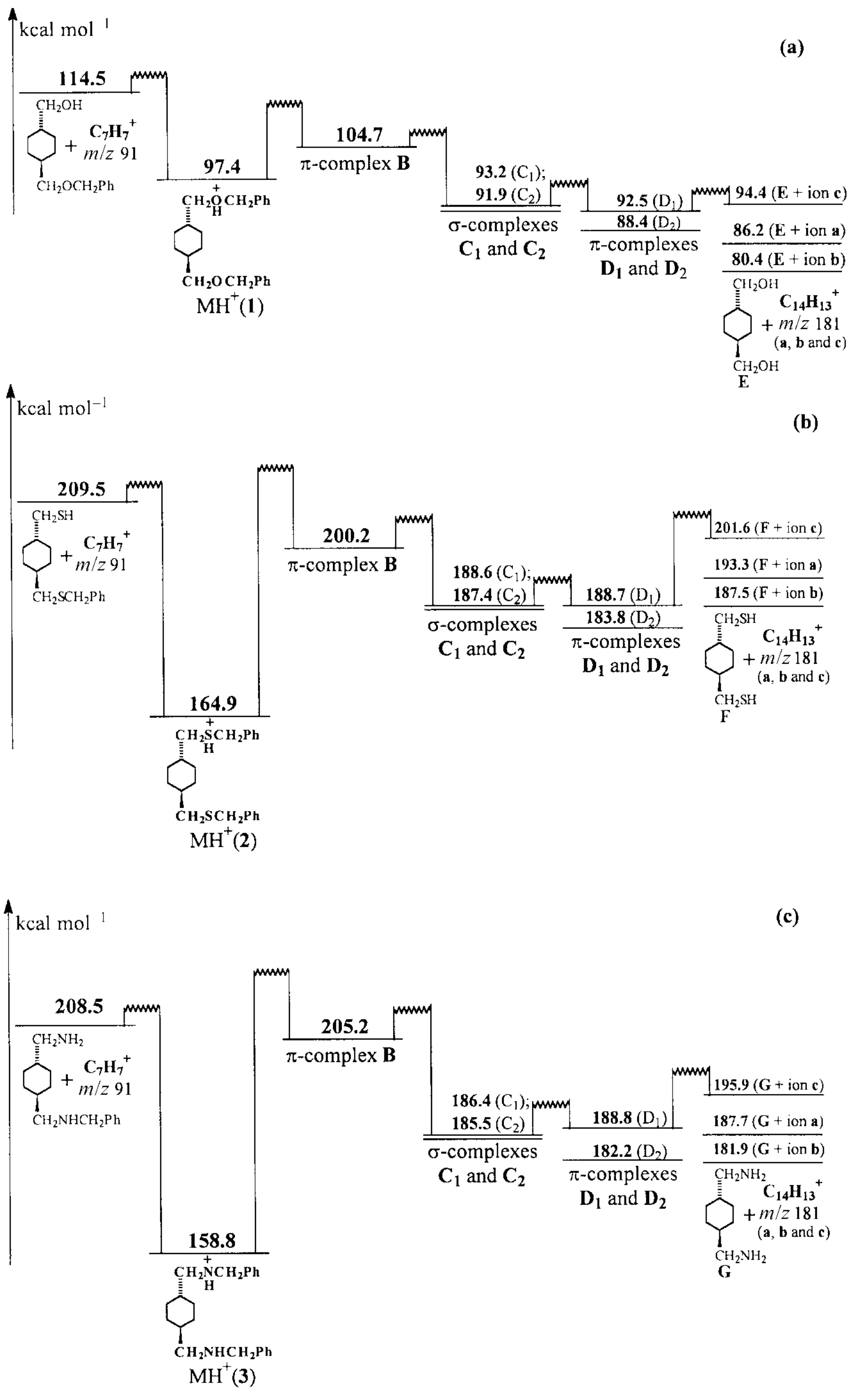


Fig. 4 Schematic potential energy surfaces for the reactions of formation of gas-phase *m*/*z* 181 $C_{14}H_{13}^+$ and *m*/*z* 91 $C_7H_7^+$ ions from protonated (a) *trans*-1,4-bis(benzyloxymethyl)cyclohexane (*trans*-**1**); (b) *trans*-1,4-bis(benzylthiomethyl)cyclohexane (*trans*-**2**); (c) *trans*-1,4-bis(benzylaminomethyl)cyclohexane (*trans*-**3**).

trans-**1**. Thus the computations corroborate our interpretation of the experimental data in terms of the relative efficiency of the intramolecular benzyl–benzyl interactions of the protonated dibenzyl derivatives.

Comparison of the enthalpies of formation of the π-complexes **B** and of the *m*/*z* 91 $C_7H_7^+$ ion obtained from the protonated derivatives *trans*-**1**–**3** (Fig. 4) suggests that in all three cases the generation of the *m*/*z* 181 $C_{14}H_{13}^+$ ions by rearrangement is expected to be more favourable than the formation of the *m*/*z* 91 $C_7H_7^+$ ions by simple cleavage reactions. This is in good agreement with the experimental data for *trans*-1,4-bis(benzyloxymethyl)cyclohexane **1** (see Table 1 and Fig. 2). However, the experiment shows that the formation of the benzyl cation is favoured as compared with the rearrangement process in the CI and CID mass spectra of the disulfide *trans*-**2** and the diamine *trans*-**3** (see Table 1 and Fig. 3). This behaviour suggests higher barrier energies for the rearrangement process relative to the *m*/*z* 91 $C_7H_7^+$ ion formation in derivatives **2** and **3**. The results of the energy-resolved CID measurements of compounds **2** and **3** (the increase in the abundance of the $C_7H_7^+$ ion with the decrease in the collision energy, see Fig. 3) are consistent with the latter interpretation.

Conclusions

We have shown in this work that the rearrangement of the gas-phase protonated dibenzyl derivatives resulting in the *m*/*z* 181 $C_{14}H_{13}^+$ ion formation depends dramatically on the nature of the heteroatoms connected to the benzyl moieties. While this process is highly efficient in the protonated benzyl diesters, diethers and ether-esters, it is strongly suppressed in the MH^+ ions of benzyl disulfides, and absent in those of benzyl diamines, diamides and amino-amides. We have explained this phenomenon on the basis of the different propensities of the protonated dibenzyl derivatives towards the benzyl bond heterolytic cleavages. Chemical ionization and collision-induced dissociation studies of protonated monobenzyl derivatives have demonstrated that the facility of the benzyl–heteroatom bond heterolysis follows the order: O > S > N. It should be noted that the results indicate that Field's predictions[11] hold for the heterolytic fissions of the gas-phase benzyl bonds. To the best of our knowledge, this is the first evidence of Field's Rule's validity for the cleavage of this type of chemical bond.

The energy-resolved collision induced dissociation study of the protonated diethers, disulfides and diamines has given an idea about relative energy requirements of the rearrangement in the dibenzyl derivatives with carbon–oxygen, –sulfur and –nitrogen benzyl bonds. It has been shown that the onset energies of the intramolecular benzyl–benzyl interactions in the derivatives with carbon–nitrogen benzyl bonds are significantly higher than those of the rearrangement in the benzyl disulfides and benzyl diethers. Besides, it has been observed that the rearrangement process of the benzyloxy-containing dibenzyl derivatives has lower onset energies than the simple benzyl bond cleavage, and the *m*/*z* 181 $C_{14}H_{13}^+$ ion formation from the benzyl disulfides has more significant barriers than the C–S benzyl bond cleavage.

It should be finally pointed out that the striking dependence of the efficiency of the rearrangement of the protonated dibenzyl derivatives on the nature of the benzyl bond heteroatoms not only provides an insight into the details of the mechanistic pathway of this process, but also offers information that may be important in the application of mass spectrometry to the solution of structural problems in organic chemistry.

Experimental

Mass spectrometry

The gas chromatographic–chemical ionization mass spectrometric analysis (CI-GC-MS) and CID measurements were carried out on a Finnigan TSQ-70B triple-stage quadrupole mass spectrometer. The compounds **1**–**6** were introduced as mixtures of the *cis*- and *trans*-stereoisomers. The epimeric pairs of **1**, **2** and **6** were separated on the capillary column DB-5 (0.25 µm film thickness, 30 m × 0.25 mm id capillary column, the temperature was programmed from 60 to 280 °C at 20 °C min^{-1}). The scan rate was 1 scan s^{-1}. The elution sequence for the stereoisomers in the GC–MS analyses was as follows: *cis*-**1** followed by *trans*-**1**, *cis*-**2** by *trans*-**2** and *cis*-**6** by *trans*-**6**. CI measurements were performed at 150 °C ion source temperature and 0.4 Torr (indicated) reagent gas (isobutane, methane). CID measurements were performed with argon as the target gas (0.3 mTorr, indicated) at 10–60 eV collision energies (indicated). All the data presented in each table and those of Figs. 1–3 were obtained on the same day under identical experimental conditions, in order to ensure reliable comparisons.

Materials

Commercial benzyl alcohol **8**, benzyl mercaptan **9** and benzylamine **10** were used.

1,4-Bis(benzyloxymethyl)cyclohexane **1** (mixture of *cis*-**1** and *trans*-**1**) was synthesized from *cis*- and *trans*-cyclohexane-1,4-dimethanol and benzyl bromide by a previously reported procedure.[22]

1,4-Bis(benzylthiomethyl)cyclohexane **2** (mixture of *cis*- and *trans*-isomers): thionyl chloride (2 ml, 0.028 mol) was added dropwise to a vigorously stirred mixture of *cis*- and *trans*-cyclohexane-1,4-dimethanol (0.5 g, 3.5 mmol) and pyridine (0.05 ml) at such a rate that the temperature remained at 5–10 °C. When the addition was completed, the ice bath was removed and the mixture was kept overnight at 70 °C and then at reflux for 3 h. Thionyl chloride was evaporated *in vacuo*. The residue was poured into water and the aqueous solution was extracted with diethyl ether. The ethereal extract was washed with 10% sodium hydrogen carbonate solution and water, dried with magnesium sulfate, and concentrated to afford *cis*- and *trans*-cyclohexane-1,4-dimethyl chloride (92%). The obtained dichloride (0.58 g, 3.2 mmol), in dry ether (2 ml), was added dropwise to magnesium turnings (0.19 g, 8 mmol) and absolute ether (15 ml), and the mixture was refluxed gently until only a small residue of unreacted magnesium remained. Then the solution was cooled and finely powdered sulfur was added (0.26 g, 8 mmol). The reaction mixture was refluxed for 1 h, cooled in an ice bath and treated with drops of benzyl bromide (1.54 g, 9 mmol). After refluxing for 12 h the cooled solution was vigorously stirred with aqueous ammonium chloride, the organic layer separated, and the aqueous phase was extracted with diethyl ether. The combined organic phase was washed with 10% aqueous $NaHCO_3$, water, dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure to afford *cis*- and *trans*-1,4-bis(benzylthiomethyl)cyclohexane **2** (yield 53%).

1,4-Bis(benzylcarbamoyl)cyclohexane **5** (mixture of *cis*-**5** and *trans*-**5**) was synthesized from epimeric cyclohexane-1,4-dicarboxylic acid dichlorides and benzylamine.[32] The diacid chlorides were obtained by reaction of *cis*- and *trans*-cyclohexane-1,4-dicarboxylic acid with thionyl chloride.[33]

cis- and *trans*-1,4-bis(benzylaminomethyl)cyclohexanes **3** and 1-(benzylaminomethyl)-4-(benzylcarbamoyl)cyclohexane **4** (mixture of *cis*- and *trans*-epimers) were prepared by lithium aluminum hydride reduction[34] (complete or partial) of diamide **5**.

1-(Benzyloxymethyl)-4-(benzyloxycarbonyl)cyclohexane **6** (mixture of *cis*-**6** and *trans*-**6**) was synthesized by partial etherification of *cis*- and *trans*-cyclohexane-1,4-dimethanol (by benzyl chloride and 50% aqueous sodium hydroxide solution)[35] to yield the corresponding benzyl monoether, subsequent oxidation of the hydroxymethyl group with pyridinium dichromate[36] to afford 4-(benzyloxymethyl)cyclohexanecarboxylic acid and benzylation of the carboxylic group (see preparation of the diesters **7**).

cis- and *trans*-dibenzyl cyclohexane-1,4-dicarboxylates **7** were synthesized by esterification (in toluene solution) of a mixture of *cis*- and *trans*-cyclohexane-1,4-dicarboxylic acids with benzyl alcohol in the presence of a catalytic amount of toluene-*p*-sulfonic acid.[37]

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