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Stereospecific elimination of dihydropyran from protonated tetrahydropyranyl (THP) difunctional derivatives upon chemical ionization and collision-induced dissociation: intramolecular interactions in polyfunctional ions

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Abstract

Tetrahydropyranyl (THP) ethers of *cis*-1-methoxymethyl-, 1-benzyloxymethyl-, and 1-hydroxymethyl-4-cyclohexane methanols and of *cis*-1,4-dihydroxycyclohexane, and THP ester of *cis*-1,3-cyclohexane dicarboxylic acid (*cis*-**3**–*cis*-**7**, respectively) exhibit low abundance MH^+ ions and undergo efficient elimination of dihydropyran (DHP) upon isobutane chemical ionization (CI). In contrast to this behavior, the *trans* isomers give rise to highly abundant MH^+ ions, whereas the elimination of dihydropyran affords low abundance $[MH-DHP]^+$ ions. A similar stereospecific behavior has been also observed under collision-induced dissociation (CID) conditions. Tetrahydropyranylium ion (*m/z* 85), obtained by a simple C–O bond dissociation, is abundant in the CI and CID mass spectra of both stereoisomers in all the examined systems. The high stereoselectivity suggests intermediacy of internal proton bridging of the two adjacent basic sites in the formation of the $[MH-DHP]^+$ ions from the MH^+ ions of the *cis* isomers. Thermochemical analysis indicates stabilized proton bridged structures for the $[MH-DHP]^+$ ions. A mechanistic pathway has been proposed for the DHP elimination, based on the stereospecificity of this process and on its thermochemistry. (Int J Mass Spectrom 210/211 (2001) 545–556) © 2001 Elsevier Science B.V.

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1. Introduction

Stereochemical effects in mass spectrometry have been of continuous interest during the past four decades. The primary goal of many of those works has been their potential use for configurational assignments in numerous organic systems. Of particular interest has been the potential of the distinctive behavior of stereoisomers under various ionization conditions in the determination of gas-phase ion structures and in the investigation of the variety of mechanistic pathways of fragmentation of organic ions in the gas phase [1,2].

In the course of our recent studies of bond-forming benzyl–benzyl and other group interactions in a variety of protonated difunctional benzyl derivatives [3–7] we have observed a highly stereoselective

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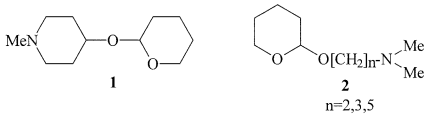
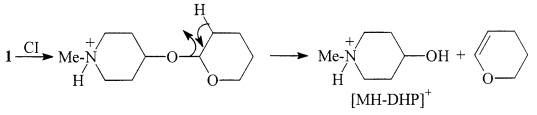
behavior in the isobutane chemical ionization (CI) mass spectra of numerous stereoisomeric tetrahydropyranyl (THP) derivatives and in the collision-induced dissociation (CID) spectra of their MH^+ ions. The *cis* isomers undergo a very efficient elimination of dihydropyran (DHP) in contrast to the *trans* isomers. The results of the investigation of this fragmentation and of its stereochemistry and mechanism are presented in this work.

The elimination of DHP from THP derivatives upon isobutane and methane CI was reported in 1973 in the case of the THP ethers of *N*-methylpiperidin-4-ol **1** and of *N*,*N*-dimethylaminoalkanols **2** [8]:



(1)

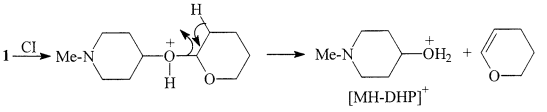
A mechanistic pathway has been proposed for this elimination, involving protonation at the nitrogen atom followed by a 1,3-hydrogen migration from position 3 in the THP moiety to the exocyclic O atom and C–O bond cleavage, both occurring at locations remote from the site of protonation (Scheme 1) [8].



Scheme 1.

This mechanism has been criticized in 1981 on the basis of the results of CI mass spectral measurements of **1** using deuterium labeled reagent gas (CD_4), which showed involvement of the external deuteron in the subsequent elimination of water from the $[MH-DHP]^+$ ion [9]. Based on these results an alternative mechanistic pathway has been proposed for the elimination of DHP, whereby the reacting MH^+ ions are protonated at the less basic ether group (Scheme 2) [9].

It should be pointed out that the stereospecificity of the DHP elimination from the MH^+ ions of a variety of difunctional THP derivatives, observed in the course of the present work, is incompatible with the two mechanisms proposed in Schemes 1 and 2, and it suggests a mechanistic pathway which involves an interaction between the two basic groups.



Scheme 2.

2. Experimental

2.1. 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 stereoisomeric pairs **2**–**7** and **12** were introduced as mixtures and separated on the capillary column DB-5 (0.25 μm film thickness, 30 m $\times$ 0.25 mm i.d. capillary column, the temperature was programmed from 60 to 280 °C at 15 °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*-**3** followed by *trans*-**3**, *cis*-**4** by *trans*-**4**, *cis*-**5** by *trans*-**5**, *cis*-**6** by *trans*-**6**, and *trans*-**7** by *cis*-**7** (*trans*-1,3-cyclohexane dicarboxylates have been previously shown to be followed by *cis* isomers [3,10]). CI measurements were performed at 150 °C ion source temperature and 0.4 Torr (indicated) reagent gas pressure (isobutane, acetonitrile). CID measurements were performed with argon as the target gas (0.3 mTorr, indicated) at 30 eV collision energy (indicated). All the data presented in each table were obtained on the same day under identical conditions, in order to ensure reliable comparisons.

2.2. Materials

1-Tetrahydropyranoxymethyl-4-hydroxymethyl-cyclohexane **5** (mixture of *cis*-**5** and *trans*-**5**): A cool (ice bath) solution of cyclohexane-1,4-dimethanol (*cis* and *trans* mixture, 100 mg, 0.69 mmol), freshly distilled dihydropyran (104 mg, 1.24 mmol) and a

Table 1
Isobutane–CI mass spectral data (relative abundances, %) of tetrahydropyranyl ethers **3–6** (additional fragments in the mass spectra are listed in the footnotes)

Compound	Ion				
	MH^+	$[MH–DHP]^+$	$[MH–THPOH]^+$	Tetrahydropyranylium cation (m/z 85)	$[MH–H_2O]^+$
cis-**3**[a]	0.4	63	6	100	. . .
trans-**3**[b]	100	0.5	17	31	. . .
cis-**4**[c]	0.2	100	0.5	34	. . .
trans-**4**[d]	58	13	4	100	. . .
cis-**5**[e]	25	16	10	100	2
trans-**5**[f]	99	<0.1	6	100	1
cis-**6**[g]	5	45	0.1	100	4
trans-**6**[h]	59	0.2	2	100	47

[a] *m/z* 109 (3%).
[b] *m/z* (3%).
[c] *m/z* 91 $C_7H_7^+$ (3%); *m/z* 125 (3%).
[d] *m/z* 91 $C_7H_7^+$ (13%); $[MH-92]^+$ (6%); *m/z* 109 (1%); *m/z* 125 (21%); $[MH-86]^+$ (12%); *m/z* 143 (13%).
[e] *m/z* 109 (3%); *m/z* 169 (2%).
[f] *m/z* 109 (4%); *m/z* 169 (38%).
[g] *m/z* 81 (3%); *m/z* 155 (3%); *m/z* 167 (5%); *m/z* 173 (14%); *m/z* 103 (0.2%).
[h] *m/z* 81 (3%); *m/z* 103 (5%).

catalytic amount of *p*-toluenesulfonic acid monohydrate in of dry methylene chloride (10 ml) was stirred at 0 °C for 10 min, and at room temperature for additional 1.25 h. The mixture was diluted with ether, washed with aqueous sodium hydrogen carbonate and brine, dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The *cis*-**5** and *trans*-**5** mixture was obtained in 70% yield after purification on a silica gel column [hexane-ethyl acetate (5:1)].

Compounds **6**, **8**–**12** were synthesized from the corresponding diols in the same manner. Benzene-*ortho*, *meta*, and *para* dimethanols were prepared by lithium aluminum hydride reduction [11] of phthalic, isophthalic and terephthalic acids. In the case of **12** (mixture of *cis*-**12** and *trans*-**12**) twice the usual amount of dihydropyran was used for the preparation of the di-THP ether.

Cis- and *trans*-1,3-bis(tetrahydropyranoxycarbonyl)cyclohexanes **7**. A mixture of *cis*- and *trans*-1,3-cyclohexane dicarboxylic acids (100 mg, 0.58 mmol) in anhydrous ethers (10 ml) was refluxed with dihydropyran (195 mg, 2.32 mmol) and *p*-toluenesulfonic acid monohydrate (catalytic amount) for 2 h. The usual work up with ether and evaporation of the solvent under reduced pressure afforded a mixture of the THP-diesters *cis*-**7** and *trans*-**7** (yield 93%).

Compounds **3** and **4** (*cis* and *trans* mixtures) were prepared by tetrahydropyranylation of the corresponding *cis*- and *trans*-1-methoxy- and -1-benzyloxy-4-hydroxymethylcyclohexanes. The monoethers were synthesized from cyclohexane-1,4-dimethanol (*cis* and *trans* mixture) by reaction with sodium hydride and iodomethane or benzyl bromide (in THF) following previously described procedures [12,13].

3. Results and discussion

3.1. Stereospecific behavior of tetrahydropyranyl derivatives

The isobutane CI mass spectral data of tetrahydropyranyl ethers of *cis*- and *trans*-1-methoxymethyl-, 1-benzyloxymethyl-, and 1-hydroxymethyl-4-cyclohexane methanols *cis*-**3**, *trans*-**3**, *cis*-**4**, *trans*-**4**, *cis*-**5**, *trans*-**5**, of *cis*-, and *trans*-1,4-dihydroxycyclohexanes *cis*-**6** and *trans*-**6** structures shown in Eq. 2 are listed in Table 1 (isobutane CI mass spectra of **3** and **4** are

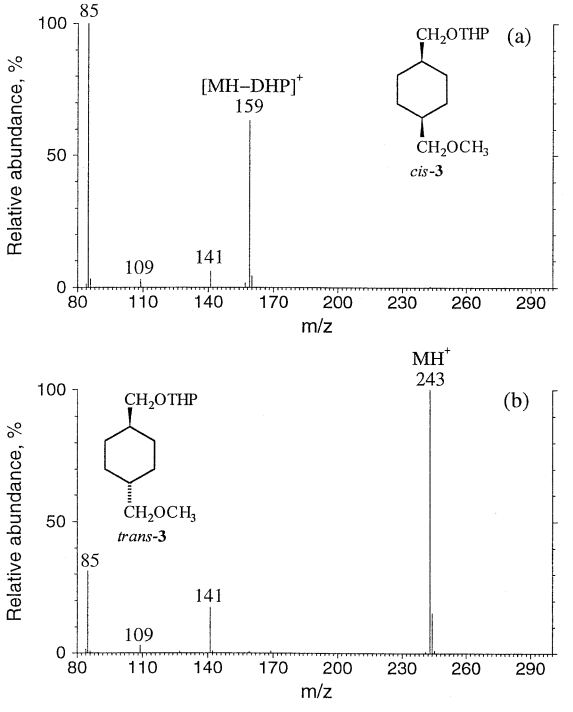


Fig. 1. Isobutane CI mass spectra of (a) *cis*- and (b) *trans*-1-methoxymethyl-4-(tetrahydropyranoxymethyl)cyclohexanes (*cis*-**3** and *trans*-**3**).

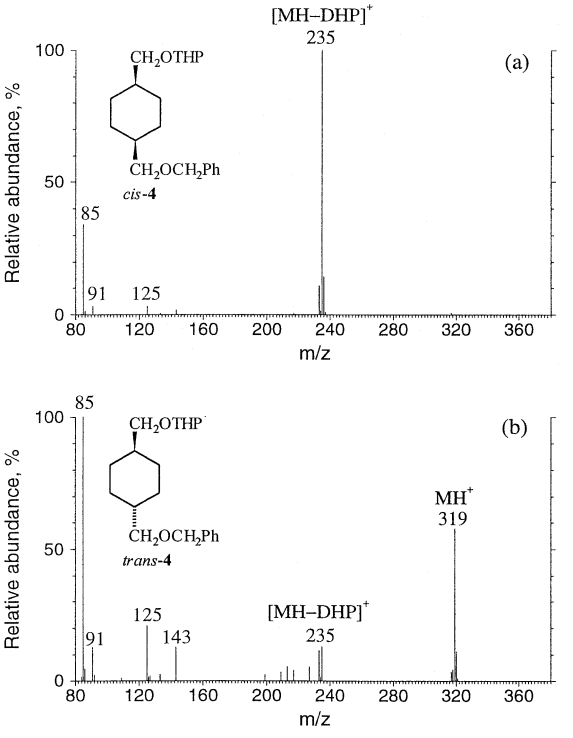
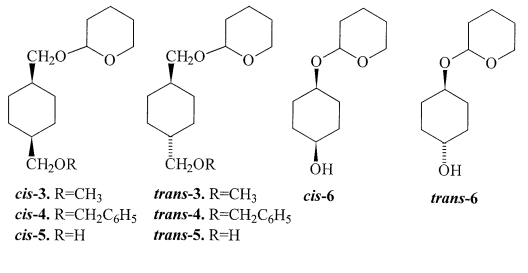
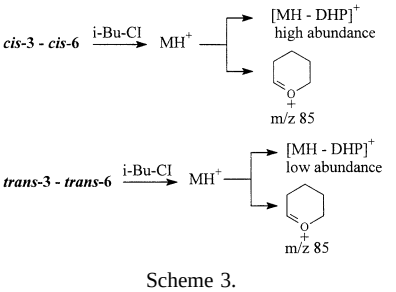


Fig. 2. Isobutane CI mass spectra of (a) *cis*- and (b) *trans*-1-benzyloxymethyl-4-(tetrahydropyranoxymethyl)cyclohexanes (*cis*-**4** and *trans*-**4**).

shown in Figs. 1 and 2). The mass spectra of the stereoisomers exhibit an entirely different behavior. The MH^+ ions of the *cis* isomers are of relatively low abundance (<1% for *cis*-**3** and for *cis*-**4**, 25% for *cis*-**5** and 5% for *cis*-**6**), and they undergo efficient elimination of dihydropyran (DHP) affording abundant $[MH-DHP]^+$ ions (Scheme 3). In contrast, the *trans* isomers give rise to highly abundant MH^+ ions (100% relative abundance for *trans*-**3**, 58% for *trans*-**4**, 99% for *trans*-**5**, and 59% for *trans*-**6**), whereas the elimination of dihydropyran affords low abundance $[MH-DHP]^+$ ions (<1% for *trans*-**3** and *trans*-**6**, 17% for *trans*-**4** and <0.1% for *trans*-**5**). A similar stereospecific behavior has been also observed under CID conditions (see Table 2). Tetrahydropyranylium ion (*m/z* 85), obtained by a simple C–O bond dissociation, is abundant in the CI and CID mass spectra of both stereoisomers in all the examined systems. Other fragments observed in the isobutane CI and CID mass spectra are listed in Tables 1 and 2.



(2)



Scheme 3.

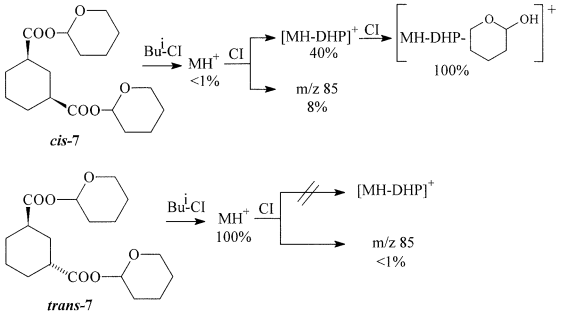
Table 2
CID[a] mass spectral data[b,c] of MH^+ ions obtained from the tetrahydropyranyl ethers *trans*-**3**, *trans*-**4**, *cis*- and *trans*-**5**, and *cis*- and *trans*-**6**

	Ion			
Compound	$[MH–DHP]^+$	$[MH–THPOH]^+$	tetrahydropyranylium cation (m/z 85)	$[MH–H_2O]^+$
trans-**3**[d]	0.2	46	52	. . .
trans-**4**[e]	4	0.2	100	. . .
cis-**5**[f]	17	5	100	1
trans-**5**[g]	<0.1	31	84	0.2
cis-**6**[h]	100	19	80	5
trans-**6**[i]	0.3	30	100	1

[a]30 eV collision energy.
[b]Relative abundances (%) are normalized to the most abundant fragment ion.
[c]CID spectra of *cis*-**3** and *cis*-**4** were not measured because of the low abundance of the MH^+ ions in the Bu^i–CI mass spectra.
[d]Additional fragments in the spectrum: *m/z* 109 (100%); *m/z* 67 (16%).
[e]Additional fragments: *m/z* 91 $C_7H_7^+$ (89%); $[MH-92]^+$ (0.2%); *m/z* 109 (10%); *m/z* 125 (17%); *m/z* 143 (5%); *m/z* 213 (10%).
[f]Additional fragments: *m/z* 109 (14%); *m/z* 67 (2%).
[g]Additional fragments: *m/z* 109 (100%); 67 (19%).
[h]Additional fragments: *m/z* 81 (51%); 103 (4%).
[i]Additional fragments: *m/z* 81 (96%); *m/z* 103 (36%).

The stereospecific behavior of the DHP elimination is not limited to THP-alkoxy- and hydroxyethers. The THP-diesters of *cis*- and *trans*-1,3-cyclohexane dicarboxylic acids, *cis*-**7** and *trans*-**7**, also exhibit an analogous stereospecific behavior: negligible MH^+ ion and abundant $[MH-DHP]^+$ and $[MH-DHP-THPOH]^+$ (and/or $[MH-2DHP-H_2O]^+$) ions (40% and 100%, respectively) in the isobutane CI mass spectrum of *cis*-**7**, in contrast to an abundant (100%) MH^+ ion and no elimination of DHP in that of *trans*-**7** (Scheme 4).

Isobutane CI and CID (of MH^+ ion) mass spectra of the monofunctional (tetrahydropyranoxymethyl)-



Scheme 4.

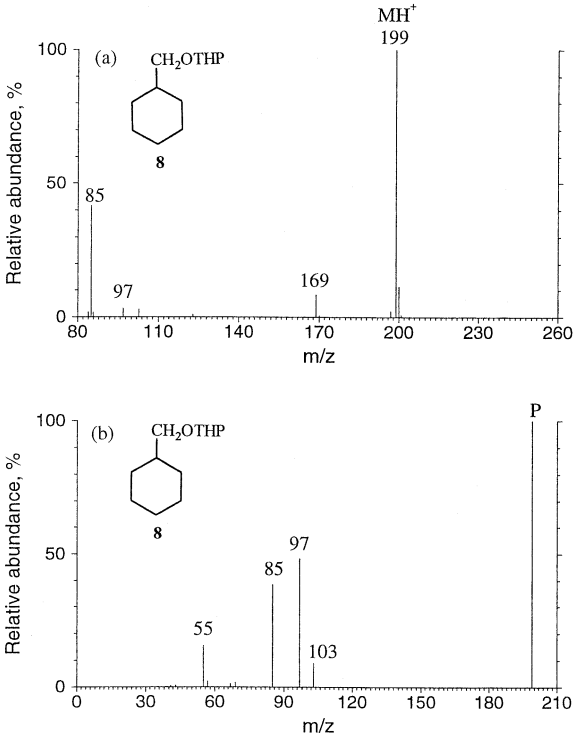
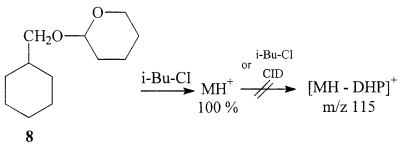


Fig. 3. (a) Isobutane CI mass spectrum of (tetrahydropyranoxymethyl)cyclohexane **8**; (b) CID mass spectrum (30 eV collision energy) of the MH^+ ion of **8**.



Scheme 5.

cyclohexane **8** are shown in Fig. 3. No elimination of dihydropyran takes place in this material either under CI nor under CID conditions (Scheme 5). This finding suggests that the elimination of dihydropyran from THP ethers does not occur if there is no additional basic site in the MH^+ ion.

3.2. Effect of distance between the two basic sites

The reluctance of the MH^+ ion of (tetrahydropyranoxymethyl)cyclohexane **8** to undergo the DHP elimination indicates the necessity of intramolecular interaction between the tetrahydropyranoxy group and another basic function in the DHP elimination. The *cis*-stereospecificity of this process, observed in systems **3**–**7**, is consistent with this requirement. An additional support for this steric requirement has been obtained in the CI and CID measurements of the mono-THP ethers of *ortho*-, *meta*-, and *para*-di(hydroxymethyl)benzenes **9**–**11** (Tables 3 and 4). Only the *ortho* isomer **9** affords the DHP elimination product $[MH-DHP]^+$ upon CI (63%) and CID (100%). No elimination has been detected in the *meta* and *para* isomers **10** and **11** in which the two oxygen functions are distant (Scheme 6).

Table 3
Isobutane–CI mass spectral data (relative abundances, %) of tetrahydropyranyl derivatives **9**–**11** (additional fragments in the spectra are given in the footnotes)

	Compound		
Ion	**9**[a]	**10**[b]	**11**[c]
MH^+	100	100	73
$[MH–DHP]^+$	63	<0.1	<0.1
$[MH–THPOH]^+$	4	2	6
m/z 85 THP^+	23	64	72
$[MH–H_2O]^+$	24	25	100

[a] *m/z* 105 (2%); *m/z* 177 (3%).
[b] *m/z* 105 (11%); *m/z* 147 (3%); *m/z* 169 (3%); *m/z* 177 (3%).
[c] *m/z* 159 (3%); *m/z* 169 (4%); *m/z* 177 (4%).

An exception in this respect is the case of *cis*- and *trans*-1,4-di(tetrahydropyranoxymethyl)cyclohexanes *cis*-**12** and *trans*-**12**, wherein both stereoisomers undergo extensive elimination of DHP under isobutane CI and CID conditions (see and Fig. 4). This behavior may be explained by a possible interaction between the two THP moieties, which may be brought to proximity in a nonstrained conformation in both stereoisomers. As expected, significant difference is observed between the two stereoisomers in the subsequent elimination of the second molecule of DHP from their $[MH-DHP]^+$ ions (see Scheme 7): only *cis*-**12** exhibits the resulting $[MH-2DHP]^+$ ion under CI and CID conditions.

The presence of the $[MH-DHP]^+$ ion (relatively low abundance) in the isobutane CI mass spectrum of *trans*-1-benzyloxymethyl-4-(tetrahydropyranoxymethyl)cyclohexane *trans*-**4**, as opposed to its negligibility in *trans*-**3**, -**5**, and -**6** (Tables 1 and 2), suggests a possible interaction between the benzyl and the THP moieties, in which the phenyl group serves as a basic site. This interaction is possible also in the *trans* isomer in an unstrained conformation. Such unstrained interactions between the THP group and other basic moieties are not possible in *trans*-**3**, -**5**, and -**6**. The lower abundance of the $[MH-DHP]^+$ ion in the CI mass spectrum of *trans*-**4**, as compared with that of *trans*-**12**, may result from the lower basicity of the phenyl group as compared with that of the THP moiety [14].

3.3. DHP elimination upon acetonitrile CI

An interesting observation has been made when the acetonitrile CI mass spectrum of (tetrahydropyranoxymethyl)cyclohexane **8** was measured. As expected (*vide ante* and Scheme 5), no elimination of dihydropyran has been observed from the MH^+ ion. However the $[M+H+CH_3CN]^+$ attachment ion undergoes this elimination process, giving rise to a relatively abundant $[M+H+CH_3CN-DHP]^+$ fragment (Scheme 8).

A similar behavior has been observed in the

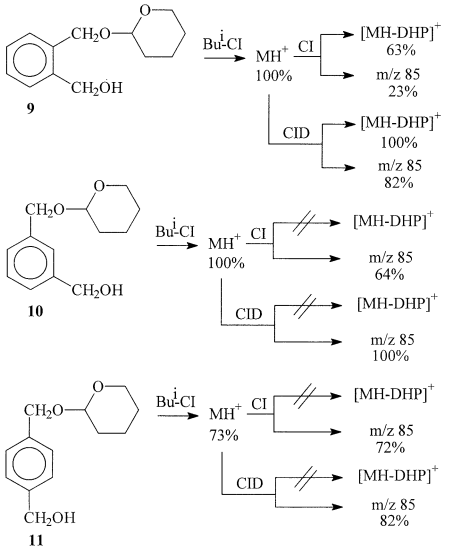
Table 4
CID[a] mass spectral data[b] of MH^+ ions obtained from tetrahydropyranyl derivatives **9–11**

Ion	Compound		
	9[c]	**10**[d]	**11**[e]
$[MH–DHP]^+$	100	<0.1	<0.1
$[MH–THPOH]^+$	89	76	100
m/z 85 THP^+	82	100	82
$[MH–H_2O]^+$	5	24	17

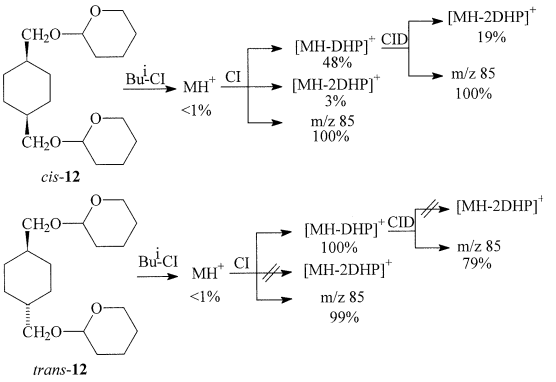
[a]30 eV collision energy.
[b]The relative abundances (%) are normalized to the most abundant fragment ion.
[c]Additional fragments in the spectrum: *m/z* 93 (12%); *m/z* 105 (2%).
[d]Additional fragment: *m/z* 105 (21%).
[e]Additional fragment: *m/z* 93 (3%).

CH_3CN CI mass spectrum of *trans*-1-benzoxymethyl-4-(tetrahydropyranoxymethyl)cyclohexane *trans*-**4**, which showed relatively inefficient elimination of DHP upon isobutane CI (see Table 1). The DHP elimination from the attachment $[M+ H+CH_3CN]^+$ ion is the major fragmentation observed upon acetonitrile CI (relative abundance 100% of the $[M+H+CH_3CN\text{-}DHP]^+$ ion, see Scheme 9).

The occurrence of efficient DHP elimination from the $[M+H+CH_3CN]^+$ ions of **8** and *trans*-**4** suggests, that the external acetonitrile of the attachment ion



Scheme 6.

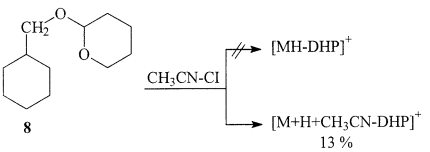


Scheme 7.

moiety plays the role of the additional basic site, which facilitates this process. A plausible mechanistic pathway of this fragmentation from the $[M+H+CH_3CN]^+$ ions of **8** is proposed in Scheme 10. The proton-bound acetonitrile acts as a base attracting a proton, presumably from position 3 of the THP moiety, thus catalyzing the elimination of DHP.

3.4. Thermochemical considerations

The results of the CI-MS and CID measurements of the examined THP difunctional derivatives show two major competitive fragmentations occurring in the MH^+ ions: elimination of DHP and formation of the *m/z* 85 THP^+ ion by a simple C–O bond cleavage. The monofunctional THP derivative **8** gives rise exclusively to the *m/z* 85 THP^+ ion (Scheme 5). The enthalpies (ΔH_r) of the two processes in the THP ethers of ethanol, propanol, and butanol were compared, using the experimental values of enthalpies of formation ΔH_f [15] of the tetrahydropyranylium cation (THP^+, 132 kcal/mol) (1 cal=4.184 J), of neutral dihydropyran (DHP, −27 kcal/mol), and of the neutral and protonated alcohols. The comparison is shown in Scheme 11. Because we did not have the



Scheme 8

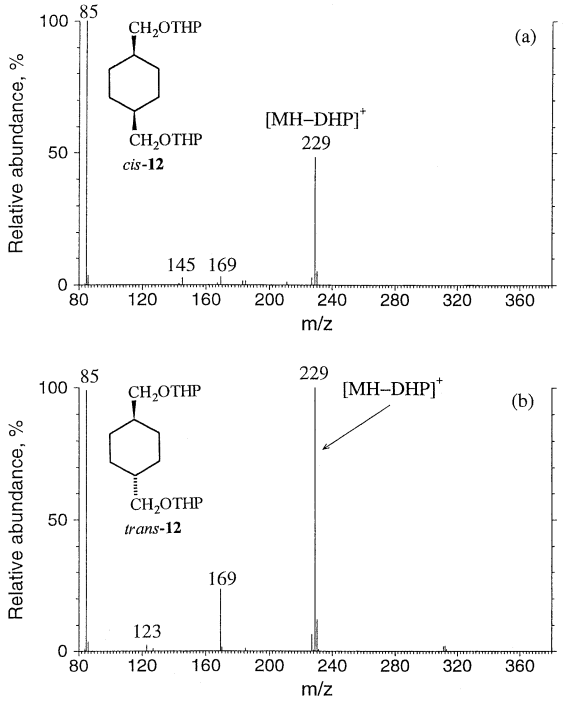
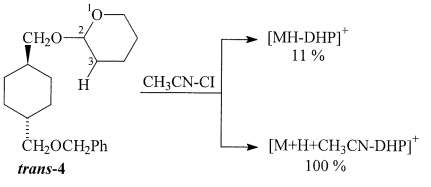
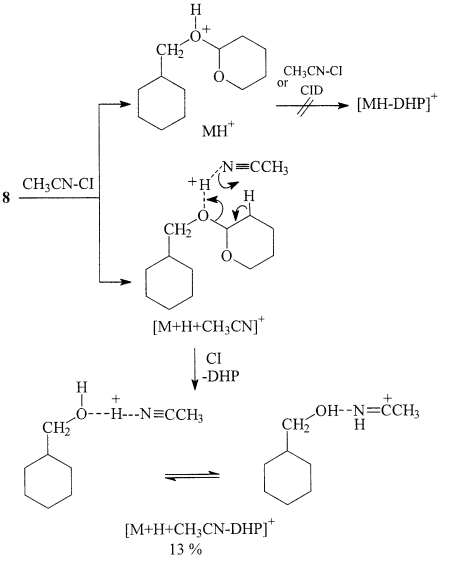


Fig. 4. Isobutane CI mass spectra of (a) *cis*- and (b) *trans*-1,4-di(tetrahydropyranoxymethyl)cyclohexanes (*cis*-**12** and *trans*-**12**).

enthalpies of formation (ΔH_f) of the MH^+ ions of the THP ethers, the comparison was made on the values of the sums $\Delta H_f(MH^+) + \Delta H_r$. The results show that the enthalpy of the reaction leading to the formation of the *m/z* 85 THP^+ ion is considerably lower in the three examined THP derivatives than that of the DHP elimination: by 21 kcal/mol in the THP ether of ethanol and by 18-19 kcal/mol in the ethers of *n*-propanol and *n*-butanol. This finding is consistent with the exclusive formation of the *m/z* 85 THP^+ ion from the MH^+ ion of the monofunctional ether **8**. However, the relatively high abundance of the $[MH-DHP]^+$ ions, observed in the isobutane CI and



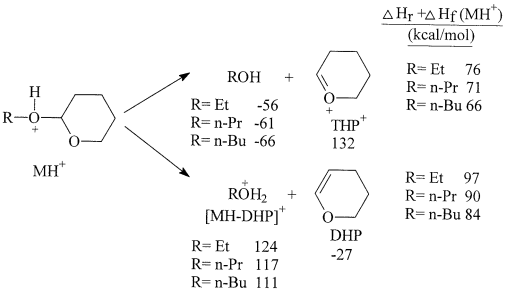
Scheme 9.



Scheme 10.

CID mass spectra of the THP derivatives of the *cis* isomers in the difunctional series **3**–**7** and in **9**, needs explanation.

The formation of the *m/z* 85 THP^+ ion is a simple bond cleavage, and it is reasonable to assume that the difference between its activation energy and the enthalpy of the reaction must be low. The activation energy of the DHP elimination is expected to be considerably higher than that of the formation of the *m/z* 85 ion (at least by ~18 kcal/mol), unless the presence of a stabilizing interaction is assumed in the $[MH-DHP]^+$ ions, resulting in lowering the enthalpy of the DHP elimination. Internal hydrogen bonding between the two basic sites in the *cis* isomers in the difunctional series may account for such stabilization



Scheme 11.

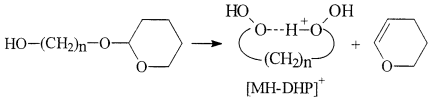
Table 5
Isobutane–CI and CID[a,b] (of MH^+ ions) mass spectral data (relative abundances, %) of tetrahydropyranyl derivatives **13–15**

	i-Bu–CI, RA%			CID, RA%		
Ion	**13**[c]	**14**[c]	**15**[c,d]	**13**	**14**	**15**
$[MH–DHP]^+$	<0.1	5	88	<0.1	10	100
$[MH–THPOH]^+$	*e*	*e*	2	<0.1	2	16
m/z 85 THP^+	45	76	55	100	100	57
$[MH–H_2O]^+$	1	3	2	<0.1	0.2	0.2

[a]30 eV collision energy.
[b]Relative abundances (%) are normalized to the most abundant fragment ion.
[c]RA% of the MH^+ ion — 100%.
[d]Additional fragments in the spectrum: *m/z* 129(7%); *m/z* 147 (3%).
[e]*m/z* value is below the range of the CI measurements (>*m/z* 60).

of the $[MH-DHP]^+$ ions, and consequently lower the activation energy of the DHP elimination to the level of the formation of the *m/z* 85 ion. Such stabilizing interaction could also explain the previously reported efficient elimination of DHP from the MH^+ ions of **1** and **2** [8,9].

The proposed stabilizing interaction by a hydrogen bond between the two basic sites, lowering the enthalpies and activation energies of the DHP elimination from the MH^+ ions of difunctional precursors, finds support in the CI and CID behavior of the protonated mono-THP ethers of 1,2-ethane diol **13**, 1,3-propane diol **14** and 1,4-butane diol **15** (see Table 5). The $[MH-DHP]^+$ ion is absent in the spectra of **13**, it is of relatively low abundance in those of **14** and highly abundant in **15** (Scheme 12). The thermochemical data obtained for the elimination of DHP from the three THP derivatives (listed in Scheme 13, based on experimental data [15]) show, that the enthalpy of the DHP elimination is considerably higher (by 11 kcal/mol) than that of the competing formation of the *m/z* 85 THP^+ ion in **13**, and somewhat lower in the case of **14** and **15** (by 2 and 5 kcal/mol). These results stem from the relative stabilities of the proton bridged structures of the protonated



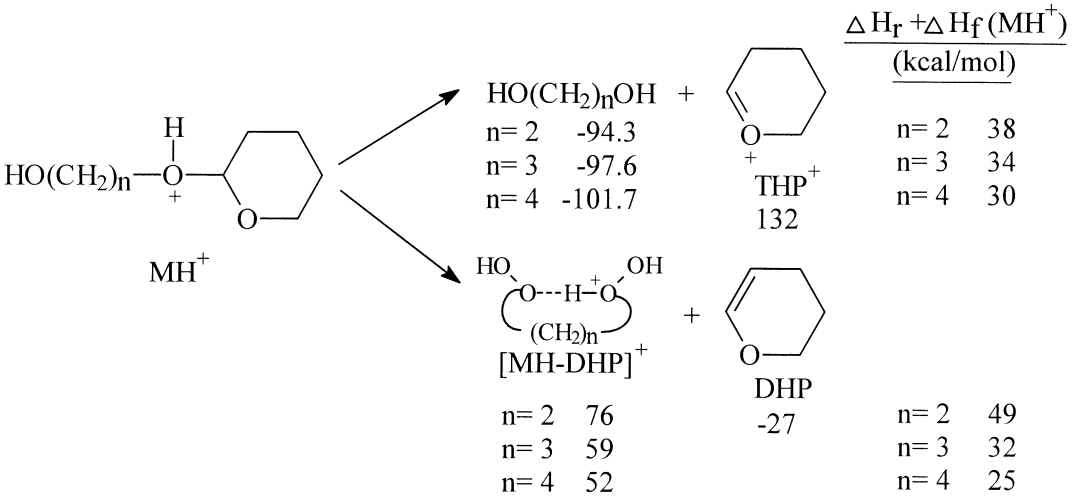
13. n=2 <1%
14. n=3 5%
15. n=4 88%

Scheme 12.

diols, which are reflected in their proton affinities [15]: 195.0 kcal/mol for 1,2-ethane diol (obtained from **13**), 209.4 kcal/mol for 1,3-propane diol (obtained from **14**) and 218.8 kcal/mol for 1,4-butane diol (obtained from **15**), and they are consistent with the relative abundances of the $[MH-DHP]^+$ ions (Table 5 and Scheme 12).

3.5. Mechanism of the rearrangement

A mechanistic pathway for the elimination of DHP from the MH^+ ions of the THP derivatives of the difunctional *cis* isomers is proposed in Scheme 14, based on the results that have been discussed previously. This pathway involves formation of an ion–neutral complex [16–20] as the initial step of the two major competing processes, the formation of the THP^+ ion [route (a)] and the elimination of DHP [route (b)]. The internal hydrogen bond between the two basic sites stabilizes the protonated-bridged cations to a considerably greater extent than the neutral species. The enthalpies of formation of neutral homologous diols shown in Scheme 13 differ, as expected for homologous series, by 3–4 kcal/mol for each additional methylene, in contrast to 17 and 7 kcal/mol per methylene in the corresponding protonated species. Therefore the effect of proton bridging on the rate of route (b) in the case of **15**, affording protonated 1,4-butane diol, is more pronounced than that of route (a), resulting in enhanced formation of the $[MH-DHP]^+$ ion. A similar argument also holds for



Scheme 13.

the stereospecific elimination of DHP from the difunctional *cis* isomers *cis*-**3**–*cis*-**7** (Tables 1 and 2 and Scheme 4) and for the highly specific elimination from the *ortho*-hydroxyether **9** in contrast to the *meta* and *para* analogues **10** and **11** (Scheme 6). Only isomers with adjacent basic sites may afford the stabilized proton bridged $[MH-DHP]^+$ ions by way of route (b) in competition with route (a).

It is noteworthy, that the observed elimination of DHP from the MH^+ ions of the diethers *trans*-**4** and *trans*-**12** (Tables 1 and 2, Scheme 7) indicates formation of internal proton bridging, involving the phenyl moiety in the case of *trans*-**4** and the ring O-atom in *trans*-**12**, which is possible in these ions despite their *trans*-geometry.

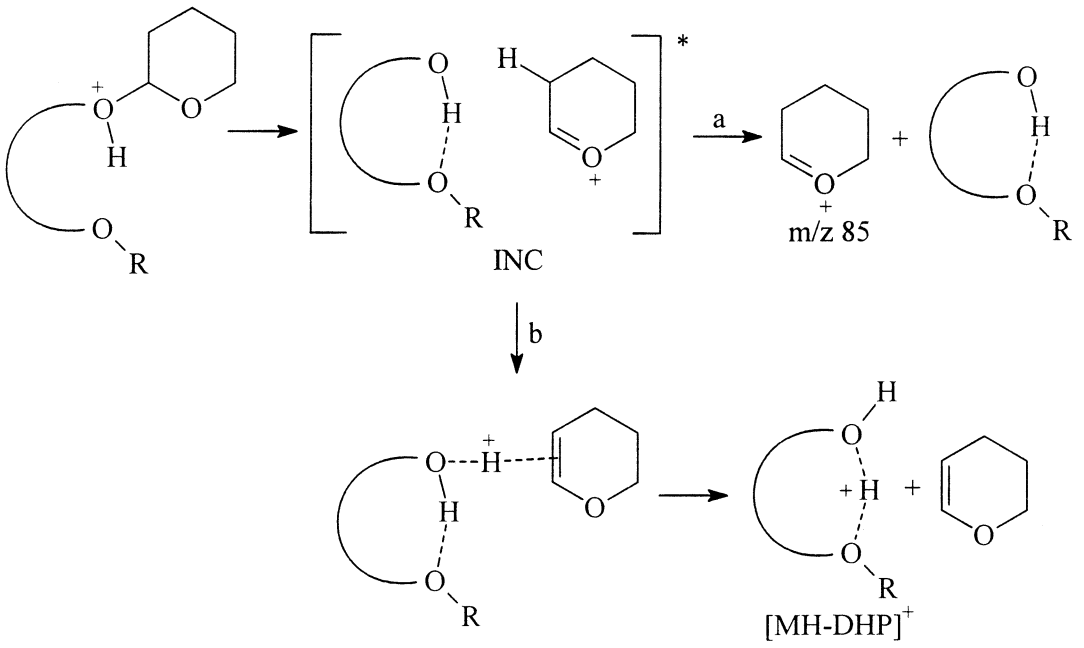
4. Conclusions

In this work, it has been shown that the MH^+ ions of difunctional THP derivatives undergo elimination of dihydropyran (DHP) upon isobutane CI and CID, when the distance between the two basic functions is small enough to enable internal proton bridging. The stereospecificity of this process together with its thermochemistry led to a proposed mechanistic pathway shown in Scheme 14. This mechanism is also consistent with the previously reported elimination of DHP from amino-THP ethers **1** and **2** [8]. The two previously proposed mechanisms (see Schemes 1 and 2 [8,9]) do not explain the role of the second basic site (the amino groups in **1** and **2**) in the DHP elimination.

It is important to note here a unique feature of the behavior of the stereoisomeric THP derivatives examined in this work. It has been shown before, that stabilization of the MH^+ ions by internal hydrogen bonding may be used in the configurational assignment of a variety of stereoisomeric diols, diethers, and other difunctional analogues. Stereoisomers with adjacent basic functions afford abundant proton bridged MH^+ ions under CI conditions, whereas counterparts with remote functions, which cannot be stabilized by proton bridging, undergo fragmentations resulting in much less abundant MH^+ ions in their CI mass spectra [1,2,21–24].

An inverse behavior has been observed in the isobutene CI mass spectra of the stereoisomeric THP ethers **3**–**6**, that have been explored in the present work: the *trans* isomers exhibit much more abundant MH^+ ions than the *cis* counterparts (Table 1). The efficient elimination of dihydropyran kinetically destabilizes the proton bridged MH^+ ions of the *cis* stereoisomers, resulting in strong reduction of their abundance, in contrast to the *trans* analogs, which do not undergo elimination of DHP.

Another unique feature of the stereospecific DHP



Scheme 14.

elimination from THP derivatives is connected with the proposed intermediacy of an ion–neutral complex in its mechanism (Scheme 14). Usually the relative freedom of motion of the constituents of the complex results in non-stereospecific formation of the dissociation products. The stereospecificity of the elimination of DHP, observed and discussed in this work, results from thermochemical requirements. It is the stabilization by proton bridging, possible only in the *cis* derivatives, that makes the formation of the ion-neutral complex and the subsequent expulsion of DHP [by route (b)] energetically accessible. The endothermicity of the DHP elimination in non-stabilized systems (such as the *trans* isomers), as compared with the competitive simple cleavage shown in Scheme 13, results in the suppression of the formation of the $[MH-DHP]^+$ ions.

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