Effect on Conformation on Proton Affinities of Stereoisomeric Ethers

C. Denekamp and A. Etinger Department of Chemistry, Technion—Israel Institute of Technology, Haifa, Israel

R. H. Fokkens

Institute of Mass Spectrometry, University of Amsterdam, 1018WS Amsterdam, The Netherlands

N. Khaselev and A. Mandelbaum[†] Department of Chemistry, Technion—Israel Institute of Technology, Haifa, Israel

N. M. M. Nibbering[†]

Institute of Mass Spectrometry, University of Amsterdam, 1018WS Amsterdam, The Netherlands

The proton affinity (*PA*) of *cis*-4-*tert*-butylcyclohexyl methyl ether with an axial methoxy group is higher by ~0.1 kcal mol⁻¹ (1 kcal = 4.184 kJ) than the *trans* isomer with the equatorial ether group. The gas-phase basicity shows a similar small difference of 0.1 kcal mol⁻¹ between the two stereoisomeric ethers. A greater difference in *PA* has been observed between the stereoisomeric 4-phenylcyclohexyl methyl and ethyl ethers (1.0 and 1.2 kcal mol⁻¹, respectively), in favour of the *cis* isomers with the equatorial ether groups. The latter result is explained by the internal hydrogen bond with the π -system of the phenyl ring.

INTRODUCTION

Various aspects of the effect of stereochemistry on the fragmentation behaviour of ions in the gas phase have been extensively investigated during the past three decades. The results of these investigations have been summarized in a number of reviews.¹⁻⁶ Much less is known about stereochemical effects on the energetics of gas-phase ions. A number of works have been published on the ionization energies of stereoisomers.⁴ However, the effect of stereochemistry on proton affinities (*PA*) has attracted much less attention.

The effect of steric hindrance on gas-phase basicities, proton affinities and rates of gas-phase protonation has been explored in substituted pyridines and ben-zenes.⁷⁻¹¹ The data obtained for *tert*-butyl-substituted pyridines suggest that there is no effect of steric hindrance on proton affinities and on gas-phase basicities in this system. On the other hand, ion cyclotron resonance (ICR) studies led to the conclusion that the rate of proton transfer between cations and bases involving 2,6-di-tert-butylpyridine are much slower than those for other substituted pyridines. These results led to the conclusion that the N-H bond in protonated 2,6-di-tertbutylpyridine is normal, but the steric hindrance has an effect on the rate of approach of the proton to the equilibrium position. This steric effect on the rate of protonation has not been observed in 1,3,5-tri-tertbutylbenzene (and in other less crowded analogues), which supposedly form protonated π -complexes.¹¹

CCC 1076-5174/95/081174-05 © 1995 by John Wiley & Sons, Ltd. In this work we considered the question of whether axial and equatorial bases differ in their proton attachment behaviour in the gas phase. We are not aware of previous reports on such comparative studies.

RESULTS AND DISCUSSION

The differences between the proton affinities of stereoisomers are expected to be small (if any). They may be smaller than the experimental errors in PA measurements. It therefore may not be easy to estimate such differences from the measured individual PA values of the stereoisomers. Direct measurement of the difference (ΔPA) using suitably labelled stereoisomers seems to be the most promising way to obtain a reliable estimate. The kinetic method for measurement of proton affinities¹² is a suitable technique for such measurements of very small differences in proton affinities. This technique is based on the measurement of abundance ratios of the two protonated products AH⁺ and BH⁺ formed by dissociation of proton-bound hetero-dimers $[A \cdots H \cdots B]^+$ in the gas phase. The difference between the PA values of the bases B and A is obtained from the equation $\ln[AH^+]/[BH^+] = \Delta PA/RT$, where T is the effective temperature which may be estimated by independent calibration experiments.¹²⁻¹⁴ The values of Tobtained by such estimates are in the range 400-600 K.^{13,14} The uncertainty in the value of T has an effect on the size of ΔPA , but not on its sign.

Methyl and ethyl ethers of *cis*- and *trans*-4-*tert*-butyland -phenylcyclohexanols 1, 2 and 3 were chosen as first candidates for the study of the effect of conformation of the base group on PA. The methoxy and ethoxy

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[†] Authors to whom correspondence should be addressed.

groups are axial in the cis ethers 1c-3c and equatorial in the trans isomers 1t-3t. The measurement of ion abundance ratios of the products of dissociation of protonbound hetero-dimers of isomers is possible only if one of the two components of the dimer is isotopically labelled. Deuterium-labelled ethers d_4 -1c, d_4 -1t, d_3 -1c, d_3 -1t, d_4 -2c, d_4 -2t, d_4 -3c and d_4 -3t were prepared for this purpose. The proton-bound dimers were generated under chemical ionization conditions from labelled and unlabelled isomeric ethers, and abundance ratios were measured for the protonated molecules of the ethers (MH⁺ of the 'monomers'), obtained by dissociation in the second quadrupole (Q_2) of a triple quadrupole mass spectrometer without collisions. Under these conditions no dissociation of the protonated molecules of the ethers was observed, and no exchange of the external proton with the deuterium atoms was detected. Measurements were also performed for pairs of unlabelled and labelled ethers of identical configurations in order to eliminate a deuterium isotope effect on PA.



The results of the ΔPA measurements are given in Table 1. The effective temperature used for the data in

Table 1 was 400 K. The results show a small difference between the proton affinities of the deuterium-labelled and unlabelled ethers. This effect of deuterium substitution on PA has recently been reported.^{15–17}

The results presented in Table 1 for the epimeric 4-*tert*-butylcyclohexyl methyl ethers show that the *PA* of the *cis* isomer 1c with the axial methoxyl is higher by 0.12 ± 0.02 kcal mol⁻¹ (1 kcal = 4.184 kJ) than that of the equatorial ether 1t. The ΔPA difference due to the conformational effect was obtained as follows from the data obtained for 1 and d₄-1 (four top lines in Table 1):

(1)
$$MH^+(1c) + M(d_4-1c) \rightarrow M(1c) + MH^+(d_4-1c)$$

$$\Delta PA_1 = -0.02 \text{ kcal mol}^{-1}$$

(2)
$$MH^+(1t) + M(d_4-1t) \rightarrow M(1t) + MH^+(d_4-1t)$$

 $\Delta PA_2 = -0.06 \text{ kcal mol}^{-1}$

(3)
$$MH^+(1c) + M(d_4-1t) \rightarrow M(1c) + MH^+(d_4-1t)$$

 $\Delta PA_3 = 0.06 \text{ kcal mol}^{-1}$

(4)
$$MH^+(1t) + M(d_4-1c) \rightarrow M(1t) + MH^+(d_4-1c)$$

$$\Delta PA_4 = -0.13 \text{ kcal mol}^{-1}$$

The equation $MH^+(1c) + M(1t) \rightarrow M(1c) + MH^+(1t)$, which is free of isotope effects, is obtained by the summation ((3) - (4) + (1) - (2))/2 of the above equations and consequently

$$\Delta PA = (\Delta PA(3) - \Delta PA(4) + \Delta PA(1) - \Delta PA(2))/2$$

= (0.06 + 0.13 - 0.02 + 0.06)/2
= 0.115.

There may be some uncertainty in the precise value owing to the uncertainty in the effective temperature, but it is certain that ΔPA between axial and equatorial

Table 1. Results of ΔPA measurements on axial and equatorial ethers by the kinetic method

A	B	{AH+]/[BH+]*	△PA (kcal mol ⁻¹)	Assignment
1c	d∡-1c	0.97 ± 0.01	-0.02	Isotope effect
1t	d₄-1t	0.93 ± 0.01	-0.06	Isotope effect
1c	d₄-1t	1.08 ± 0.01	0.06	Isotope and conformational effect
1t	d1c	0.85 ± 0.005	-0.13	Isotope and conformational effect
1c	1t		0.12 ± 0.02	Conformational effect
1c	d₃-1c	0.89 ± 0.01	-0.09	Isotope effect
1t	d ₃ -1t	0.91 ± 0.01	-0.07	Isotope effect
1c	d ₃ -1t	1.08 ± 0.01	0.06	Isotope and conformational effect
1t	d ₃ -1c	0.76 ± 0.01	-0.22	Isotope and conformational effect
1c	1t		0.13 ± 0.02	Conformational effect
2c	d₄-2c	0.94 ± 0.01	-0.05	Isotope effect
2t	d₄-2t	0.97 ± 0.01	-0.02	Isotope effect
2c	d₄-2t	4.42 ± 0.1	1.1	Isotope and conformational effect
2t	d₄-2c	0.19 ± 0.01	-1.3	Isotope and conformational effect
2c	2t		1.2 ± 0.1	Conformational effect
3c	d₄-3c	0.95 ± 0.01	-0.04	Isotope effect
3t	d3t	0.99 0.01	-0.01	Isotope effect
3c	d3t	3.05 ± 0.05	0.9	Isotope and conformational effect
3t	d₄-3c	0.27 ± 0.02	-1.0	Isotope and conformational effect
3c	3t		0.98 ± 0.1	Conformational effect

^a Average of at least three independent measurements, with more than ten abundance ratio measurements in each experiment.



4-*tert*-butylcyclohexyl is remarkably small (Scheme 1). The highest estimate could reach 0.18 kcal mol^{-1} if the effective temperature were assumed to be as high as 600 K.

The difference between the gas-phase basicities, $\Delta\Delta G$, of the cis- and trans-4-tert-butylcyclohexyl methyl ethers was measured by use of Fourier transform (FT) (ICR) mass spectrometry. To this end, labelled cis (or trans) and unlabelled trans (or cis) ethers were introduced in a well defined pressure ratio into a low pressure FTICR cell. That is, first the intensities of the molecular ion peaks in the FTICR electron impact (EI) mass spectra of the individual ethers were determined as a fraction of the total ionization. For the ethers studied (see below), these turned out to be 89×10^{-3} for 1c, 92×10^{-3} for **d₄-1c**, 88×10^{-3} for 1t and 94×10^{-3} for d_a -1t. Subsequently, these results were taken into account to adjust the required pressure ratio of the introduced ethers on the basis of the intensities of their corresponding molecular ion peaks.

Then, following EI ionization and the generation of protonated molecules by self chemical ionization (CI), either of the protonated molecules was isolated by ejection of all other ions from the cell. Subsequently, their decaying abundance due to proton transfer to the other stereoisomeric molecules and the rising abundance of the latter were monitored as a function of the reaction time until an equilibrium was reached, that is, when the ratio of the abundances of both protonated stereoisomeric molecules became constant.

An example is given in Fig. 1, where (A) shows the establishment of the equilibrium between the protonated stereoisomeric molecules of a 3:1 mixture of unlabelled 1c and labelled d_4 -1t, following isolation of protonated 1c in the cell. Figure 1(B) shows in a similar way the establishment of this equilibrium following isolation of protonated d_4 -1t in the cell.

From Fig. 1, it can easily be concluded that the unlabelled *cis* ether 1c is more basic than the labelled

trans ether d_4 -1t. Assuming as temperature T = 340 K and the equilibrium abundance ratio of 4.50 for the protonated stereoisomeric ether molecules obtained from Fig. 1(A), the gas-phase basicity difference $\Delta\Delta G$ between the unlabelled *cis* 1c and labelled *trans* d_4 -1t ether molecules is calculated to be 0.30 kcal mol⁻¹. From Fig. 1(B), a similar $\Delta\Delta G$ value of 0.30 kcal mol⁻¹ is calculated for this pair of stereoisomers.

Table 2 summarizes the results of all $\Delta\Delta G$ measurements made for the *cis* and *trans* methyl ethers. The data indicate that on average the gas-phase basicity of *cis*-4-*tert*-butylcyclohexyl methyl ether is 0.1 kcal mol⁻¹ larger than that of *trans*-4-*tert*-butylcyclohexyl methyl ether, which agrees well with the results obtained with use of the kinetic method (see above).

We do not propose an explanation for the origin of the small conformational effect observed in the above measurements. *Ab initio* calculations will be performed in order to answer this question.

The difference between the proton affinities of *cis*and *trans*-4-phenyl-1-alkoxycyclohexanes 2 and 3 (with axial and equatorial alkoxyl groups, respectively) is significantly greater than that of the *tert*-butyl analogues. It is 1.2 kcal mol⁻¹ for the methyl and 1.0 kcal mol⁻¹ for the ethyl ethers. The higher *PA* values of the axial phenylcyclohexyl ethers are explained by the internal hydrogen bond with the π -system of the phenyl ring (Scheme 2).

EXPERIMENTAL

Mass spectrometry

The ΔPA measurements by the kinetic method were performed with a Finnigan TSQ70B triple quadrupole mass spectrometer using the CI volume in the EI/CI ion source. The ion source temperature was 120 °C. The ~1:1 mixtures of the pairs of ethers were admitted into the ion source via a probe until a reasonable abundance was observed for the expected protonated heterodimers. The protonated dimers were transmitted through the first quadrupole (Q-1), their dissociation was achieved in Q-2 without collisions (no gas was admitted into Q-2) and the abundance ratios of the products were obtained by a Q-3 scan.

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A	в	[A]/[B]	Isolated MH+	[AH+]/[BH+]*	∆∆G ^b (kcał mol ⁻¹)	Assignment
1c	d₄-1t	1	AH+	2.03	0.5	Isotope and conformational effect
1c	d₄-1t	1	BH+	1.89	0.4	Isotope and conformational effect
1c	d1t	3	AH+	4.50	0.3	Isotope and conformational effect
1c	d -1t	3	BH⁺	4.50	0.3	Isotope and conformational effect
1c	d,-1t	0.33	AH+	0.70	0.5	Isotope and conformational effect
1c	d1t	0.33	BH⁺	0.25	-0.2	Isotope and conformational effect
d,-1c	1t	1	AH+	0.75	-0.2	Isotope and conformational effect
d1c	1t	1	BH+	0.89	-0.1	Isotope and conformational effect
d,-1c	1t	2	AH+	1.50	-0.2	Isotope and conformational effect
d₄-1c	1t	2	BH⁺	1.41	-0.2	Isotope and conformational effect

Table 2. Results of gas-phase basicity ($\Delta\Delta G$) measurements on axial and equatorial ethers by FTICR

^a Average of three measurements.

^b Estimated experimental uncertainty is 0.2 kcal mol⁻¹.



reaction time (s)

Figure 1. Relative intensities of the peaks due to protonated stereoisomeric molecules of a 3:1 mixture of unlabelled 1c and labelled d_4 -1t as a function of reaction time following isolation of protonated 1c, m/z 171 (\Box) (A) or protonated d_4 -1t, m/z 175 (\diamondsuit) (B) in the FTICR cell. For further experimental details, see text.



Scheme 2

The FTICR experiments were performed with use of a Bruker Spectrospin CMS 47X Fourier transform ion cyclotron resonance mass spectrometer, equipped with a 4.7 T magnet and an external ion source. Detailed descriptions of the instrument and the general operating procedure for ion manipulation and detection have been provided previously.¹⁸⁻²⁰.

The samples were introduced from two separate reservoirs at 340 K through leak valves directly into the cell via a dual heated liquid line up to a total pressure of 1×10^{-7} mbar (ionization gauge reading) (1 bar = 10^5 Pa). The filament current was 3.7 A and 70 eV electrons were used to ionize the sample molecules. The [M + H]⁺ ions were mass selected²⁰ from the ion mixture and effectively thermalized by helium gas, which was admitted into the FTICR cell through a pulsed valve for 80 ms up to a maximum pressure of $\sim 10^{-6}$ mbar.

Materials

Cis and trans-2,2,6,6,- d_4 -4-tert-butyl-1-methoxycyclohexane (d_4 -1c and d_4 -1t). 2,2,6,6- d_4 -tert-butylcyclohexanone was prepared by equilibration of 4-tert-butylcyclohexanone with DCl and D₃PO₄ (obtained by mixing PCl₅ and D₂O) in anhydrous tetrahydrofuran. Reduction of 2,2,6, 6- d_4 -4-tert-butylcyclohexanone with lithium aluminium hydride in diethyl ether yielded trans-2,2,6,6- d_4 -4-tertbutylcyclohexanol (85%). Predominant formation of cis-2,2,6,6- d_4 -4-tert-butylcyclohexanol (80%) was achieved by hydrogenation of 2,2,6,6- d_4 -4-tertbutylcyclohexanone with Raney nickel in methanol at 1 atm. The ethers were obtained by reaction of the alcohols (500 mg) with sodium hydride (60%, 200 mg, washed with hexane) in anhydrous tetrahydrofuran (5 ml) at 40 °C, followed by addition of iodomethane (1 g). The resulting cis- and trans-2,2,6,6,- d_4 -4-tert-butyl-1methoxycyclohexanes d_4 -1c and d_4 -1t were purified by chromatography on a silica gel column (eluted with dichloromethane–hexane (1:3)).

Cis and trans-4-tert-butyl-1- d_3 -methoxycyclohexane (d_3 -1c and d_3 -lt). The d_3 -methyl ethers were prepared from cis and trans-4-tert-butylcyclohexanols by a similar reaction with sodium hydride in anhydrous tetrahydrofuran followed by addition of d_3 -methyl tosylate (prepared from p-toluenesulphonyl chloride and d_4 -methanol).

Cis- and trans-2,2,6,6- d_4 -4-phenyl-1-methoxy- and -ethoxycyclohexanes (d_4 -2c, d_4 -2t, d_4 -3c and d_4 -3t). These materials were synthesized from 4-phenylcyclohexanone by a procedure similar to that used for d_4 -1c and d_4 -1t.

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