

## Review Commentary

# Gas-phase stability of tertiary carbenium ions and rates of solvolysis of tertiary derivatives

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Received 27 August 1999; revised 30 January 2000; accepted 4 February 2000

**ABSTRACT:** The stability of tertiary carbenium ions was determined in the gas phase by ion cyclotron resonance (ICR) and by dissociative proton attachment (DPA). The rate constants for solvolysis of bridgehead derivatives correlate well with the stabilities of bridgehead carbenium ions, as determined by DPA and by ICR, but the ICR data of strained ions do not correlate, indicating rearrangements under the conditions of the ICR experiment. Simple acyclic tertiary derivatives solvolyze faster than predicted on the grounds of the stability of the respective carbenium ions. The effect of nucleophilic solvent participation on the rate of methanolysis of tertiary derivatives was investigated with (*R*)-3-chloro-3,7-dimethyloctane (**17**), which reacts with 77% inversion and 23% racemization. Copyright © 2000 John Wiley & Sons, Ltd.

**KEYWORDS:** solvolysis; carbenium ions; dissociative proton attachment; nucleophilic solvent participation; stereochemistry

## INTRODUCTION

The solvolytic reactivity of bridgehead derivatives has been the subject of many investigations in the past. Early empirical force-field calculations have been used to rationalize the structural effects on the rate constants of solvolysis in terms of strain changes between the bridgehead compound and the developing carbenium ion, which was assumed to be close to the transition state of the reaction in terms of energy and structure.<sup>1,2</sup> However, since the calculations were empirical, and since the force-fields used were adjusted such as to provide an optimum correlation with the experimental data, the significance of the calculations is questionable. In order to remedy this situation, we determined the stability of bridgehead- and bridgehead-like tertiary carbenium ions by ion cyclotron resonance (ICR) techniques. Heterolytic bond dissociation energies  $D^0(\text{R}^+ - \text{Br}^-)$  were obtained either from the equilibrium constant for bromide exchange between carbenium ions, or from the gas-phase basicity of olefins, and were successfully correlated with the rate constants for solvolysis over a rate range of ca 12 log units.<sup>3</sup> The

correlation was, however, only partially satisfactory, because the value for the 1-norbornyl derivative was found significantly below the correlation line, while simple acyclic and monocyclic derivatives such as *tert*-butyl solvolyzed much faster than expected on the grounds of the stability of the respective carbenium ions, and were, therefore, found above the correlation line. The deviation of the norbornyl derivative was tentatively ascribed to rearrangement of the highly strained 1-norbornyl cation to a more stable species of unknown structure in the ICR spectrometer. The enhanced rate of acyclic and monocyclic derivatives was attributed in part to nucleophilic solvent participation, and in part to the lower degree of charge development in the transition state for solvolysis as compared with the charge of free ions in the gas phase.<sup>3,4</sup> The observation of rearrangements occurring during the ICR experiments casts doubt on the entire set of data obtained by this method. The present study was initiated with the objective of backing up the correlation between the gas-phase stability of carbenium ions and the rate of solvolysis of their precursors, and to examine the importance of nucleophilic solvent participation in the solvolysis of tertiary acyclic derivatives.

## RESULTS AND DISCUSSION

### Stability of bridgehead carbenium ions in the gas phase

A series of tertiary bromides was subjected to bromide

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Contract/grant sponsor: Swiss National Science Foundation;

Contract/grant number: 20-5281.97; Contract/grant number: 21-45790.95.

Contract/grant sponsor: DGIYT; Contract/grant number: PB96-0927-CO2-01.

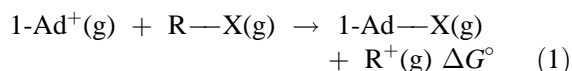
**Table 1.** Stability of carbenium ions in the gas phase and solvolytic reactivity of tertiary derivatives (values in kcal mol<sup>-1</sup>)

No.	Compound	$\Delta G^\circ$ (DPA) <sup>a</sup> (X = Br av)	$\Delta G^\circ$ (ICR) <sup>b</sup> Br exchange	GB (ICR) <sup>c</sup> olefin basicity	$\Delta G^\circ$ (ICR) from GB	$\Delta \log k^a$
1	2-Methyl-2-bicyclo[2.2.2]octyl			197.7	10.9	5.0
2	2-Methyl-2-adamantyl			198.6	8.9	3.5
3	2-Methyl-2-norbornyl			198.7	6.0, 3.4 <sup>d</sup>	5.1
4	1-Adamantyl	0.0	0.0			0.0
4a	3,5-Dimethyl-1-adamantyl		0.6			—
5	2,3,3-Trimethyl-2-butyl		+1.6 <sup>e</sup>			2.9
6	2- <i>exo</i> -Norbornyl	-2.9	-2.9			-1.1
7	7-Methyl-7-norbornyl			189.7	-4.5	-2.1
8	2-Methyl-2-butyl		-3.5 (-1.3) <sup>d</sup>			3.4
9	2-Methyl-2-propyl	-5.2	-5.8 (-5.5) <sup>d</sup>			2.8
10	1-Bicyclo[2.2.2]octyl	-7.9	-8.1 <sup>e</sup>			-3.6
11	10-Tricyclo[5.2.1.0 <sup>4,10</sup> ]decyl		-8.9 <sup>e</sup>			-5.7
12	Cubyl	-16.4	(-9.1) <sup>e</sup>			-7.9
13	3-Noradamantyl	-16.9	(-9.0) <sup>e</sup>			-6.9
14	1-Norbornyl	-27.0	(-8.9) <sup>e</sup>			-10.1

<sup>a</sup> Ref. 7.<sup>b</sup> This work.<sup>c</sup> Revised values from Refs. 3 based on new NIST scale.<sup>8</sup><sup>d</sup> Data from Refs. 3.<sup>e</sup> Data from Ref. 3.

exchange by ICR. Satisfactory agreement with data from the literature was observed for simple aliphatic cations such as 2-methyl-2-propyl (**9**) and 2-methyl-2-butyl (**8**) and for relatively stable bicyclic or polycyclic ions such as 1-adamantyl (**4**), 1-bicyclo[2.2.2]octyl (**10**) and the secondary 2-norbornyl (2-bicyclo[2.2.1]heptyl, **6**) cations (Table 1). In contrast, the experimental stabilities determined for strained bridgehead cations such as cubyl (**12**) 3-noradamantyl (**13**), 1-norbornyl (**14**) and others (1- and 4-homocubyl) were essentially meaningless and could not be correlated with anything (J.-L. M. Abboud, E. W. Della, P. Müller, R. Notario and J.-C. Rossier, unpublished work). We were forced to the conclusion that the experimental method was inadequate for the observation of strained bridgehead cations, and the project was put aside pending a more appropriate approach.

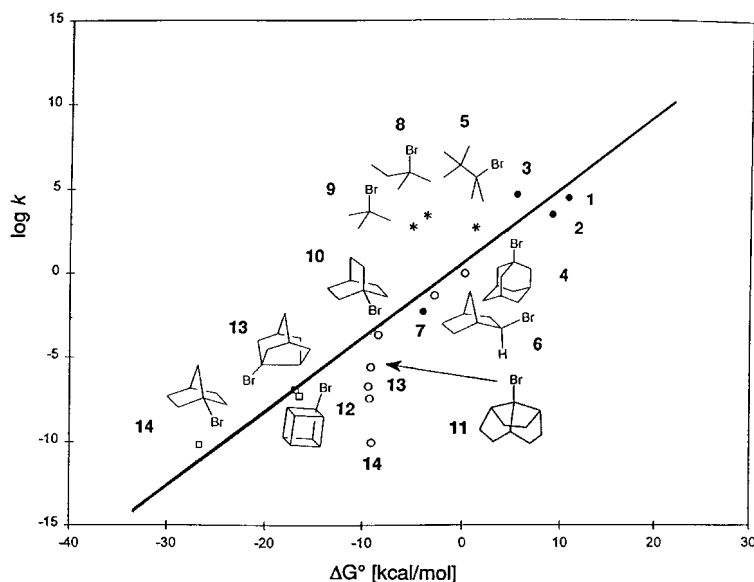
More recently, Abboud and co-workers<sup>5,6</sup> have developed a method for the determination of the stability of carbenium ions in the gas phase by dissociative proton attachment (DPA) using Fourier transform ion cyclotron resonance (FTICR) spectroscopy. In this approach, an organic halide or alcohol is protonated with an acid BH<sup>+</sup> to afford an ion-molecule complex which dissociates almost without activation energy to R<sup>+</sup> and XH. The onset of carbenium ion formation as a function of the gas-phase acidity of BH<sup>+</sup> is observed by FTICR. Carbenium ions are ranked according to their stability relative to adamantyl according to the equation



This is formally equivalent to a ranking of ion stabilities

according to the pK<sub>R+</sub> scale, but in the absence of solvent. Details of the method have been reported.<sup>5,6</sup> The DPA method allows one to obtain reproducible data on strained carbenium ions, which are not observable by conventional ICR techniques, because the ions are generated with less excess energy than when they are formed upon electron impact, so that rearrangements occur less frequently. The approach has been applied to carbenium ions spanning the full range of bridgehead reactivity (23 log units), and excellent correlations of log *k* vs  $\Delta G^\circ$  were obtained, indicating that no rearrangements of the ions had occurred.<sup>7</sup> In addition, the experimental ion stabilities correlated very well with the Gibbs free energies for hydride transfer of R-H to the 1-adamantyl cation, as calculated by *ab initio* methods at the MP2-6/311G\*\* level. On the grounds of these correlations with experiment and theory, we believe that the DPA data are reliable.

With the DPA data in hand, the ICR results may be evaluated. The data are collected in Table 1. All energies are expressed as Gibbs free energies in kcal mol<sup>-1</sup> (1 kcal = 4.184 kJ) relative to 1-adamantyl according to Eqn. (1). The DPA data in column 3 are from Ref. 7. They refer to average values for bromides. Data obtained with other leaving groups are converted to bromides by appropriate leaving group corrections.<sup>7</sup> The ICR data for bromide exchange are in column 4. They were originally determined as heterolytic bond dissociation energies  $D^\circ(\text{R}^+-\text{Br}^-)$  with 2-*exo*-norbornyl bromide as reference.<sup>4</sup> The equilibrium data for olefin protonation afford gas-phase basicities (GB) from which proton affinities (PA) may be derived. Enthalpies of formation of the carbenium ions can be calculated provided the enthalpies of formation of the olefins are known [ $\Delta H_f^\circ(\text{MH}^+)$ ]



**Figure 1.** Plot of  $\log k$  vs  $\Delta G^\circ$  for solvolysis of tertiary derivatives. The correlation line is defined by the DPA data of bridgehead derivatives ( $\log k = 0.44\Delta G^\circ + 0.50$ ).<sup>7</sup> Filled circles, ICR data from gas-phase basicity of olefins; open circles, ICR data for bridgehead bromides; asterisks, ICR data for acyclic bromides; open squares, DPA data for **12–14**

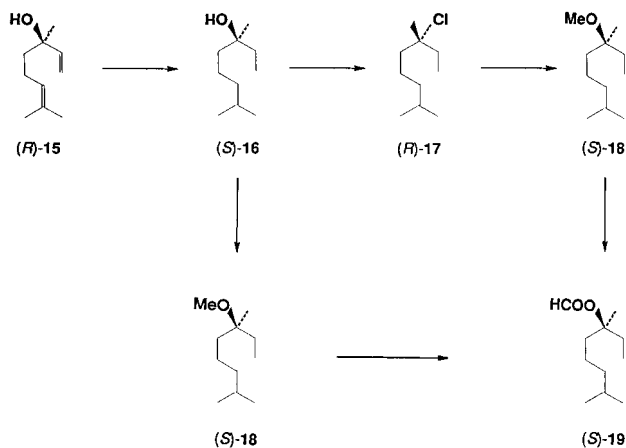
$= \Delta H_f^\circ(\text{M}) + \Delta H_f^\circ(\text{H}^+) - \text{PA}(\text{M})$ ]. The basicity scale for the reference bases used in these experiments has been changed (NIST scale)<sup>8</sup> and, therefore, column 5 lists the revised *GB* values. The  $D^\circ(\text{R}^+ - \text{Br}^-)$  values in column 6 were calculated from  $\Delta H_f^\circ(\text{R}^+) = \Delta H_f^\circ(\text{RBr}) - \Delta H_f^\circ(\text{Br}^-) + D^\circ(\text{R}^+ - \text{Br}^-)$ .<sup>3,4</sup> Originally, the ICR data were reported as enthalpies and are, therefore, not strictly comparable to the DPA results in column 3. However, since their experimental determination was based on equilibrium constants, they referred originally also to Gibbs free energies. A constant entropy correction had to be applied for their conversion into enthalpies. In the context of this account we restrict ourselves to relative energies, so that the entropy term cancels out, and the data in columns 3, 4 and 6 are comparable.

Figure 1 is a plot of  $\log k$  for bridgehead solvolysis vs the stability of bridgehead carbenium ions ( $\Delta G^\circ$ ) according to Eqn. (1). The regression line refers to the DPA results reported in Ref. 7. The slope of the correlation is now 0.44, significantly lower than the 0.59 reported for the correlation of  $\log k$  with the ICR data.<sup>3,4</sup> Figure 1 shows that the ICR data collected from olefin protonation (filled circles) are in reasonable agreement with the DPA line, although there is some scatter. In the absence of rearrangements, the values of  $\Delta G^\circ$  for reaction (1) obtained from olefin protonation should be as valid as those obtained from bromide exchange. However, in most cases, the experimental heats of formation of the olefins which are required for the determination of  $\Delta H_f^\circ(\text{R}^+)$  and those of the corresponding bromides, needed to calculate  $D^\circ(\text{R}^+ - \text{Br}^-)$ , are not available. In our determination we used experimental values from the literature for the olefins of **1**

and **7** and MM2 values for those pertaining to **2** and **3**.<sup>4</sup> MM2 values were used throughout for the enthalpies of  $\text{R}-\text{Br}$ . These approximate procedures tend to increase the uncertainties of the  $\Delta G^\circ$  values and are probably the reason for the deviation of the experimental points from the DPA line. More significant discrepancies occur in the ICR data obtained from bromide exchange (open circles). While the results for 1-adamantyl (**4**), 2-norbornyl (**6**) and 1-bicyclo[2.2.2]octyl (**10**) fit the DPA line well, the plot deteriorates when strained ions such as **12–14** are involved. These compounds are found much below the line, and the ICR stabilities differ very strongly from the DPA values. Since the DPA values of these compounds (DPA values for **12–14** indicated by open squares) are in agreement with the solvolytic reactivity and with the theoretically calculated ion stabilities,<sup>7</sup> the ICR data must, therefore, refer to rearranged ions of unknown structure and are incorrect. The ICR value for the 10-perhydrotriquinacenylium cation (**11**) is at the limits of credibility, and may also be affected by rearrangements. Unfortunately, we were unable to obtain a reproducible value for **11** by DPA.

### Nucleophilic participation in the solvolysis of tertiary aliphatic derivatives

Figure 1 also contains data for the solvolysis and stability of simple acyclic tertiary derivatives such as 2-methyl-2-propyl (**9**), 2-methyl-2-butyl (**8**) and 2,3,3-trimethyl-2-butyl (**5**). The  $D(\text{R}^+ - \text{Br}^-)$  value for this latter compound was taken from the literature.<sup>4,9</sup> The aliphatic tertiary derivatives solvolyze faster than predicted by the



Scheme 1

DPA line, and the deviation is strongest in the case of 2-methyl-2-propyl (**9**). This rate enhancement is usually ascribed to nucleophilic participation in the case of acyclic tertiary derivatives, a pathway not available to bridgehead compounds owing to steric reasons.

The hypothesis of nucleophilic solvent participation in the solvolysis of tertiary derivatives is based on the observation of the remarkable solvent effect on the rates of solvolysis in solvents of high and low nucleophilicities. The rate ratio for solvolysis of 1-adamantyl vs. *tert*-butyl (2-methyl-2-propyl) derivatives varies from ca 1:5000 in EtOH<sup>10</sup> to 1600 in MeOH<sup>11</sup> and 1:2.4<sup>12</sup> in 97% aqueous HFIP. The occurrence of significant differential solvent participation in the solvolysis of acyclic and monocyclic derivatives is unlikely, however, since their rate constants are correlated, together with those of bridgehead derivatives, when plotted against the strain difference between R—X and R<sup>+</sup>.<sup>2,4</sup> In addition, the tertiary neopentyl derivative **5**, which should be far less subject to nucleophilic solvent assistance,<sup>13,14</sup> solvolyses also at an enhanced rate, although the deviation is much less pronounced than in the case of *tert*-butyl (**9**).

The detailed nature of nucleophilic solvent participation in the solvolysis of tertiary derivatives and its magnitude are poorly understood.<sup>15,16</sup> Intuitively, one would expect that the interaction between the solvent and the reacting carbon atom in the transition state of the reaction should result in partial or total, according to the precise mechanism, inversion of configuration.

The stereochemistry of the solvolysis of tertiary acyclic derivatives is only poorly established. Hughes *et al.* investigated the methanolysis of (*R*)-(-)-3-chloro-3,7-dimethyloctane (**17**) at 60°C.<sup>17</sup> The reaction proceeded with 34% inversion of configuration and 66% racemization. Their work was severely criticized by Doering and Zeiss, because the optical purity of the starting chloride **17** had not been determined.<sup>18</sup> These latter authors, in turn, investigated the methanolysis of optically active hydrogen 2,4-dimethylhexyl 4-phthalate

in boiling MeOH and found 54% inversion of configuration and 46% racemization. In both investigations the reliability of the results suffered from the low values of the optical rotation of the samples which were in the range of only a few degrees. We have now reinvestigated the steric course of the solvolysis of tertiary derivatives with **17** using enantiomer separation by GC on chiral columns. The chloride **17** is readily available from optically active (*R*)-(-)-linalool (**15**) of 78% enantiomeric excess (ee) ( $[\alpha]_D^{20} = -0.55(\text{neat})$ ) (Scheme 1). Catalytic hydrogenation afforded (*S*)-(-)-3,7-dimethyloctan-3-ol (tetrahydrolinalool, **16**),<sup>19</sup> the enantiomers of which could be separated by GC (Betadex 120 column) with the *S*-isomer appearing first. The (*S*)-(-)-alcohol was converted to the (*R*)-chloride (**17**) without loss of enantiomeric purity {separation by GC, Gammadex, major enantiomer having longer retention time,  $[\alpha]_D^{20} = -0.48$  ( $c = 41.8$ , CHCl<sub>3</sub> for 78% ee)} by reaction with SOCl<sub>2</sub> in Et<sub>3</sub>N.<sup>17,20</sup> The *R*-configuration of the chloride **17** follows from the sign of the optical rotation and from conversion back to (*S*)-**16** in aqueous MeOH. Solvolysis was carried out with 0.10 mmol of chloride (*R*)-**17** in dry MeOH (2.0 ml) containing 2.0 equiv. of 2,6-di-*tert*-butylpyridine at 25°C for 6 days GC-MS analysis of the reaction mixture revealed the presence of four olefins (50%), which were not further investigated, the expected methyl ether **18** (40%) and 10% of unreacted chloride **17** of 78% ee. Since enantiomer separation of **18** by GC or HPLC failed, it was converted to the formate ester **19** via oxidation with RuCl<sub>3</sub>-NaIO<sub>4</sub>.<sup>21</sup> The absolute configuration of the ester **19** was determined to be *S* by comparison of the GC retention time (Betadex, major enantiomer having shorter retention time) which was identical with that of a sample of (*S*)-**19** synthesized by methylation of the (*S*)-alcohol **16** to the (*S*)-ether **18**, ( $[\alpha]_D^{20} = -2.68$  [ $c = 58.9$ , CHCl<sub>3</sub> for 78% ee]) followed by oxidation to the formate ester **19** as above. The ee of the formate **19** resulting from the methanolysis was 60.2%. Thus the reaction of the chloride proceeds at 25°C with 77% inversion and 23% racemization. This is more than reported by Hughes *et al.*<sup>17</sup> but compares well with the reported 54% inversion for hydrogen 2,4-dimethylhexyl 4-phthalate in refluxing MeOH considering the different temperatures and leaving groups. The discrepancy with the results of Hughes *et al.*<sup>17</sup> may be due to experimental uncertainties. The  $[\alpha]_D$  value of the methanolysis product **18** was only -0.70, whereas that of a sample prepared from the alcohol (*S*)-**18** had  $[\alpha]_D = -2.03$ . In our experience, the determination of optical rotations with a precision beyond the decimal point is problematic, in particular if the purity of the samples may not be verified by GC.

The present data confirm the involvement of nucleophilic participation during the solvolysis of tertiary acyclic derivatives. The effect is much less than expected on the grounds of the rate enhancement of *tert*-butyl derivatives relative to that of bridgehead compounds.

However, it is known that nucleophilic participation decreases with an increase in steric hindrance and with an increase in charge stabilization,<sup>22</sup> and since the degree of solvent participation in the solvolysis of **17** and the stability of the carbenium ion derived from **17** are unknown, it appears premature to draw conclusions from the single result in MeOH. More extensive stereochemical and kinetic investigations are clearly required. Research in this direction is in progress.

### Acknowledgements

This work was supported by the Swiss National Science Foundation (Grant Nos 20-5281.97 and 21-45790.95) and by the Spanish DGIYT (Grant No. PB96-0927-CO2-01)

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