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ACID-CATALYSED SOLVOLYSIS OF OPTICALLY ACTIVE 1-PHENYL-1-METHOXYETHANE. THE ROLE OF ION–MOLECULE PAIR INTERMEDIATES

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The acid-catalysed solvolysis of (*R*)-1-phenyl-1-methoxyethane was studied in mixtures of dilute aqueous perchloric acid and acetonitrile at 50 °C. The rate of loss of optical activity (k_α) was found to be the same as the rate of solvolysis (k_{solv}) at both low and high water contents of the solvent. These results are not in accord with literature data on racemization and oxygen exchange of 1-phenylethanol in water, which has been discussed in terms of interconversion of chiral ion–dipole pair intermediates. The mechanistic implications of the results are discussed.

INTRODUCTION

Recent studies of some acid-catalysed solvolysis reactions of ethers have revealed that the initially formed carbocationic intermediates are ion–molecule pairs having significant lifetimes.[1–3] These species are analogous to the contact ion pairs of solvolysis reactions of substrates with negatively charged leaving groups. For example, it has been concluded that the acid-catalysed hydrolysis of an allylic methyl ether proceeds via ion–molecule pair intermediates since the production of allylic alcohols was accompanied by the formation of a rearranged allylic ether.[1] The latter is produced by an intramolecular rearrangement of the initially formed localized ion–molecule pair. Another example is the solvolysis of the anthranyl ether **A-OMe** (Scheme 1).[2] The alcohol **A-OH** is formed nine times faster than the rearranged anthracene product **B-OH**. Thus, it was concluded that the localized ion–molecule pair is trapped much faster by solvent water than it dissociates to the 'free' diffusionally-equilibrated delocalized anthracene carbonation.

This paper describes a study of the acid-catalysed solvolysis of 1-phenyl-1-methoxyethane (**1**), employing racemization of the optically active ether as a potential probe of internal return. The possibility of detecting internal return by comparing the rates of solvolysis and loss of optical activity was considered to be good since the oxygen exchange of the corresponding alcohol in dilute aqueous acid has been shown to be slower than racemization.[4] Moreover, using modern separation and analytical methods, the inversion without oxygen exchange of the alcohol was recently found to be relatively fast.[5] However, this work shows that the rate of loss of optical activity accompanying the solvolysis of **1** is the same as the rate of solvolysis. The mechanistic implications of the results are discussed.

RESULTS

The acid-catalysed solvolysis of 1-phenyl-1-methoxyethane (**1**) in acetonitrile–water mixtures provides quantitatively 1-phenylethanol (**2**) and a trace of styrene (**3**) [equation (1)]. The kinetics of the reactions were studied by a sampling-quench high-performance liquid chromatographic (HPLC) procedure. The loss of optical activity (k_α) which accompanies the solvolysis of the ether (*R*)-1-phenyl-1-methoxyethane was followed by polarimetry [equation (2)]. The measured rate constants and reaction conditions are recorded in Table 1. The racemization of (*R*)-1-phenylethanol was found to be about eleven times faster than the solvolysis of **1**, $k_{rac} = 214 \times 10^{-6}\,s^{-1}$ in 0·75 M $HClO_4$ in 25 vol. % acetonitrile–water at 49·95 °C.

$$\mathrm{H^+ + \underset{\mathbf{1}}{PhCH(Me)OMe} \xrightarrow{k_{solv}} \underset{\mathbf{2}}{PhCH(Me)OH} + \underset{\mathbf{3}}{PhCH{=}CH_2}} \quad (1)$$

$$\mathrm{H^+ + (\mathit{R})\text{-}PhCH(Me)OMe \xrightarrow{k_\alpha} (\mathit{R},\mathit{S})\text{-}PhCH(Me)OMe + (\mathit{R},\mathit{S})\text{-}PhCH(Me)OH + PhCH = CH_2} \quad (2)$$

The racemization of optically active **1** has not been

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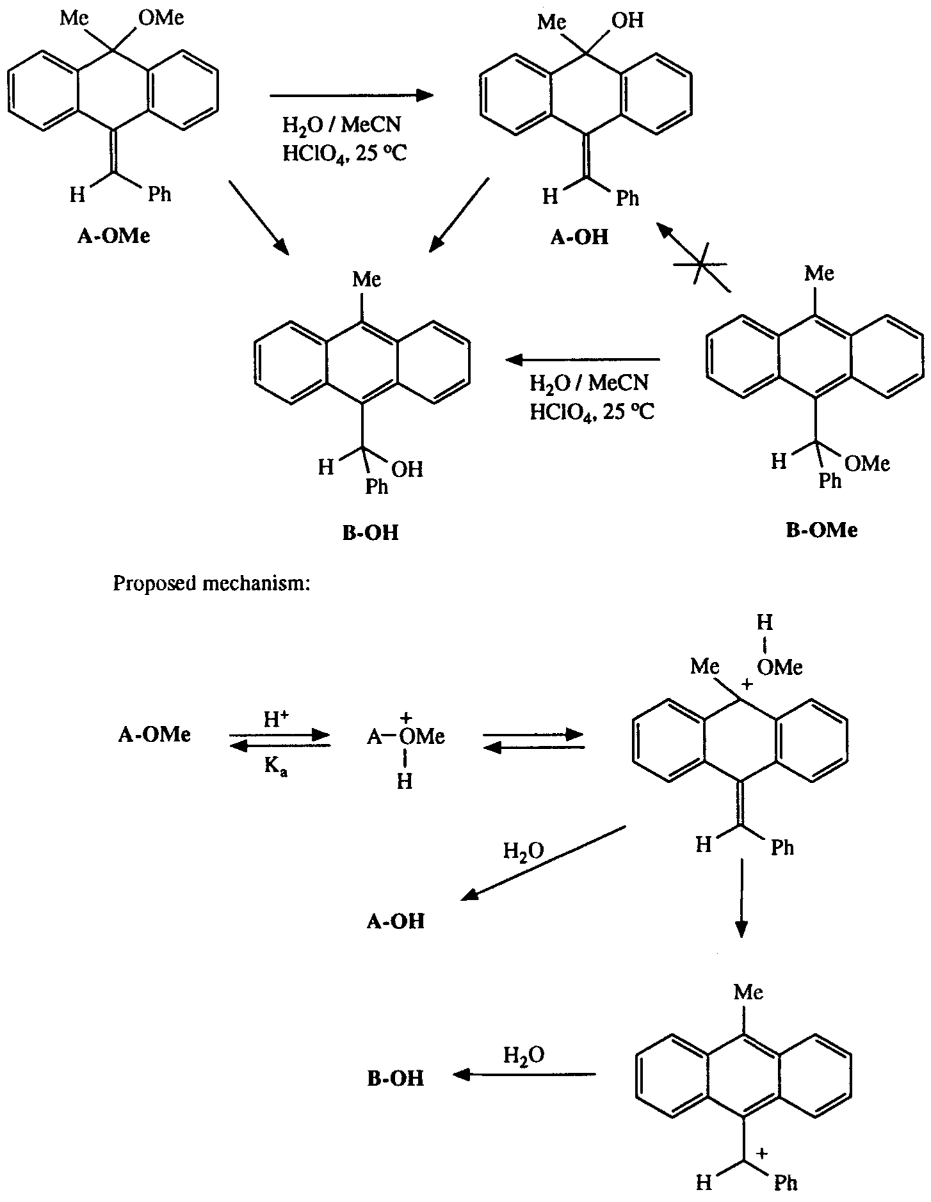
studied separately, e.g. by analysing partially reacted (R)-**1** for optical purity. Such an experiment should not give any further information because of the similar polarimetric and solvolytic reaction rates (Table 1).

DISCUSSION

The measured ratio $k_\alpha/k_{\text{solv}} = 0{\cdot}99$ at both low and high water contents of the solvent (Table 1) indicates a stepwise carbocation mechanism (S_N1). The classical S_N1 mechanism involving a racemic 'free' carbocation is expected to yield $k_\alpha/k_{\text{solv}} = 1$. In contrast, a concerted one-step mechanism (S_N2) with inversion at the central carbon corresponds to a ratio $k_\alpha/k_{\text{solv}} = 2$. A mechanism in which the initially formed chiral ion–molecule pair undergoes internal return with partial or complete racemization is expected to yield a ratio larger than unity, i.e. $k_\alpha/k_{\text{solv}} > 1$. The results are



Scheme 1

Table 1. Rate constants and reaction conditions for the acid-catalysed solvolysis of **1** in acetonitrile–water

Solvent	Temperature (°C)	$10^6 k_{\mathrm{solv}}$,[a] (s^{-1})	$10^6 k_{\alpha}$,[b] (s^{-1})	$k_{\alpha}/k_{\mathrm{solv}}$
25 vol.% MeCN[c]	25·00	0·3		
	49·95	19·8	19·7	0·99
	60·00	80		
90·9 vol.% MeCN[d]	49·95	1·00	0·99	0·99

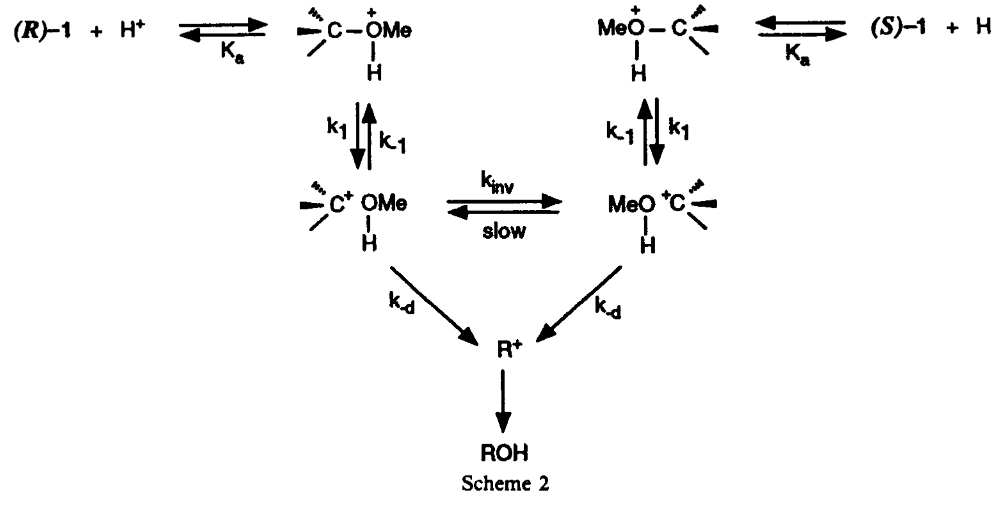
[a] The rate constant for the disappearance of **1** to **2** and **3** [equation (1)]. The maximum error in k_{solv} at 50 and 60 °C is estimated to be ±4%.
[b] The polarimetric rate constant. The maximum error in k_{α} is estimated to be ±4%.
[c] $[HClO_4] = 0{\cdot}75$ M.
[d] $[HClO_4] = 0{\cdot}091$ M.

surprising in the light of results obtained from a number of studies of solvolysis of substituted and unsubstituted 1-phenylethyl derivatives. Thus, scrambling of ^{18}O in unreacted ring-substituted 1-phenylethyl 4-nitrobenzoates has been reported,[6] and a significant amount of return has been estimated for the 1-(4-methylphenyl)carbocation pentafluorobenzoate ion pair in 50% aqueous trifluoroethanol.[7] Partial racemization of unreacted 1-phenylethyl chloride has also been reported.[8]

However, more surprising is the comparison of the present results with ^{18}O exchange and racemization studies of 1-phenylethanol in water at 64·5 °C.[4,5] Thus, Grunwald *et al.*[4] reported a ratio of racemization to exchange of optically active alcohol of $k_{\mathrm{rac}}/k_{\mathrm{ex}} = 1{\cdot}22$. A recent study of the same system under comparable reaction conditions gave $k_{\mathrm{rac}}/k_{\mathrm{ex}} = 1{\cdot}19$ and it was reported that the labelled alcohol undergoes inversion without oxygen exchange with a rate comparable to the rates of oxygen exchange with inversion and oxygen exchange without inversion.[5] Moreover, oxygen-exchange studies of a number of secondary and tertiary alcohols suggest that the water leaving group is associated with the carbocation as a short-lived complex.[9] However, some of the studied substrates yield less stable secondary carbocations, which may not have a significant lifetime in the presence of water. Dietze and Jencks[10] suggested that the acid-catalysed reactions of butan-2-ol and propane-1,2-diol are concerted.

The results of this work are consistent with the mechanism shown in Scheme 2. The hydronated ether ionizes (k_1) to a chiral ion–molecule pair, which undergoes separation ($k_{-\mathrm{d}}$) to a racemic diffusionally-equilibrated carbocation much faster than it undergoes inversion (k_{inv}) of the configuration of the ion–molecule pair. The internal return (k_{-1}) is presumably fast since methanol is more nucleophilic than water and the intermediate formed from the alcohol has been found to collapse quickly to covalent material.[4,5] Accordingly, the difference between the solvolysis mechanisms of the ether and the alcohol is that the inversion of the ion–molecule pair formed from the ether is slow whereas the corresponding process for the intermediate formed from the alcohol is relatively fast. The reason for this difference is not known but solvation differences of the leaving groups of the ion–molecule pairs should be of importance. Thus, the apparently different behaviours of the ether and the alcohol may be due to an intrinsic difference between the solvation of the leaving groups OH_2 and ORH. The difference in solvent, 25 vol. % acetonitrile and pure water, is less likely to be the cause. The reorganization (k_{inv}) to the inverted ion–molecule pair may be the result either of movement of the leaving group or of rotation of the carbocation itself.

An alternative variant of the Scheme 2 mechanism that is also able to accommodate the experimental data



Scheme 2

is slow internal return (k_{-1}). The inversion process (k_{inv}) may then be fast. However, as discussed above, slow internal return is not very likely since the return of the ion–molecule pair formed from the alcohol is fast and the ion–methanol pair is expected to collapse even faster because of the higher nucleophilicity of methanol. It has been found that the diffusionally-equilibrated 1,1-diphenylethyl carbocation reacts 6–7 times faster with a methanol molecule than with a water molecule in aqueous solution.[11] Moreover, the assumption that the dissociation of the ion–molecule pair is relatively slow is supported by the conclusion that other methyl ethers, which form more stable carbocations, react through this type of intermediate.[1–3]

The acid catalysis of the formation of the ion–molecule pair is presumably of specific type owing to the relative instability of the carbocation intermediate.[3,12,13] A progressive increase in the Brønsted coefficient α is the result of decreasing carbocation stability.[11] Accordingly, general base catalysis has been detected for the reaction of the 4-methoxy-substituted carbocation with alcohols in aqueous solution but has not been detected for the 4-methyl-substituted carbocation.[12]

A small amount of alcohol formation by a concerted reaction, S_N2 or 'S_N2_{ip}', is plausible [equation (3)]. Moreover, a slight enatiomeric excess of (*S*)-**2** may be the result of a stepwise mechanism by shielding the front side of the carbocation by the leaving group. Of course, this case is kinetically indistinguishable from the S_N2 mechanism. However, according to the kinetic results, such a direct nucleophilic attack on the chiral ion–molecule pair or protonated ether to give product alcohol with inversion of configuration, i.e. (*S*)-**2** from (*R*)-**1**, cannot be a major reaction route.

$$\begin{tikzcd}
(R)\text{-}\mathbf{1} \arrow[rr, "k_{AB}"] \arrow[dr, "k_{AC}"'] & & (S)\text{-}\mathbf{2} \arrow[dl, "k_{BC} = 214 \times 10^{-6}\,\mathrm{s}^{-1}"] \\
& (R,S)\text{-}\mathbf{2} &
\end{tikzcd}$$

$$k_{\mathrm{solv}} = k_{AB} + k_{AC} \qquad (3)$$

This is illustrated in Figure 1 for the case when $k_{AB} = 0$ and for $k_{AB} = k_{AC}$, and employing the measure rate constants given in Table 1 and the exact integrated rate-constant expression of equation (3). The experimental kinetic data for the loss of optical activity of (*R*)-**1** agrees with curve 1 without any detectable deviation from a pseudo-first-order behaviour. Curve 2, on the

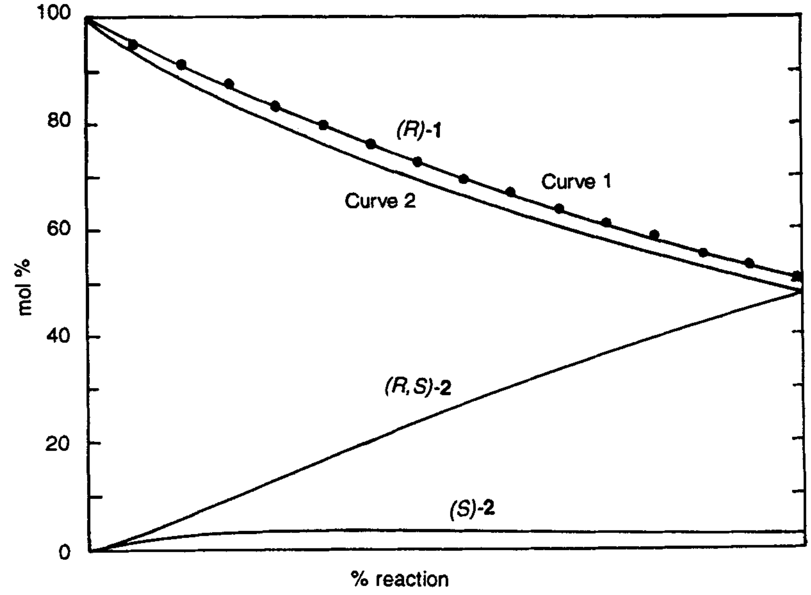


Figure 1. Time dependence of reaction of (*R*)-**1** to (*S*)-**2** and (*R*,*S*)-**2** in 25 vol.% acetonitrile in aqueous perchloric acid at 49·95 °C. The curves shown were computer simulated employing the exact integrated rate-constant expressions of equation (3) and assuming $k_{AB} + k_{AC} = 19{\cdot}8 \times 10^{-6}\,\mathrm{s}^{-1}$. Curve 1, which shows the decrease in (*R*)-**1** with time for any ratio of k_{AB}/k_{AC} or, equivalently, the decrease in optical activity for the case that $k_{AB} = 0$, agrees without any significant deviation from the experimental polarimetric data. Curve 2 [equal to curve 1 – the (*S*)-**2** curve] shows the corresponding decrease in optical activity (k_α) that accompanies the reaction of (*R*)-**1** if $k_{AB} = k_{AC}$. The experimentally measured decrease in optical rotation of the reaction of (*R*)-**1**, recalculated to mol%, is plotted as dots (see Experimental)

other hand, is not consistent with the experimental data. Thus, a plausible concerted, or stepwise, route with inversion has to be considerably slower than the route through the unshielded carbocation intermediate. [A referee suggested analysis of the hydrolysis and stereochemical processes by employing the following reaction scheme:

$$\begin{tikzcd}
(R)\text{-}\mathbf{1} \arrow[rr, "k_{AB}"] \arrow[dr, "k_{AC}"'] & & (S)\text{-}\mathbf{2} \arrow[dl, shift left, "k_{BC}"] \\
& (R)\text{-}\mathbf{2} \arrow[ur, shift left, "k_{CB}"] &
\end{tikzcd}$$

However, this simulation is analogous to that in equation (3) and Figure 1 and does not provide a more precise estimate of the amount of inversion.]

EXPERIMENTAL

General procedures. NMR analyses were performed with a Varian XL 300 spectrometer. HPLC analyses were carried out with a Hewlett-Packard 1090M liquid chromatograph equipped with an HP 1050 variable-wavelength detector and a C_8 reversed-phase column ($100 \times 2{\cdot}1$ mm i.d.). The mobile phase was a solution of acetonitrile in water. Polarimetric measurements were carried out with a Perkin-Elmer Model 241 polarimeter thermostated with water from a Heto 01 PT 623 thermostat. The accuracy of the temperature was higher than ±0·10 °C.

Materials. 1-Phenylethanol (**2**) (Aldrich) was used for the synthesis of the racemic ether and for calibration purposes. The optically active alcohol (*R*)-1-phenylethanol, which was used for the preparation of the optically active ether, was purchased from Sigma. Styrene (**3**) (Aldrich) was used for calibration purposes. Acetonitrile and methanol were of spectroscopic quality and were used as solvents without further purification.

1-Phenyl-1-methoxyethanol (**1**). This was synthesized from the alcohol by two methods, HCl-catalysed solvolysis in refluxing methanol or methylation with refluxing methyl iodide in the presence of freshly prepared silver oxide as catalyst.[14] The latter method was the only method used for preparation of (*R*)-1-phenyl-1-methoxyethane. Neither of the methods gave complete methylation. The desired product was separated from unreacted starting material and styrene by means of semipreparative HPLC on a C_8 reversed-phase column using methanol–water as eluent followed by microdistillation. The pure (*R*)-1-phenyl-1-methoxyethane had a specific rotation of $0{\cdot}10[\alpha]^{25}_{D} = 8{\cdot}38$ (neat).

Kinetics and product studies. The reaction solutions were prepared by mixing the acetonitrile with the cosolvent at room temperature, *ca* 22 °C. The reaction vessel was either a thermostated 10-cm polarimeter microcell of quartz with a volume of 1 ml or a 2-ml HPLC flask, sealed with a gas-tight PTFE septum, which was placed in an aluminium block in the water thermostat. The reactions were initiated by fast addition of the substrate to the thermostated reaction solution by means of a syringe. The decrease in optical rotation of the reactions at 436 nm was followed for at least three half-lives. The rate constants (k_α) were calculated by means of a nonlinear regression computer program. Very good pseudo-first-order behaviour was observed. Not even the initial part of the reaction showed a deviation from a simple first-order behaviour.

The kinetics of the solvolysis reactions were derived by a sampling technique. An aliquot of the acidic reaction solution was neutralized with a mixture of sodium hydroxide and sodium acetate in water–acetonitrile followed by analysis of reactants and products by HPLC. The concentration of each component of the reaction mixture (mol%) was calculated from the areas and the relative response factors. The rate constant of the disappearance of the substrate was obtained from slopes of ln(mol% **1**) versus time. The estimated errors are considered as maximum errors derived from maximum systematic errors and random errors.

The curves in Figure 1 for the reactions of equation (3) were obtained by computer simulation by employing the following integrated rate-constant expressions:[15]

$$\text{mol\% } (R)\text{-}\mathbf{1} = a \exp(-m_1 t) + (100 - a)\exp(-m_2 t)$$
$$\text{mol\% } (S)\text{-}\mathbf{2} = b \exp(-m_1 t) - b \exp(-m_2 t)$$
$$\text{mol\% } (R,S)\text{-}\mathbf{2} = 100 - \text{mol\% } (R)\text{-}\mathbf{1} - \text{mol\% } (S)\text{-}\mathbf{2}$$

where

$$\begin{aligned}
a &= 100(k_{AB} + k_{AC} - m_2)/(m_1 - m_2) \\
b &= 100k_{AB}/(m_2 - m_1) \\
m_1 &= [(k_{AB} + k_{AC} + k_{BA} + k_{BC})^2/4 - k_{AB}k_{BC} \\
&\quad - (k_{BA} + k_{BC})k_{AC}]^{1/2} \\
&\quad + (k_{AB} + k_{AC} + k_{BA} + k_{BC})/2 \\
m_2 &= -\ [(k_{AB} + k_{AC} + k_{BA} + k_{BC})^2/4 - k_{AB}k_{BC} \\
&\quad - (k_{BA} + k_{BC})k_{AC}]^{1/2} \\
&\quad + (k_{AB} + k_{AC} + k_{BA} + k_{BC})/2
\end{aligned}$$

The measured angles in a kinetic run with (*R*)-**1** were converted into mol% by the relation $(\text{mol\%})_t = 100(\text{angle})_t/(\text{angle})_{t=0}$ and are plotted in Figure 1.

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REFERENCES

1. A. Thibblin, *J. Chem. Soc., Perkin Trans 2*, 1629 (1987).
2. A. Thibblin, *J. Chem. Soc., Chem. Commmun.*, 697 (1990).
3. A. Thibblin, *J. Chem. Soc, Perkin Trans 2*, 1195 (1992).
4. E. Grunwald, A. Heller and F. S. Klein, *J. Chem. Soc.*, 2604 (1957).
5. M. V. Merritt, S. J. Bell, H.-J. Cheon, J. A. Darlington, T. L. Dugger, N. B. Elliott, G. L. Fairbrother, C. S. Melendez, E. V. Smith and P. L. Schwartz, *J. Am. Chem. Soc.* **112**, 3560 (1990).
6. H. L. Goering, R. G. Briody and G. Sandrock, *J. Am. Chem. Soc.* **92**, 7401 (1970).
7. J. P. Richard and W. P. Jencks, *J. Am. Chem. Soc.* **106**, 1373 (1984).
8. V. J. Shiner, Jr., S. R. Hartshorn and P. C. Vogel, *J. Org. Chem.* **38**, 3604 (1973).
9. (a) D. A. Bunton, A. Konasiewicz and D. R. Llewellyn, *J. Chem. Soc.* 604 (1955); (b) D. A. Bunton and D. R. Llewellyn, *J. Chem. Soc.* 3402 (1957); (c) H. L. Goering and R. E. Dilgren, *J. Am. Chem. Soc.* **82**, 5744 (1960); (d) C. A. Bunton and R. B. Henderson, *Tetrahedron Lett.* 1829 (1963); (e) J. Manassen and F. S. Klein, *J. Chem. Soc.* 4203 (1960); (f) R. H. Boyd, R. W. Taft, Jr, A. P. Wolf and D. R. Christman, *J. Am. Chem. Soc.* **82**, 4729 (1960); (g) K. P. Herlihy, *Aust. J. Chem.* **34**, 107 (1981); (h) K. P. Herlihy, *Aust. J. Chem.* **35**, 2221 (1982).
10. P. E. Dietze and W. P. Jencks, *J. Am Chem. Soc.* **109**, 2057 (1987).
11. A. Thibblin, *J. Phys. Org. Chem.* **5**, 367 (1992).
12. J. P. Richard and W. P. Jencks, *J. Am. Chem. Soc.* **106**, 1396 (1984).
13. C. A. Bunton, F. Davoudazedeh and W. E. Watts, *J. Am. Chem. Soc.* **103**, 3855 (1981).
14. K. Mislow, *J. Am. Chem. Soc.* **73**, 4043 (1951).
15. A. Thibblin, *J. Am. Chem. Soc.* **105**, 853 (1981).