Formation and stability of organic zwitterions — The carbon acid pK_as of the trimethylsulfonium and tetramethylphosphonium cations in water[1]

Ana Rios, AnnMarie C. O'Donoghue, Tina L. Amyes, and John P. Richard

Abstract: We report second-order rate constants of $k_{DO} = 7.5 \times 10^{-4}$ and 9.9×10^{-5} (mol/L)$^{-1}$ s^{-1} for exchange for deuterium of the first methyl proton of the trimethylsulfonium and tetramethylphosphonium cations, respectively, in D_2O at 25 °C and $I = 1.0$ (KCl). The data were analyzed to give the following carbon acidities for these cationic carbon acids in water: $(CH_3)_3S^+$, pK_a = 28.5; $(CH_3)_4P^+$, pK_a = 29.4. These acidities are close to those of the neutral carbon acids acetonitrile and dimethylacetamide. This provides evidence that a portion of the stabilization of the cyanomethyl carbanion is due to resonance delocalization of negative charge from carbon to cyano nitrogen.

Key words: carbon acids, carbanions, ylides, proton transfer.

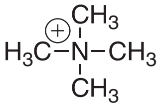
Résumé : Opérant dans le D_2O, à 25 °C et une valeur de $I = 1,0$ (KCl), on a déterminé que les constantes de vitesse du deuxième ordre pour l'échange du deutérium du premier proton méthyle des cations triméthylsulfonium et tétraméthylphosphonium sont respectivement de $k_{DO} = 7,5 \times 10^{-4}$ et $9,9 \times 10^{-5}$ (mol/L)$^{-1}$ s^{-1}. Les données ont été analysées pour en tirer les acidités carboniques suivantes pour ces acides carboniques cationiques dans l'eau: $(CH_3)_3S^+$, pK_a = 28,5 et $(CH_3)_4P^+$, pK_a = 29,4. Ces acidités se rapprochent de celles d'autres acides carboniques, tel l'acétonitrile et le diméthylacétamide. Ces résultats montrent qu'une portion de la stabilization du carbanion cyanométhyle est due à une délocalization de résonance de la charge négative du carbone vers l'azote du groupe cyano.

Mots clés : acides carboniques, carbanions, ylures, transfert de proton.

[Traduit par la Rédaction]

Introduction

We are interested in characterizing the effects of strongly electron-withdrawing substituents on carbon acidity and have reported the kinetic and thermodynamic acidities of a variety of weak carbon acids in water (1–12). The very low carbon acidity of methane (13) is increased by substituents that provide polar and (or) resonance stabilization of negative charge at the methyl carbanion; and the most powerful purely polar stabilization of a methyl carbanion is provided by a cationic group at a neighboring atom. In 1955 Doering and Hoffmann (14) reported rate constants for deprotonation of the tetramethylammonium, tetramethylphosphonium, and trimethylsulfonium cations by hydroxide ion at several temperatures. Their data showed that the tetramethylammonium cation is a significantly weaker carbon acid than the tetramethylphosphonium and trimethylsulfonium cations. Thus, the ylides of phosphonium and sulfonium cations are stabilized relative to the corresponding ylides of ammonium cations by the greater polarizability of phosphorus and sulfur than of nitrogen, and possibly by hyperconjugation (15, 16) and back-bonding from carbon to the *d*-orbitals of phosphorus and sulfur (17).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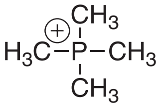
Me_4N^+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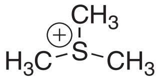
$(CH_3)_3S^+$

Me_3S^+

In recent years there have been several studies that document the relatively strong carbon acidity of alkyl sulfonium (18–26) and alkyl phosphonium (27, 28) cations. However, the carbon acid pK_as for the parent tetramethylphosphonium and trimethylsulfonium cations in aqueous solution have not been reported. To this end, we have determined the rate constants for deprotonation of the tetramethylphosphonium cation (**Me_4P^+**) and trimethylsulfonium cation (**Me_3S^+**) in D_2O at 25 °C, using modern NMR methods to monitor transfer of deuterium from the solvent to carbon acid. Our results agree well with the results of Doering and Hoffmann (14); they extended earlier work by showing that there is no catalysis of deprotonation of these cationic carbon acids by buffer bases. An analysis of these data by the methods that we have developed to determine equilibrium carbon acidities in water (1–

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12) provides the carbon acid pK_as for deprotonation of **Me_4P^+** and **Me_3S^+** in water.

Experimental

Materials

All organic and inorganic chemicals were reagent grade or better and were used without further purification. Trimethylsulfonium methyl sulfate, tetramethylphosphonium chloride, tetramethylammonium chloride, quinuclidine hydrochloride, 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), 2,2,2-trifluoroethanol (TFE), and KOD (40% wt, +98% D) were from Aldrich. Deuterium oxide (99.9% D) and deuterium chloride (35% *w*/*w*, 99.5% D) were from Cambridge Isotope Laboratories.

Preparation of solutions

The acidic proton of quinuclidine hydrochloride was exchanged for deuterium before use as described previously (1). TFE and HFIP were dissolved directly in D_2O (99.9% D), but at no time did this introduce >0.5 atom% of protium into the solvent. Quinuclidine, trifluoroethanol, and HFIP buffers were prepared by dissolving their acidic forms and KCl in D_2O followed by the addition of KOD to give the desired acid:base ratio or pD at I = 1.0 (KCl).

Solution pD was determined at 25 °C using an Orion Model 720A pH meter equipped with a Radiometer GK2321C or pHC4006-9 combination electrode. Values of pD were obtained by adding 0.40 to the observed reading of the pH meter (29). The concentration of deuterioxide ion at any pD was calculated from eq. [1], where $K_w = 10^{-14.87}$ (mol/L)^2 is the ion product of D_2O at 25 °C (30) and γ_{OL} = 0.79 or 0.75 is the apparent activity coefficient of lyoxide ion under our experimental conditions determined by the GK2321C or the pHC4006-9 electrode, respectively (2).

$$[1] \qquad [\mathrm{DO}^-] = \frac{10^{\mathrm{pD}-\mathrm{p}K_w}}{\gamma_{OL}}$$

^{1}H NMR spectroscopy

^{1}H NMR spectra at 500 MHz were recorded in D_2O at 25 °C on a Varian Unity Inova 500 spectrometer. The relaxation times for the methyl protons of **Me_3S^+** and **Me_4P^+**, determined for 10 mmol/L solutions of substrate at I = 1.0 (KCl), were found to be in the range of T_1 = 6 to 7 s. The relaxation delay between pulses was at least 10-fold greater than the longest T_1 of the protons of interest. Chemical shifts were reported relative to HOD at 4.67 ppm. Baselines were subjected to a first-order drift correction before the determination of the integrated peak areas.

Kinetic measurements

All reactions were carried out in D_2O at 25 °C and a constant ionic strength of 1.0 maintained with potassium chloride. The deuterium exchange reactions of **Me_3S^+** and **Me_4P^+** in buffered solutions were initiated by mixing solutions of the substrate and the buffer at the same pD and ionic strength (I = 1.0, KCl) to give a final substrate concentration of 10 mmol/L. The reactions of **Me_4P^+** and **Me_4N^+** in alkaline solutions of D_2O were initiated by mixing solutions of the substrate and KOD at the same ionic strength (I = 1.0, KCl) to give a final substrate concentration of 10 mmol/L. At timed intervals an aliquot (600 μL) was removed from the reaction mixture and the pD was adjusted to 7 to 8 by the addition of concentrated DCl and 50 μL of 0.4 mol/L phosphate buffer in D_2O. The aliquots were either analyzed immediately by ^{1}H NMR spectroscopy or were frozen for analysis at a later time.

The exchange for deuterium of the first proton of the methyl groups of **Me_3S^+** was followed by monitoring the disappearance of the singlet at 2.911 ppm owing to the CH_3 groups and the appearance of the triplet at 2.899 ppm (J_{HD} = 2 Hz) owing to the CH_2D groups, by ^{1}H NMR. The exchange for deuterium of the first proton of the methyl groups of **Me_4P^+** was followed by monitoring the disappearance of the doublet at 1.867 ppm (J_{HP} = 16 Hz) owing to the CH_3 groups and the appearance of the doublet of triplets at 1.852 ppm (J_{HP} = 16 Hz, J_{HD} = 2.5 Hz) owing to the CH_2D groups. The reactions were followed during the exchange for deuterium of up to 25% and 5% of the first proton of the methyl groups of **Me_3S^+** and **Me_4P^+**, respectively.

$$[2] \qquad R = \frac{A_{CH_3}}{A_{CH_3} + \frac{A_{CH_2D}}{2}}$$

$$[3] \qquad \ln R = -k_{obsd}t$$

Values of R, which is a measure of the progress of the deuterium exchange reaction (4, 31), were calculated according to eq. [2], where A_{CH_3} and A_{CH_2D} are the integrated areas of the signals owing to the CH_3 and CH_2D groups, respectively. During the early stages of the reaction of **Me_3S^+**, it was possible to obtain baseline separation of only the most upfield peak of the triplet owing to the CH_2D groups. In these cases, the total integrated area of the triplet due to the CH_2D groups (A_{CH_2D}) was obtained by multiplying the integrated area of the resolved peak by three, and the area of the singlet owing to the CH_3 groups (A_{CH_3}) was obtained as the difference between the total peak area for both the singlet and the triplet and A_{CH_2D} (2). For the reaction of **Me_4P^+**, only the most upfield peak of the doublet of triplets due to the CH_2D groups was cleanly resolved. The area of the doublet of triplets due to the CH_2D groups (A_{CH_2D}) was obtained by multiplying the integrated area of the resolved peak by six, and the area of the doublet due to the CH_3 groups (A_{CH_3}) was obtained as the difference between the total peak area for all the signals and A_{CH_2D}.

Semilogarithmic plots of reaction progress (R) against time were linear with negative slopes equal to k_{obsd} (s^{-1}, eq. [3]), which is the rate constant for exchange of a *single* proton of the substrate.

A triplet at 3.164 ppm (J = 0.5 Hz) was observed for the four equivalent methyl groups of the tetramethylammonium cation. No signal for a CH_2D group was observed after the incubation of the substrate in the presence of 1.0 mol/L KOD at 25 °C for 16 days. Several spurious signals appeared during this prolonged reaction time, but no attempt was made to assign these signals.

Table 1. First-order rate constants for exchange for deuterium of the first proton of $\mathbf{Me_4P^+}$ and $\mathbf{Me_3S^+}$ in D_2O at 25 °C and I = 1.0 (KCl).

Carbon acid	Brønsted base	f_B[a]	$[B]_T$ (mol/L)[b]	pD	$[DO^-]$ (mol/L)[c]	k_{ex} (s^{-1})[d]
$(CH_3)_4P^+$	DO^-				0.29	2.8×10^{-5}
					0.22	2.2×10^{-5}
					0.17	1.6×10^{-5}
					0.13	1.2×10^{-5}
					0.042	3.9×10^{-6}
	$CF_3CH_2O^-$	0.2	0.092	12.22	2.83×10^{-3}	3.1×10^{-7}
			0.18	12.30	3.40×10^{-3}	3.6×10^{-7}
			0.28	12.34	3.73×10^{-3}	3.4×10^{-7}
			0.37	12.37	4.00×10^{-3}	3.7×10^{-7}
$(CH_3)_3S^+$	$(CF_3)_2CHO^-$	0.90	0.05	10.77	1.01×10^{-4}	1.0×10^{-7}
			0.10	10.77	1.01×10^{-4}	9.6×10^{-8}
			0.25	10.83	1.15×10^{-4}	9.8×10^{-8}
			0.50	10.91	1.39×10^{-4}	1.1×10^{-7}
	Quinuclidine	0.20	0.05	11.50	5.40×10^{-4}	3.7×10^{-7}
			0.20	11.47	5.04×10^{-4}	3.3×10^{-7}
		0.40	0.05	11.92	1.42×10^{-3}	9.0×10^{-7}
			0.20	11.89	1.32×10^{-3}	7.6×10^{-7}
	$CF_3CH_2O^-$	0.10	0.05	12.04	1.87×10^{-3}	1.42×10^{-6}
			0.20	12.12	2.25×10^{-3}	1.42×10^{-6}

[a] Fraction of the Brønsted catalyst in the reactive basic form.
[b] Total concentration of the Brønsted catalyst.
[c] Concentration of deuterioxide ion at the pD of the experiment calculated from eq. [1].
[d] Observed first-order rate constant for deuterium exchange determined by ^1H NMR spectroscopy.

Results

The exchange for deuterium of the first proton of the methyl groups of $\mathbf{Me_3S^+}$ and $\mathbf{Me_4P^+}$ in D_2O at 25 °C and I = 1.0 (KCl) was followed by ^1H NMR spectroscopy at 500 MHz (Scheme 1). Deuterium exchange at $\mathbf{Me_3S^+}$ results in disappearance of the singlet at 2.911 ppm owing to the CH_3 groups and appearance of an upfield-shifted triplet at 2.899 ppm owing to the CH_2D groups. Similarly, exchange at $\mathbf{Me_4P^+}$ results in disappearance of the doublet at 1.867 ppm and the appearance of a doublet of triplets at 1.852 ppm owing to the CH_2D groups. The deuterium isotope effect on the ^1H NMR chemical shift and the H–D coupling constant are similar to those observed in our previous work (1, 2, 4–6, 9, 10, 32, 33).

First-order rate constants (k_{obsd} (s^{-1})) for exchange for deuterium of a *single* proton of the cationic carbon acids were determined as the slopes of semilogarithmic plots of reaction progress R (eq. [2]) against time according to eq. [3] (not shown). The reaction of $\mathbf{Me_3S^+}$ to give the monodeuteriated product occurs nine times as fast as the exchange of a *single* proton of the reactant, so that $k_{ex} = 9k_{obsd}$ where k_{ex} (s^{-1}) is the first-order rate constant for exchange of the first proton of the reactant to give the monodeuteriated product (Scheme 1A) (4, 31). Similarly, the reaction of $\mathbf{Me_4P^+}$ to give the monodeuteriated product occurs 12 times as fast as the exchange of a *single* proton of the reactant, so that $k_{ex} = 12k_{obsd}$ (Scheme 1B) (4, 31).

Scheme 1.

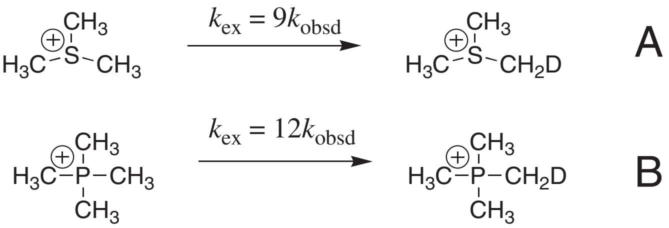


Table 1 gives the values of k_{ex} (s^{-1}) for the deuterium exchange reactions of $\mathbf{Me_3S^+}$ and $\mathbf{Me_4P^+}$ in the presence of various concentrations of deuterioxide ion or added buffers in D_2O at 25 °C and I = 1.0 (KCl). There is no significant change in the value of k_{ex} for the deuterium exchange reaction of $\mathbf{Me_4P^+}$ as the concentration of trifluoroethanol buffer is increased from 0.092 to 0.37 mol/L at pD 12.3. Similarly, the value of k_{ex} for the deuterium exchange reaction of $\mathbf{Me_3S^+}$ is independent of the concentration of added hexafluoroisopropanol, quinuclidine, or trifluoroethanol buffers (Table 1). The absence of buffer catalysis of deuterium exchange shows that, in basic solution, these cationic carbon acids are deprotonated exclusively by the solvent.

Figure 1 shows the dependence of k_{ex} (s^{-1}) on the concentration of deuterioxide ion in D_2O for the deuterium exchange reaction of $\mathbf{Me_4P^+}$. The slope of this correlation gives $k_{DO} = 9.9 \times 10^{-5}$ $(mol/L)^{-1}$ s^{-1} (eq. [4]) where k_{DO} is the second-order rate constant for deuterium exchange catalyzed by the deuterioxide ion.

$$[4] \qquad k_{ex} = k_{DO}[DO^-]$$

Fig. 1. Dependence of k_{ex} (s^{-1}) for exchange for deuterium of the first proton of $\mathbf{Me_4P^+}$ on the concentration of deuterioxide ion in D_2O at 25 °C and I = 1.0 (KCl). The slope gives the second-order rate constant (k_{DO}) for DO^--catalyzed deuterium exchange.

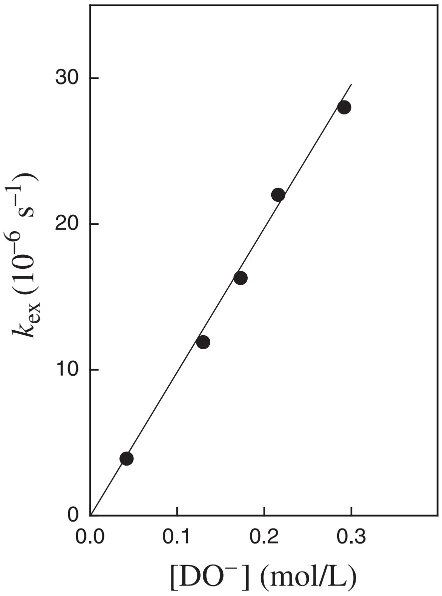


Figure 2 shows the pD–rate profiles for the deuterium exchange reactions of $\mathbf{Me_4P^+}$ (●) and $\mathbf{Me_3S^+}$ (◆). In cases where values of k_{ex} were determined over a range of buffer concentrations (Table 1), the values of pD and k_{ex} for the reaction at the lowest buffer concentration were used for Fig. 2. The solid line through the data for $\mathbf{Me_4P^+}$ was calculated from the value of $k_{DO} = 9.9 \times 10^{-5}$ $(mol/L)^{-1}$ s^{-1} using eq. [5]. A value of $k_{DO} = 7.5 \times 10^{-4}$ $(mol/L)^{-1}$ s^{-1} for $\mathbf{Me_3S^+}$ was determined from the fit of the data to eq. [5] (10). Figure 2 also shows data for the deuterium exchange reactions of acetonitrile (■) (4) and dimethylacetamide (▲) (10) taken from our earlier work.

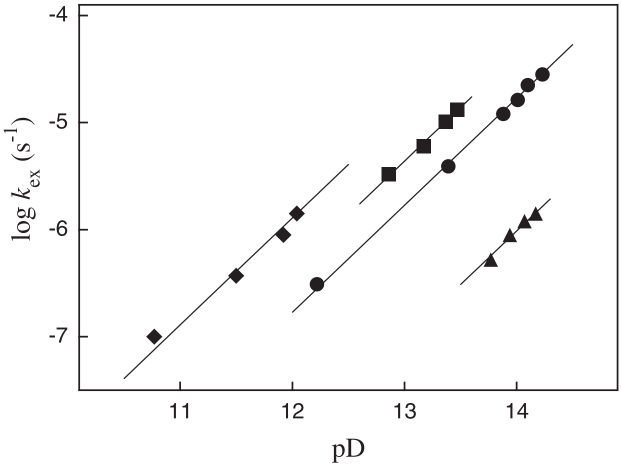
$$[5] \qquad \log k_{ex} = \log\left(\frac{k_{DO}K_w}{\gamma_{OL}}\right) + pD$$

There was no detectable formation of a CH_2D group after the reaction of $\mathbf{Me_4N^+}$ in 1.0 mol/L KOD in D_2O at 25 °C for 16 days. During this time, the appearance of several unidentified NMR signals showed that there were other reaction(s) of $\mathbf{Me_4N^+}$, but these were not characterized. A peak for a CH_2D group that is 1% of the area of the peak due to the CH_3 groups could have been easily detected in these experiments. This was used to calculate an upper limit of $k_{DO} < 4 \times 10^{-8}$ $(mol/L)^{-1}$ s^{-1} for the deuterium exchange reaction of $\mathbf{Me_4N^+}$ catalyzed by deuterioxide ion.

Discussion

The present work was initiated for the following reasons: (1) We wanted to determine second-order rate constants for the deuterioxide ion catalyzed deuterium exchange reactions of $\mathbf{Me_4P^+}$ and $\mathbf{Me_3S^+}$ using modern analytical methods and under the same conditions used in our other studies of the acidity of weak carbon acids. (2) We wanted to determine if these deuterium exchange reactions are catalyzed by buffer bases. (3) We wanted to obtain pK_as for these cationic carbon acids in water and to draw comparisons with the other data that we have reported over the last decade or so.

Fig. 2. pD–rate profiles of k_{ex} for deuterioxide ion catalyzed exchange for deuterium of the first proton of $\mathbf{Me_3S^+}$ (◆, this work), $\mathbf{Me_4P^+}$ (●, this work), CH_3CN (■, data from ref. 4), and $CH_3C(O)NMe_2$ (▲, data from ref. 10) in D_2O at 25 °C and I = 1.0 (KCl).



In 1955 Doering and Hoffmann (14) monitored the deuterium exchange reactions of several cationic carbon acids in D_2O by combustion of the recovered carbon acid to a mixture of D_2O and H_2O, whose deuterium enrichment was then determined by the "method of the falling drop". Table 2 shows that the second-order rate constants (k_{DO}) for deuterioxide-ion-catalyzed exchange of the first proton of $\mathbf{Me_4P^+}$ and $\mathbf{Me_3S^+}$ determined here agree to within 33% with the earlier values of Doering and Hoffmann (14). The slightly higher values reported in the earlier work were obtained at a temperature of 26.8 °C compared with 25 °C used in this work.

Rate-determining step for hydron exchange

The rate constant (k_{DO}) for exchange of the first proton of these cationic carbon acids in D_2O may be limited either by the chemical step of proton transfer from the substrate to deuterioxide ion (k_p, Scheme 2), or if this step is reversible ($k_{-p} >> k_{reorg}$), by the rate constant for reorganization of solvent to place a molecule of D_2O in a position to deliver a labeled hydron to the ylide, $k_{reorg} \approx 10^{11}$ s^{-1} (Scheme 2) (4, 11, 34). It has been shown in earlier work that reorganization of solvent is largely rate-determining for the lyoxide ion catalyzed deprotonation of cyanoalkanes (4). The following comparisons between proton transfer at cyanoalkanes and at $\mathbf{Me_4P^+}$ and $\mathbf{Me_3S^+}$ provide strong evidence that these reactions proceed with the common rate-determining step of solvent reorganization.

(1) There is a simple correlation between the decreasing importance of buffer catalysis of carbon deprotonation on moving from dihydroxyacetone phosphate (35) to acetamide (10) (Scheme 3) and the increasing reactivity and decreasing lifetime of the carbanion product of carbon deprotonation (10). No buffer catalysis is observed for the limiting case where the reorganization of solvent

Table 2. Kinetic and thermodynamic acidity of simple weak carbon acids in aqueous solution.

Carbon acid	k_{DO} ((mol/L)$^{-1}$ s^{-1})[a]	k_{HO} ((mol/L)$^{-1}$ s^{-1})[b]	k_{HOH} (s^{-1})[c]	pK_a[d]	pK_a (CH$_3$)[e]
$(CH_3)_4N^+$	$<4\times10^{-8}$[f]	$<1.7\times10^{-8}$[g]	10^{11}	>32.8	>33.4
$(CH_3)_4P^+$	9.9×10^{-5}[h] (1.2×10^{-4})[i]	4.1×10^{-5}[g]	10^{11}	29.4	30.0
$(CH_3)_3S^+$	7.5×10^{-4}[h] (1.0×10^{-3})[i]	3.1×10^{-4}[g]	10^{11}	28.5	29.0
CH_3CN[j]	2.7×10^{-4}	1.1×10^{-4}	10^{11}	28.9	28.9
$CH_3C(O)NMe_2$[k]	5.7×10^{-6}	2.9×10^{-6}[k]	7.3×10^{9}[k]	29.4	29.4

Note: At 25 °C and I = 1.0 (KCl).

[a] Second-order rate constant for deprotonation of the carbon acid by deuterioxide ion in D_2O.

[b] Second-order rate constant for deprotonation of the carbon acid by hydroxide ion in H_2O.

[c] First-order rate constant for protonation of the carbanion by solvent water, estimated as $k_{\mathrm{HOH}} = k_{\mathrm{reorg}} = 10^{11}$ s^{-1}, where k_{reorg} is the rate constant for solvent reorganization (see text).

[d] Acidity of the carbon acid in water, calculated according to eq. [6] of the text.

[e] Statistically corrected acidity of a *single methyl* group of the carbon acid.

[f] Upper limit calculated as the rate constant for a reaction that would have given a value of R = 1/1.005 (eq. [2]) after 16 days (see text).

[g] Calculated from the value of k_{DO} using the relationship $k_{\mathrm{HO}} = k_{\mathrm{DO}}/2.4$, where 2.4 is the maximum secondary solvent deuterium isotope effect on the reactivity of lyoxide ion (see text).

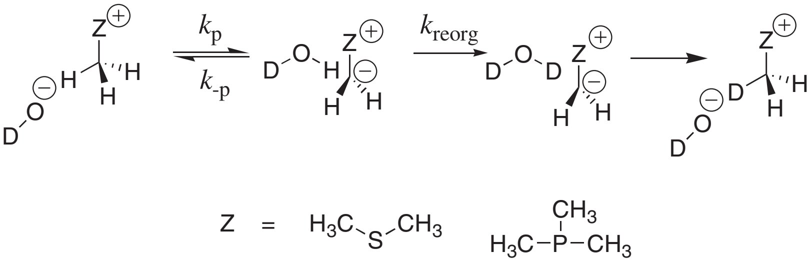
[h] Data from Table 1.

[i] Data from ref. 14.

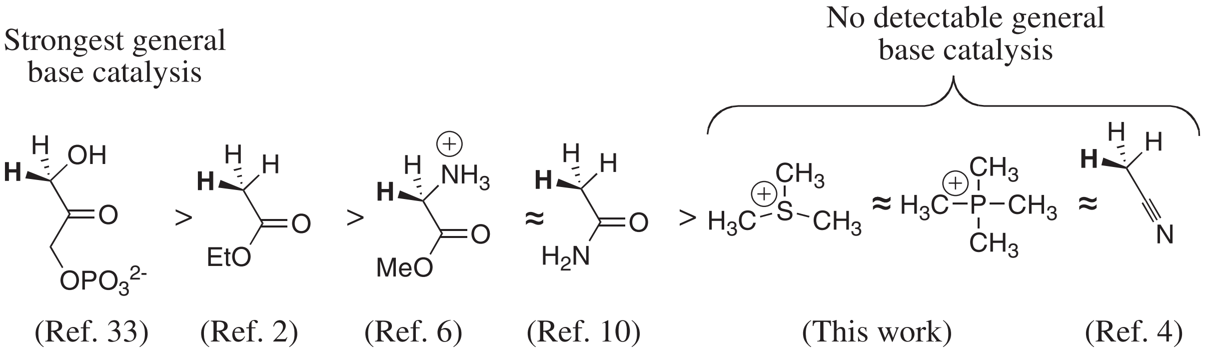
[j] Data for acetonitrile were taken from ref. 4.

[k] Data for dimethylacetamide were taken from ref. 10.

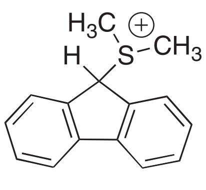
Scheme 2.



Scheme 3.



to place a molecule of D_2O in a position to deliver a labeled hydron to the carbanion is rate-determining, because it is not possible for the buffer catalyst to increase the rate of solvent reorganization. Therefore, the observation that there is no buffer catalysis of carbon deprotonation either of cyanoalkanes (4) or of **Me_4P^+** and **Me_3S^+** (this work) is consistent with a common rate-determining step of solvent reorganization (k_{reorg}, Scheme 2) for these three proton transfer reactions.



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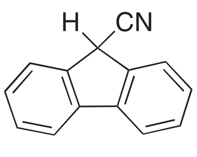

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(2) There are similar intrinsic rate constants at $\Delta pK_a = 0$ of $k_o \approx 10^4$ (mol/L)$^{-1}$ s^{-1} for deprotonation of the dimethyl-9-fluorenylsulfonium ion (**1**) by primary amines in water–DMSO (95:5) (20) and $k_o \approx 10^{3.6}$ (mol/L)$^{-1}$ s^{-1} for deprotonation of 9-cyanofluorene (**2**) in water–DMSO (90:10) (18). This shows that the α-SMe_2^+ and α-CN substituents have similar effects on the Marcus intrinsic barrier for proton transfer at carbon. The rate constants $k_{DO} = 2.7 \times 10^{-4}$ (mol/L)$^{-1}$ s^{-1} for deprotonation of acetonitrile (4) and $k_{DO} = 7.5 \times 10^{-4}$ (mol/L)$^{-1}$ s^{-1} for deprotonation of $\mathbf{Me_3S^+}$ (this work) are also similar. The reactions, which proceed with similar rate constants and Marcus intrinsic barriers, also have a similar thermodynamic drive force (12, 36, 37). Therefore, if $k_{-p} > k_{reorg} \approx 10^{11}$ s^{-1} for deprotonation of CH_3CN, as proposed in earlier work (4, 34), then the same relationship must hold for deprotonation of $\mathbf{Me_3S^+}$. We are not aware of any data that would allow us to estimate the effect of an α-PMe_3^+ substituent on the intrinsic barrier to deprotonation of carbon.

Carbon acid pK_as

Table 2 gives the carbon acid pK_as for deprotonation of $\mathbf{Me_4P^+}$ and $\mathbf{Me_3S^+}$ in water obtained in this work. These pK_as were calculated using eq. [6] derived from Scheme 4 where k_{HO} is the second-order rate constant for deprotonation of the carbon acid by hydroxide ion in H_2O (Table 2), $k_{HOH} = k_{reorg} = 10^{11}$ s^{-1} is the first-order rate constant for protonation of the carbanion zwitterion by solvent water (4, 10, 11, 34), and $K_w = 10^{-14}$ (mol/L)^2 is the ion product of water.

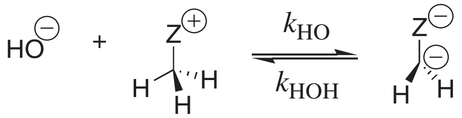
$$[6] \qquad pK_a = pK_w + \log\left(\frac{k_{HOH}}{k_{HO}}\right)$$

The values of k_{HO} (Table 2) were calculated from the corresponding rate constants for deprotonation of the carbon acids by deuterioxide ion (Table 1) using the relationship $k_{HO} = k_{DO}/2.4$ where 2.4 is the maximum secondary solvent deuterium isotope effect on the reactivity of lyoxide ion (38). This is appropriate because almost the entire difference in the basicity of deuterioxide and hydroxide ions will be expressed in the transition state for carbanion formation when solvent reorganization is rate-determining for exchange (4). The principle of microscopic reversibility requires that the reverse protonation of these carbanion zwitterions by solvent water is also limited mainly by solvent reorganization, with a rate constant on the order of that for the dielectric relaxation of water, $k_{HOH} = k_{reorg} = 10^{11}$ s^{-1} (39–41).

The greater carbon acidity of $\mathbf{Me_3S^+}$ and $\mathbf{Me_4P^+}$ than of $\mathbf{Me_4N^+}$ (Table 1) is well-known (14). It represents the greater stabilization of sulfur and phosphorus than of nitrogen ylides from polarization of charge by the larger third-row atoms and, possibly, by hyperconjugation (15, 16) and back-bonding from carbon to the d orbitals of sulfur and phosphorus (17).

We are not able to account for the difference between the reported pK_as of 28.5 (Table 2) and 18.2 (42) for deprotonation of $\mathbf{Me_3S^+}$ in water and DMSO, respectively. The change from DMSO to water causes a large decrease in pK_a when the conjugate base of the acid is a strong hydrogen bond acceptor (42), and this solvent effect on pK_a becomes less with decreasing stabilization of the conjugate base by hydrogen bonding to water. However, a substantially lower pK_a for $\mathbf{Me_3S^+}$ in the organic solvent DMSO than in water would require an unprecedented preferential solvation of the products of proton transfer by DMSO. The pK_a of 18.2 for deprotonation of $\mathbf{Me_3S^+}$ in DMSO is also inconsistent with the pK_a of 17.8 for deprotonation of the benzylic carbon of $\mathbf{Me_2(PhCH_2)S^+}$ in DMSO (24) because the α-phenyl substituent should result in a substantial increase in carbon acidity. We note that the pK_a of 18.2 for $\mathbf{Me_3S^+}$ in DMSO was reported in a Table in a review article (42), but to the best of our knowledge, it has not been further documented.

Scheme 4.



Substituent effects on carbon acidity

Computational studies provide evidence for formal resonance delocalization of negative charge onto nitrogen at the cyanomethyl carbanion (43). However, it is not clear whether this delocalization of charge results in a large stabilization of this carbanion. For example, delocalization of negative charge at the acetate anion provides a simple explanation for the relatively high acidity of acetic acid. However, it has been proposed that this high acidity is largely due to inductive stabilization of negative charge by the electron-withdrawing carbonyl group (44). The following observations provide evidence that there is significant stabilization of the cyanomethyl carbanion by both polar and resonance interactions between the negative charge and the α-CN group.

(1) The polar effect of a cationic α-substituent on carbanion stability must be larger than the polar effect of the neutral α-cyano group, where the interaction is between the formal negative charge of the carbanion and the *partial* positive charge of the cyano dipole. Therefore, the essentially identical values of pK_a = 28.9 for acetonitrile (4) and pK_a = 29.0 for a *single methyl* group of $\mathbf{Me_3S^+}$ (Table 2) show that there is sufficient resonance stabilization of the cyanomethyl carbanion to balance the greater stabilization of the sulfur ylide from polarization and back-bonding effects.

(2) The Hammett substituent constants $\sigma = 0.82$ for p-NMe_3^+ and $\sigma = 0.66$ for p-CN (45) show that a p-NMe_3^+ substituent provides a larger stabilization of negative charge than does a p-CN substituent when the interaction occurs across a benzene ring. By comparison, the observation that pK_a = 28.9 for acetonitrile is much lower than pK_a > 33.4 for a *single methyl* group of $\mathbf{Me_4N^+}$ (Table 2) shows that an α-CN substituent provides a substantially larger stabilization of negative charge at a neighboring carbon than does an α-NMe_3^+ group. This shows that there is sufficient resonance stabilization of the cyanomethyl carbanion to balance the greater polar stabilization of the nitrogen ylide.

It is interesting that no large intrinsic barrier to proton transfer arises from the requirement for the movement of negative charge from nitrogen to carbon on moving to the transition state for protonation of α-cyano carbanions (4, 12, 46, 47). As discussed earlier (4), the proton transfer to α-cyano carbanions resembles proton transfer to acetate anion (48) in that the requirement for localization of negative charge at the reacting basic atom (carbon or oxygen) proceeding to the transition state does not result in a large intrinsic barrier for proton transfer.

The α-fluorenyl group at the dimethyl-9-fluorenylsulfonium ion (**1**, pK_a = 13.7 in water–DMSO (95:5) (20)) causes a 16-unit decrease in the statistically corrected pK_a of 29.5 for a *single proton* of $\mathbf{Me_3S^+}$, while the α-fluorenyl group at 9-cyanofluorene (**2**, pK_a = 10.7 in water–DMSO (90:10) (18)) causes a larger 19-unit decrease in the statistically corrected pK_a of 29.4 for a *single proton* of acetonitrile. This shows that the addition of an α-fluorenyl group results in a larger attenuation of the α-SMe_2^+ than of the α-CN substituent effect on carbon acidity. We suggest that this reflects the particularly sharp falloff ($1/r^4$) in the stabilization of negative charge by polarization onto a atom with increasing radius of separation of the interacting centers (45).

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