

Estimation of a pK_a for Protonated Dimethoxycarbene

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ABSTRACT: A pK_a is estimated for the protonation of dimethoxycarbene based on the relationship $pK_a = pK_R - pK_{H_2O}$, where K_{H_2O} and K_R are equilibrium constants for hydration of the carbene and reaction of the dimethoxymethyl carbocation with water to form dimethoxymethanol, respectively. A value of $pK_a = 15.5$ in aqueous solution is derived based on $pK_R = -5.7$ for the carbocation and an estimate of $pK_{H_2O} = -21.2$ based on a heat of formation of the carbene $\Delta H_f^\circ = -38.8 \pm 2 \text{ kcal mol}^{-1}$, calculated at the G3 level in the gas phase. This value for the pK_a compares satisfactorily with $pK_a = 11$ inferred from the dependence of experimental rate constants for reaction of the carbene with alcohols and acetic acid upon the pK_a of the oxygen acid in acetonitrile, taking account of the difference in solvents for the calculated and measured values. The calculated heat of formation of dimethoxycarbene in the gas phase is compared with an experimental value of $-52.6 \text{ kcal mol}^{-1}$ based on photoacoustic measurements of the heat of reaction of the carbene with methanol solvent to form trimethyl orthoformate. Reanalysis of the experimental data using a heat of solution of trimethyl orthoformate in methanol measured in this work suggests that the discrepancy arises in part from a difference in the heat of reaction of the carbene with methanol in solution and in the gas phase and partly (although less certainly) from a relatively high heat of solution of the carbene in methanol. Copyright © 2003 John Wiley & Sons, Ltd.

KEYWORDS: heat of formation; heat of solution; G3 calculation; carbocation; hydration

INTRODUCTION

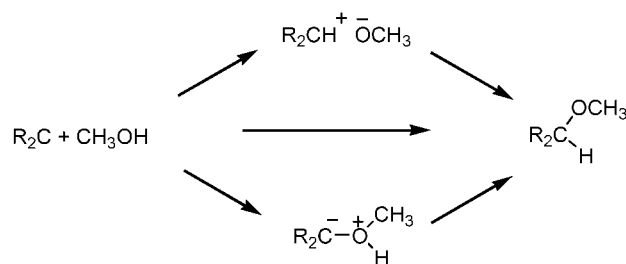
The possibility that carbenes may be subject to protonation to form carbocations has long been discussed^{1–3} and recently has been the subject of an authoritative review.¹ In the past 15 years, the use of laser flash photolysis to generate spectroscopically detectable concentrations of carbenes has provided additional evidence for this reaction path.^{4–9} It has become possible to measure rate constants for the reaction of carbenes with oxygen acids and to demonstrate (a) that these rate constants show a Brønsted-like dependence on the pK_a of the acid^{4,10} and (b) that the appropriate carbocation is formed based on measurements of UV–visible spectra.^{5–8} These observations are important because the final product could have arisen by one of three well established reaction paths in which the carbene acts as a nucleophile, an electrophile or by direct insertion (Scheme 1).^{3–5,11} They also underline the importance of establishing pK_a s for protonated carbenes.¹

In 1990, Moss and co-workers reported a study of dimethoxycarbene in which rate constants were measured for reaction with oxygen acids covering a wide range of pK_a s and including a number of alcohols and acetic acid.⁴

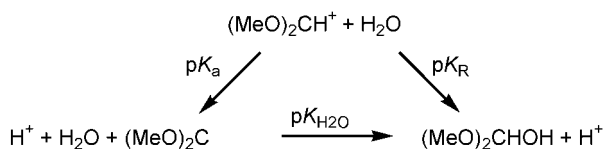
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The reactions show a marked dependence of rate constant upon acidity with values ranging from $3.2 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ for ethanol to $2.4 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ for acetic acid.

Subsequently, Pezacki argued that the rate constants are well fitted by an Eigen-like Brønsted plot in which the reactions of the strongest acids are subject to or approach diffusion control in the forward direction.¹⁰ The plot is consistent with the protonated carbene behaving as a normal acid and the dependence of $\log k$ upon $\log K_a$ approaching a slope $\alpha = 0$ for strong acids and showing a relatively sharp transition to slope $\alpha = 1$ for weaker acids. Based on this dependence, Pezacki inferred $pK_a \approx 11$ for the dimethoxycarbene, corresponding to the turning point of the Brønsted plot. A similar interpretation was suggested¹⁰ for a series of aryl(trimethylsiloxy)carbenes studied by Kirmse *et al.*, although in these cases rate



Scheme 1



Scheme 2

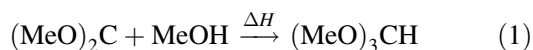
constants for the most part fell in the narrower range 10^8 – $10^9 \text{ M}^{-1} \text{ s}^{-1}$.^{6,10}

The purpose of this paper is to consider an alternative method for estimating the pK_a of the protonated dimethoxycarbene. The method makes use of a thermodynamic cycle which has been employed to interrelate pK_R and pK_a values of carbocations.¹² In previous applications of this cycle, the conjugate base arising from deprotonation of the carbocation has been an alkene. However, alkenes are isomers of carbenes and in cases where the carbocation does not possess a β -hydrogen atom, such as the dimethoxymethyl cation $(\text{MeO})_2\text{CH}^+$, the only accessible basic species is through loss of an α - rather than a β -proton to form a carbene.

The cycle for dimethoxycarbene is shown in Scheme 2. The pK_R corresponds in the normal way to reaction of the carbocation with water to form the corresponding alcohol, and the third leg of the cycle is represented by $pK_{\text{H}_2\text{O}}$ the equilibrium constant for hydration of the carbene. It is evident that if pK_R and $pK_{\text{H}_2\text{O}}$ can be measured or estimated then the pK_a for protonation of the carbene can be derived.

RESULTS

The possibility of applying Scheme 2 to dimethoxycarbene is suggested by the accessibility of pK_R values for a wide range of carbocations, based on rate measurements for the reactions of such cations with water, especially through application of laser flash photolysis studies by McClelland *et al.*¹³ Considerable effort has also been expended in evaluating a heat of formation for dimethoxycarbene [$\Delta H = -24.8 \text{ kcal mol}^{-1}$ (1 kcal = 4.184 kJ)] from measurements of the heat of reaction of the carbene with methanol to form trimethyl orthoformate [Eqn. (1)] making use of photoacoustic calorimetry.⁴ As shown in Scheme 3, this value was obtained from the difference in heats of reaction of the dimethoxydiazirine precursor used to generate the carbene **1** in the solvents methanol and pentane ($\Delta H_2 - \Delta H_1$). In methanol, in the short time-scale of the measurement ($\sim 10 \text{ ns}$), the reaction proceeds to form trimethyl orthoformate. In pentane, within the same time-scale, the reaction proceeds only to the carbene.



Combining measurements in methanol and pentane may be justified on the grounds that photolysis of the analogous fluoromethoxy diazirine (**2**) gives the same heat change in both solvents.⁴ This implies that the fluoromethoxy carbene reacts sufficiently slowly in methanol that ΔH_1 is measured in methanol as well as pentane. The solvent effect on the reaction may thus be supposed to fall within the (fairly large) error limits for the measurements of heats of reaction and it seems reasonable to conclude that the same is true of $(\text{MeO})_2\text{C}$. The heat of formation of $(\text{MeO})_2\text{C}$ in methanol may thus be inferred by combining ΔH [Eqn. (1)] with heats of formation of trimethyl orthoformate and methanol solvent making use of Eqn. (2).

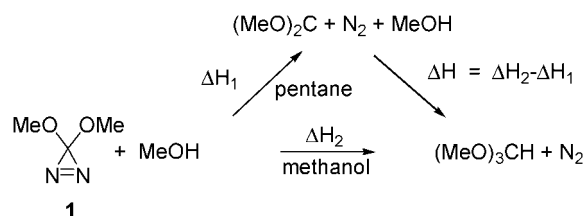
$$\Delta H_f^\circ[(\text{MeO})_2\text{C}] = \Delta H_f^\circ[(\text{MeO})_3\text{CH}] - \Delta H_f^\circ(\text{MeOH}) - \Delta H \quad (2)$$

In this paper, we report a measurement of the heat of solution of trimethyl orthoformate in methanol ($\Delta H_t^{1 \rightarrow \text{MeOH}} = 1.3 \text{ kcal mol}^{-1}$), which may be combined with ΔH_f° for the liquid ($-135.7 \text{ kcal mol}^{-1}$)¹⁶ to obtain ΔH_f° in methanol as $-134.4 \text{ kcal mol}^{-1}$ [as shown in Eqn. (3)]. Then from $\Delta H_f^\circ = -57.0 \text{ kcal mol}^{-1}$ for methanol itself and $\Delta H = -24.8 \text{ kcal mol}^{-1}$ for reaction of the carbene with methanol, Eqn. (2) yields ΔH_f° for $(\text{MeO})_2\text{C}$ as $-52.6 \text{ kcal mol}^{-1}$.

$$\Delta H_f^\circ(\text{MeOH}) = \Delta H_f^\circ(1) + \Delta H_t^{1 \rightarrow \text{MeOH}} \quad (3)$$

In practice, we are interested in ΔH_f° in aqueous solution or the gas phase rather than methanolic solution. Moss and co-workers inferred a value of $-54.7 \text{ kcal mol}^{-1}$ for the gas phase by substituting heats of formation of CH_3OH and $(\text{MeO})_3\text{CH}$ in the gas phase into Eqn. (3) and combining these values with his measurement of $\Delta H = -24.8 \text{ kcal mol}^{-1}$ for methanolic solution. However, this almost certainly underestimates $\Delta H_f^\circ(\text{g})$ because heats of formation are normally significantly greater in the gas phase than in solution (or liquid) states, as a consequence of a positive heat of vaporization of a liquid (or negative heat of transfer of the gas to solution).

A calculation of $\Delta H_f^\circ(\text{g})$ for $(\text{MeO})_2\text{C}$ was undertaken in this work, therefore, and implemented using Gaussian 98¹⁷ at the level of G3, for which a precision of $\pm 1.25 \text{ kcal mol}^{-1}$ has been claimed for small mol-



Scheme 3

ecules.¹⁸ The value of ΔH_f° obtained was -38.8 kcal mol⁻¹, which is indeed substantially less negative than the experimental value for methanolic solution.

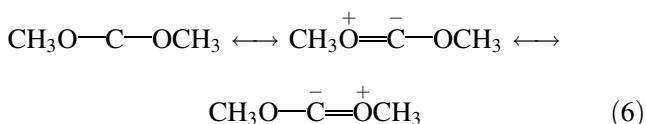
This value can be used as a starting point for calculating $\Delta G_f^\circ(\text{aq})$ for dimethoxycarbene and thence the desired equilibrium constant $pK_{\text{H}_2\text{O}}$ for hydration of the carbene (Scheme 2). If we can assign a standard entropy S° for $(\text{MeO})_2\text{C}$ in the gas phase and a free energy of transfer $\Delta G_f^{\text{g}\rightarrow\text{aq}}$ between the gas phase and water, we then obtain $\Delta G_f^\circ(\text{aq})$ for $(\text{MeO})_2\text{C}$ based on Eqn. (4). Combining this value of $\Delta G_f^\circ(\text{aq})$ with corresponding values for $(\text{MeO})_2\text{CHOH}$ and H_2O yields $pK_{\text{H}_2\text{O}}$ by use of Eqn. (5).

$$\Delta G_f^\circ(\text{aq})[(\text{MeO})_2\text{C}] = \Delta H_f^\circ(\text{g}) - T\Delta S^\circ(\text{g}) + \Delta G_f^{\text{g}\rightarrow\text{aq}} \quad (4)$$

$$pK_{\text{H}_2\text{O}} =$$

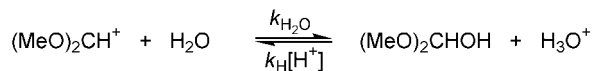
$$\frac{\Delta G_f^\circ(\text{aq})[(\text{MeO})_2\text{CHOH}] - \Delta G_f^\circ(\text{aq})[(\text{MeO})_2\text{C}] - \Delta G_f^\circ(1)[\text{H}_2\text{O}]}{2.303 RT} \quad (5)$$

Calculation of S° was carried out at the B3LYP/6-31G** level, using a harmonic oscillator approximation for the hindered rotation about the carbon oxygen bonds of the carbene arising from the resonance interaction shown in Eqn. (6).¹⁹ A value of 80.1 cal K⁻¹ mol⁻¹ was obtained. As expected, this value is close to the value of 80.2 for formaldehyde dimethylacetal, $(\text{MeO})_2\text{CH}_2$,²⁰ which may be taken as a model for the carbene. Combination of S° with $\Delta H_f^\circ(\text{g})$ gives $\Delta G_f^\circ(\text{g}) = -18.93$ kcal mol⁻¹ at 25°C .



There is no very satisfactory method for estimating the free energy of transfer of $(\text{MeO})_2\text{C}$ from gas to aqueous solution, but the value is not likely to be large so a significant error can be tolerated. Use of the COSMO procedure in Gaussian,²¹ which works reasonably well for neutral molecules, gives $\Delta G_f^{\text{g}\rightarrow\text{aq}} = -0.52$, which again is not far from the value for $(\text{MeO})_2\text{CH}_2$ (-1.0 kcal mol⁻¹). Combination with $\Delta G_f^\circ(\text{g})$ then gives $\Delta G_f^\circ(\text{aq}) = -19.45$ kcal mol⁻¹. Finally, combination of this value with $\Delta G_f^\circ(\text{aq}) = -105$ kcal mol⁻¹ for $(\text{CH}_3\text{O})_2\text{CHOH}$ ¹⁶ and $\Delta G_f^\circ = -56.69$ kcal mol⁻¹ for water yields $pK_{\text{H}_2\text{O}} = -21.2$ from Eqn. (5).

The value of K_R (and pK_R) for the dimethoxymethyl cation can now be obtained as a ratio of forward and reverse rate constants for its reaction with water as shown in Scheme 4.

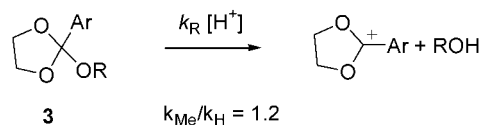


$$K_R = \frac{[(\text{MeO})_2\text{C}][\text{H}^+]}{[(\text{MeO})_2\text{CH}^+]} = \frac{k_{\text{H}_2\text{O}}}{k_{\text{H}}}$$

Scheme 4

A rate constant for reaction of the carbocation with water $k_{\text{H}_2\text{O}} = 9 \times 10^7$ can be extrapolated from values for the corresponding ethyl and isopropyl alkoxy cations, for which rate constants for reaction to form the hemioorthoesters of formic acid $[(\text{RO})_2\text{CHOH}]$ have been measured by Steenken and McClelland.²² All three rate constants have been measured for the corresponding methyl, ethyl and isopropyl alkoxy cations bearing an α -benzyl substituent $[(\text{RO})_2\text{C}^+\text{CH}_2\text{Ph}]$. The unknown value was interpolated from a log-log plot of matching alkoxy rate constants for the cations with and without a benzyl substituent, on the assumption that this plot should be linear.

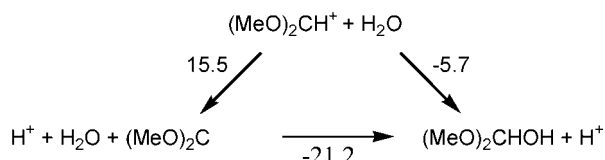
A rate constant for the reverse reaction, the acid-catalysed conversion of the orthoester to the carbocation, can be approximated by the value for the corresponding methyl ether, the trimethyl orthoformate $[(\text{MeO})_3\text{CH}]$.²³ A number of comparisons of reactions of alcohols and methyl ethers to form the same carbocation show that ratios of rate constants fall in the range 0.7 – 1.35 .^{24,25} Although the difference can be greater for acetals and hemiacetals,²⁶ for the closest analogy to our substrate, the orthoester **3**, the methyl ether is 20% faster than the alcohol. The value for trimethyl orthoformate has been corrected by a corresponding amount therefore to give $k_{\text{H}} = 1.7 \times 10^2$ M⁻¹ s⁻¹.



With these values of rate constants, we obtain $K_R = k_{\text{H}_2\text{O}}/k_{\text{H}} = 5.3 \times 10^5$ and $pK_R = -5.7$. It remains only to combine pK_R with $pK_{\text{H}_2\text{O}} = -21.2$ according to the thermodynamic cycle of Scheme 2 to obtain $pK_a = 15.5$ for the protonation of dimethoxycarbene.

DISCUSSION

The purpose of this paper was to estimate a pK_a for protonated dimethoxycarbene taking as starting point an experimental or calculated value of the heat formation of the carbene. This pK_a was to be compared with the value



Scheme 5

deduced by Pezacki from a Brønsted plot for reaction of the carbene with oxygen acids.¹⁰

We have computed $\Delta H_f^\circ = -38.8 \text{ kcal mol}^{-1}$ for $(\text{MeO})_2\text{C}$ in the gas phase based on a G3 level calculation,¹⁶ using Gaussian 98.¹⁷ As described above, this value was combined with calculated values of S° and ΔG_f° to obtain ΔG_f° for $(\text{MeO})_2\text{C}$ in aqueous solution at 25 °C. From this value, $K_{\text{H}_2\text{O}}$, the equilibrium constant for hydration of the carbene to form the hemioorthoformate $(\text{MeO})_2\text{CHOH}$, was evaluated from the known free energies of formation of reactants and products.^{16,20} Finally, combining $pK_{\text{H}_2\text{O}}$ with $pK_{\text{R}} = -5.7$ for the protonated carbene [the dimethoxy methyl cation, $(\text{MeO})_2\text{CH}^+$] allowed a pK_a to be inferred from the thermodynamic cycle shown in Schemes 2 and 5 as $pK_{\text{R}} - pK_{\text{H}_2\text{O}} = 15.5$.

Before comparing this pK_a with the value obtained by Pezacki, it is appropriate to comment on the discrepancy between $\Delta H_f^\circ = -38.8 \text{ kcal mol}^{-1}$ calculated in the gas phase and the experimental value of $\Delta H_f^\circ = -52.6 \text{ kcal mol}^{-1}$ based on photoacoustic measurements of the heat of reaction of the carbene with methanol to form trimethyl orthoformate in methanolic solution [Eqn. (1)].

Explicit evaluation of the heat of formation in methanol was made possible by measurement of a heat of solution of trimethyl orthoformate in methanol in this work. As already noted, in the original paper, for which this measurement was not available, Moss and co-workers combined $\Delta H = -24.8 \text{ kcal mol}^{-1}$ with heats of formation of methanol and trimethyl orthoformate in the gas phase to obtain $\Delta H_f^\circ = -54.5 \text{ kcal mol}^{-1}$.⁴ The supposition that this value might provide a reasonable approximation to the heat of formation in the gas phase seemed to be supported by a MINDO calculation of $\Delta H_f^\circ(\text{g}) = -61 \text{ kcal mol}^{-1}$ for the carbene.

However, the G3 level of calculation now accessible offers a more reliable estimate of $\Delta H_f^\circ(\text{g})$. Corroboration of this value is suggested by calculation of $\Delta H_f^\circ(\text{g}) = -47.0 \text{ kcal mol}^{-1}$ for CF_2 , which can be compared with several experimental measurements: -43.5 ,²⁷ -46 ²⁸ and $-49 \text{ kcal mol}^{-1}$,²⁹ and a high-level calculation, $-46.2 \text{ kcal mol}^{-1}$.³⁰ It is noteworthy that the value for CF_2 is not significantly less negative than the experimental values, as might seem to be implied by the comparison of -38.8 and $-53.8 \text{ kcal mol}^{-1}$ for gas and solution for dimethoxycarbene. A compatible value of $\Delta H_f^\circ = -44.8 \text{ kcal mol}^{-1}$ is also calculated for methoxy fluorocarbene, MeOCF .

It is clear that for comparison with the gas phase the

value of $\Delta H_f^\circ = -52.6 \text{ kcal mol}^{-1}$ in methanol needs to be corrected for the heat of transfer of the carbene from gas to solution. In principle, this heat may be estimated as the difference between values of ΔH_f° in gas and solution, i.e. $\Delta H_t^{g \rightarrow \text{MeOH}} = -52.6 + 38.8 = -13.8 \text{ kcal mol}^{-1}$. This is consistent with the expected negative value of $\Delta H_t^{g \rightarrow \text{MeOH}}$ based on recognizing that the main contribution to the heat of transfer comes from the heat of vaporization ΔH_v (see below). However, the combined errors in the measured and calculated values of $\Delta H_f^\circ(\pm 6.5 \text{ kcal mol}^{-1})$ render this estimate imprecise. We have therefore undertaken measurements of heats of solution of dimethyl carbonate, dimethoxymethane, methyl acetate and propionic acid to assess the values for these compounds as models for the heat of solution of dimethoxycarbene. The compounds are liquids and their heats of solution are small. This means that heats of transfer from the gas phase to solution are well approximated by the (negative of) heats of vaporization of the liquids. It also implies that, like heats of vaporization, the heats of transfer depend on molecular weight and polarity. Methyl acetate and propionic acid were chosen as isomers of dimethoxycarbene of differing polarity, and dimethoxymethane and dimethyl carbonate were chosen as structural analogues. The heats of transfer of the liquids ($\Delta H_t^{l \rightarrow \text{MeOH}}$) and gases ($\Delta H_t^{g \rightarrow \text{MeOH}}$) into methanol and also heats of vaporization of the liquids (ΔH_v), are given in Table 1. The relationship between these values is shown in Eqn. (7).

$$\Delta H_t^{g \rightarrow \text{MeOH}} = \Delta H_t^{l \rightarrow \text{MeOH}} - \Delta H_v \quad (7)$$

From Table 1, it is apparent that if $(\text{MeO})_2\text{C}$ had the same heat of transfer from gas to solution ($\Delta H_t^{g \rightarrow \text{MeOH}}$) as dimethyl carbonate ($-7.3 \text{ kcal mol}^{-1}$), the calculated value of ΔH_f° in the gas phase ($-38.8 \text{ kcal mol}^{-1}$) would imply a value of $-46.1 \text{ kcal mol}^{-1}$ in methanolic solution. This is still significantly less negative than the experimental value ($-52.6 \text{ kcal mol}^{-1}$), although just within the combined uncertainties of experiment and calculation.

If the heat of solution of $(\text{MeO})_2\text{C}$ was as favourable as for propionic acid, the value of ΔH_f° in solution would be $-52.0 \text{ kcal mol}^{-1}$. Such a negative value would imply a

Table 1. Heats of transfer and vaporization (kcal mol^{-1}) at 25 °C for methanolic solutions

Parameter	$(\text{MeO})_2\text{C}=\text{O}$	$(\text{MeO})_2\text{CH}_2$	MeCOOMe	EtCOOH
$\Delta H_t^{l \rightarrow \text{MeOH}}$	1.28	0.89	0.91	-0.13
$\Delta H_t^{g \rightarrow \text{MeOH}}$	-7.3	-6.1	-6.3	-13.2
ΔH_v	8.70 ^a	7.00 ^b	7.35 ^c	13.1 ^d

^a From $\Delta H_v = 5.0 + 0.41t_{\text{bp}}$ and $t_{\text{bp}} = 90.3 \text{ °C}$.³¹

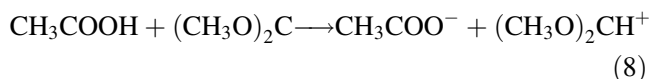
^b Ref. 32.

^c Ref. 33.

strongly polar structure for the carbene, which indeed might seem consistent with the resonance structures shown in Eqn. (6). However, the dipole moment calculated for $(\text{MeO})_2\text{C}$ in this study is 0.5 D, which is fairly small. Moreover, the free energy of transfer $\Delta G_{\text{t}}^{\text{g} \rightarrow \text{aq}}$ estimated by the COSMO method is $-0.52 \text{ kcal mol}^{-1}$, which is considerably less negative than the measured value of -4.57 for propionic acid. A small negative value of ΔG_{t} combined with a large negative ΔH_{t} implies a large entropy for transfer of the gas to solution, e.g. for $\Delta H_{\text{t}} = -13$ and $\Delta G_{\text{t}} = -0.5$, $\Delta S_{\text{t}}^{\text{g} \rightarrow \text{aq}} = -40 \text{ cal K}^{-1} \text{ mol}^{-1}$. For $\text{CH}_3\text{COOCH}_3$, for which $\Delta G_{\text{t}}^{\text{g} \rightarrow \text{aq}} = -1.42$ and $\Delta H_{\text{t}}^{\text{g} \rightarrow \text{aq}} = -6.3$, $\Delta S_{\text{t}}^{\text{g} \rightarrow \text{aq}} = -16.4 \text{ cal K}^{-1} \text{ mol}^{-1}$. These figures are unlikely to change much between water and methanol as solvents; from the value for water, and differences in values between water and methanol for other organic molecules,³⁴ $\Delta G_{\text{t}}^{\text{g} \rightarrow \text{MeOH}} \approx -1$ is implied for $(\text{MeO})_2\text{C}$.

This discussion is intended to ascertain whether the calculated value of $\Delta H_{\text{f}}^{\circ} = -38.8 \text{ kcal mol}^{-1}$ in the gas phase is reasonable. Although the difference from $-52.6 \text{ kcal mol}^{-1}$ for methanolic solution is only partially accounted for, the remaining discrepancy is not much greater than the limits of uncertainty of the photoacoustic measurements.⁴ If the $38.8 \text{ kcal mol}^{-1}$ is accepted, it remains true that its own margin of error ($\pm 2 \text{ kcal mol}^{-1}$) and approximations in estimating entropies, free energies of transfer and other contributions to establishing the thermodynamic cycle of Scheme 2 may lead to significant errors in the derived $\text{p}K_{\text{a}}$. Thus an error of $5 \text{ cal K}^{-1} \text{ mol}^{-1}$ in S° or $2.7 \text{ kcal mol}^{-1}$ in $\Delta H_{\text{f}}^{\circ}$ or ΔG_{t} corresponds to two units in $\text{p}K$. However, the uncertainties seem justified by the usefulness of gaining access even to approximate values of $\text{p}K_{\text{H}_2\text{O}}$ and $\text{p}K_{\text{a}}$. Pezacki has characterized the value of $\text{p}K_{\text{a}} = 11$ which he derived from the Brønsted plot for reaction of the carbene with oxygen acids as a 'ballpark' figure.¹⁰ The same is evidently true of our calculated value.

Within these limitations, it is apparent that $\text{p}K_{\text{a}} = 15.5$ agrees well with the Brønsted-based value. Indeed, if we recognize that the kinetic measurements upon which the Brønsted plot was based refer to acetonitrile as solvent, it seems clear that the measured value of 11 must imply a larger value for water. This is because proton transfer from the neutral oxygen acid to the neutral carbene in the Brønsted correlation must lead to charge separation in the transition state [Eqn. (8)]:



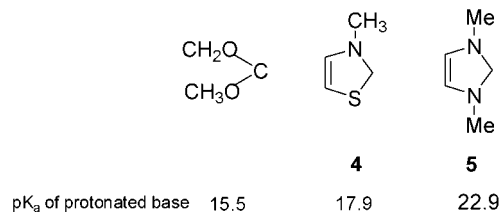
This process will be subject to a large solvent effect and the strength of acid required to achieve a thermodynamically favourable proton transfer will be less in water than in acetonitrile. Although significant polar character for dimethoxycarbene might mitigate this constraint, it is

clear that the aqueous $\text{p}K_{\text{a}}$ implied by fitting the measured rate constants to a Brønsted plot for normal acids must be substantially greater than 11.

It is reasonable to conclude therefore, that the calculated $\text{p}K_{\text{a}} = 15.5$ for $(\text{MeO})_2\text{C}$ in water is consistent with the value from the Brønsted analysis of the reaction in acetonitrile. This confirms that the mechanism of reaction of the carbene with alcohols does indeed proceed with an initial and rate-determining proton transfer. This is consistent with the behaviour of other carbenes,¹ including the reaction of α -(trimethylsiloxy)aryl carbenes, for which Kirmse *et al.* have reported the observation of carbocation spectra in their reaction with alcohols.⁶

The agreement between calculated and experimental $\text{p}K_{\text{a}}\text{S}$ also confirms the usefulness of deriving a $\text{p}K_{\text{a}}$ from the heat of formation for a carbene. Normally S° and ΔG_{t} can be estimated with good precision from calculations or comparisons with model compounds. If thermodynamic data and a $\text{p}K_{\text{R}}$ for carbocation formation are available for the alcohol formed by hydration of the carbene, a $\text{p}K_{\text{a}}$ can be estimated based on a thermodynamic cycle analogous to that for dimethoxycarbene (Schemes 2 and 5).

The number of measurements of $\text{p}K_{\text{a}}\text{S}$ for protonation of carbenes other than $(\text{MeO})_2\text{C}$ with which the results in this paper may be compared is still limited.^{1,10} Washbaugh and Jencks's value of 18.9 for the conjugate acid of **4** is representative of thiazolium ions.³⁵ Alder *et al.* reported $\text{p}K_{\text{a}} = 24$ for dissociation of the *N,N*-diisopropylimidazolium ion from measurements of relative $\text{p}K_{\text{a}}\text{S}$ in DMSO solutions,³⁶ and recently J. P. Richard and F. Rivas (unpublished results) obtained an aqueous $\text{p}K_{\text{a}} = 22.9$ for the dimethylimidazolium ion (protonated carbenes **5**) from measurements of hydrogen isotope exchange. These values are consistent with the expectation that a nitrogen substituent should be more favourable to cation formation than sulfur or oxygen. However, it will be of interest to compare these $\text{p}K_{\text{a}}\text{S}$ with values for a wider range of carbene structures in the future.



EXPERIMENTAL DETAILS AND CALCULATION

Calculations. Calculation of $\Delta H_{\text{f}}^{\circ}$ for dimethoxycarbene was carried out using the G3MP2B3 method implemented by Gaussian 98.¹⁷ Calculations were carried out for three conformations of the carbene, 'w,' sickle and 'u,' which gave energies of -38.8 , -37.8 and $-37.5 \text{ kcal mol}^{-1}$, respectively. Use of the w conformation alone

was considered to provide a good approximation to the total energy.

An entropy for $(\text{MeO})_2\text{C}$ (the w conformation) was calculated as $S^\circ = 80.12 \text{ cal mol}^{-1} \text{ K}^{-1}$ using Gaussian 98 at the B3LYP/6-31G** level with a harmonic treatment of hindered rotations.¹⁹ A value of ΔG_t° was obtained using the COSMO method at the RHF/6-31 + G* level.²¹ Standard states are 1 mol of gas at 1 atm pressure or 1 M aqueous (or methanolic) solution.

Heats of solution. Heats of transfer of the liquid to methanolic solution were determined for trimethyl orthoformate, the product of methanolysis of dimethoxycarbene, and for several models for the dimethoxycarbene itself. Heats of transfer for the liquids ($\Delta H_t^{l \rightarrow \text{MeOH}}$) were converted to heats of transfer of the gas to solution ($\Delta H_t^{g \rightarrow \text{MeOH}}$) by combination with the heat of vaporization ΔH_v using Eqn. (7).

The heats of solution were measured at 25 °C using an automated solution calorimeter which has been described previously.³⁷ In each case the heats were measured at 10 solute concentrations from successive injections of 0.20 ml of solute into 100 ml of methanol. The heat change for the accumulated injections was plotted against the total solute concentration and extrapolated to zero concentration. In all the cases studied the concentration dependence of the heats of solution was small, with differences between average and extrapolated values being less than 20 cal mol⁻¹. The following extrapolated values, each the mean of two or three independent measurements, were obtained (kcal mol⁻¹): trimethyl orthoformate, 0.86; dimethyl carbonate, 1.28; methyl acetate, 0.91; dimethoxymethane, 0.89; and propionic acid, -0.13.

The value of $\Delta H_t^{g \rightarrow \text{MeOH}}$ for trimethyl orthoformate is obtained as -8.2 kcal mol⁻¹ by substitution of $\Delta H_v = 9.1 \text{ kcal mol}^{-1}$, calculated from the b.p. of 90.3 °C using Wadso's equation, $\Delta H_v = 5.0 + 0.041t_{\text{bp}}$ for carboxylic acid esters,³¹ into Eqn. (7). The corresponding value for methanol is given by the negative of $\Delta H_v = 9.0 \text{ kcal mol}^{-1}$. The value for $(\text{MeO})_2\text{C}$ is estimated from comparison with the model compounds listed in Table 1 as described above.

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