Comparison of a protonated quinone methide and a methoxybenzyl carbocation analog

Robert A. McClelland,* Maeve M. Moriarty and Jacqueline M. Chevalier

Department of Chemistry, University of Toronto, Toronto, Ontario M5S 3H6, Canada

The ratio of rate constants for the hydration of the bis-(*p*-methoxyphenyl)methyl cation and the (*p*-hydroxyphenyl)(*p*-methoxyphenyl)methyl cation is 1.75 : 1. Thus a methoxybenzyl carbocation is a good model for a protonated *p*-quinone methide, and the stabilizing effect of hydration on the OH compound is minimal.

Quinone methides (quinomethanes) (*e.g.* **1** and **2**, Scheme 1) are a class of reactive intermediate that have recently seen considerable attention,[1–8] in part because of a potential role as cytotoxins in biological systems. These electrophilic compounds react with nucleophiles through a conjugate addition pathway which could also be viewed as a carbocation–nucleophile combination involving a benzylic cation bearing an *ortho* or *para* O⁻ group. An H⁺-catalyzed reaction has also been demonstrated. Recent studies with some *ortho* quinone methides and water have shown that this reaction occurs with specific H⁺ catalysis, with the mechanism involving pre-equilibrium formation of the protonated quinone methide (*e.g.* **3**) followed by rate-limiting reaction of this cation with the solvent.[6] The protonated quinone methide can also be viewed as a benzylic cation with an *ortho* or *para* OH group (*e.g.* **4**). In this paper we compare the reactivity of a protonated quinone methide with that of a carbocation analog to address the question as to whether the latter serves as an acceptable model for the former.
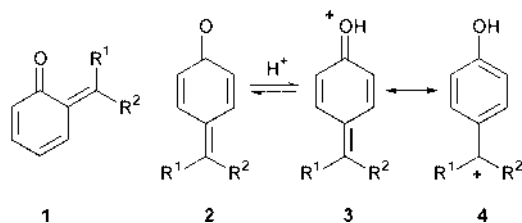
Scheme 1

The comparison involves the cations **6** and **9** (Scheme 2), as studied by laser flash photolysis in acidic aqueous solutions. The diarylmethyl cation **6** (λ_{max} at 500 nm) was obtained by irradiation of the acetate ester **5**, as has been described previously.[9,10] The quinone methide system was accessed by irradiation of the alcohol **7**, as has been described by Wan and co-workers for the analog without the methoxy group.[11] The quinone methide **8** is observed upon irradiation of **7** in aqueous solutions. This has a λ_{max} at 400 nm, and at pH 7–8 is a long-lived intermediate reacting with water in a pH independent manner with a rate constant of 0.08 s⁻¹. The decay of **8** becomes H⁺-catalyzed by pH 6. By 0.01 mol dm⁻³ H⁺, the reaction is occurring on the millisecond timescale. Moreover, the transient spectra start showing a shift of the acid–base equilibrium to the cation **9**.† The latter appears as an absorbance with a λ_{max} at 495 nm. This same absorbance is observed in concentrated sulfuric acid where the diarylcarbinol is quantitatively converted to the carbocation which is stable under these strongly acidic, weakly nucleophilic conditions.

The two systems were studied in detail in perchloric acid solutions maintaining a constant concentration of perchlorate
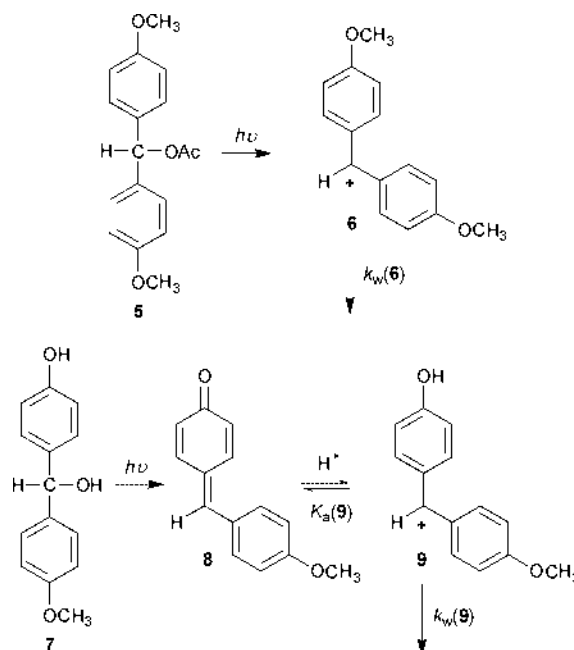
Scheme 2

ion at 1.0 mol dm⁻³ by the addition of NaClO₄. The results are shown in Fig. 1. The diarylmethyl cation **6** decays with a rate constant of 4.7×10^4 s⁻¹ in an aqueous solution containing 1.0 mol dm⁻³ NaClO₄. The effect of the salt can be seen in a comparison with the rate constant of 9.5×10^4 s⁻¹ obtained for the decay in 100% water with no salt added. Replacing Na⁺ with H₃O⁺ results in a modest rate retardation, such that by 1.0 mol dm⁻³ HClO₄ the rate constant has reduced to 3.8×10^4 s⁻¹. This is a specific salt effect,[13] probably related to the hydronium ion reducing water activity more than sodium. Within experimental error, the effect is linear, *i.e.* $k_w(\mathbf{6}) = k_w(\mathbf{6})_0 + m[H^+]$, where $k_w(\mathbf{6})_0$ is the rate constant in 1 mol dm⁻³ NaClO₄. The line drawn through the points for **6** in Fig. 1 is based on linear regression. The slope m is $-(8.1 \pm 1.2) \times 10^3$.

For the quinone methide system, the kinetics show the H⁺-dependence in dilute acid with a saturation effect in more concentrated acids associated with the equilibrium shifting to the side of the cation. The appropriate equation for this kinetic system is $k_{obs} = k_w(\mathbf{9})[H^+]/([H^+] + K_a(\mathbf{9}))$. However, the experimental data are not satisfactorily fit by this equation if $k_w(\mathbf{9})$ is taken as a constant over the range of acidities. Allowing $k_w(\mathbf{9})$ to vary with [H⁺] in a linear fashion as seen with the diarylmethyl cation gives a three parameter equation, $k_{obs} = (k_w(\mathbf{9})_0 + m[H^+])[H^+]/([H^+] + K_a(\mathbf{9}))$, which does provide an excellent fit, as shown by the curve through the data in Fig. 1. Values of the parameters obtained in this fit are $k_w(\mathbf{9})_0$, the rate constant in 1 mol dm⁻³ NaClO₄ = $(2.7 \pm 0.2) \times 10^4$ s⁻¹, $m = -(5.1 \pm 0.8) \times 10^3$ and $K_a(\mathbf{9}) = 0.15 \pm 0.01$. The line drawn in the middle of Fig. 1 is the rate constant for hydration of the cation **9**, $k_w(\mathbf{9})_0 + m[H^+]$. The difference between this line and the experimental points reflects the fraction of the cation **9** present in the
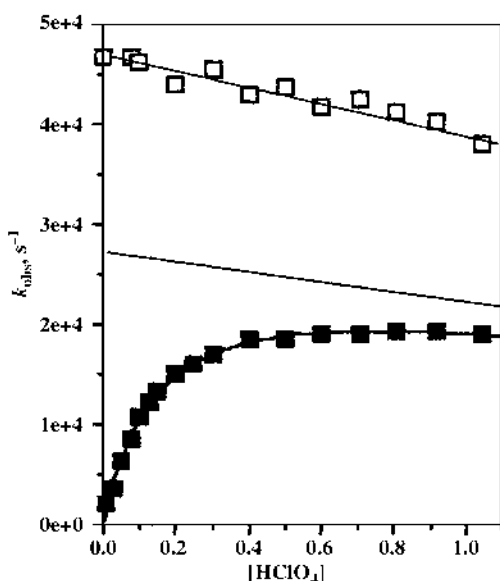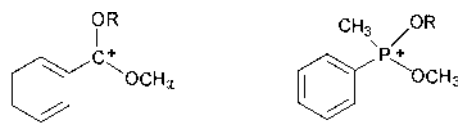
Fig. 1 Rate constants at 20 °C for the decay of the bis(4-methoxyphenyl)methyl cation **6** (open squares) and the equilibrating mixture of quinone methide **8**–cation **9** (closed squares). The ionic strength was maintained constant at 1.0 mol dm^{-3} by NaClO$_4$. The intermediates were generated by 248 nm laser irradiation of the ester **5** and alcohol **7**. The data for **6** were obtained at a monitoring wavelength of 495 nm. Rate constants for the quinone methide system were obtained at 495 nm above 0.1 mol dm^{-3} HClO$_4$, and at both 400 nm and 495 nm below this concentration (with good agreement between the two). The line drawn through the experimental points for **6** is based on linear regression. The curve through the solid points is based on the best fit to the equation $k_{obs} = (k_w(\mathbf{9})_0 + m[\mathrm{H}^+])[\mathrm{H}^+]/([\mathrm{H}^+] + K_a(\mathbf{9}))$. The line in the middle is the calculated $k_w(\mathbf{9}) = k_w(\mathbf{9})_0 + m[\mathrm{H}^+]$ based upon the values obtained in this fit.

10; R = CH$_3$, k_w = 1 x 10^5 s^{-1} **12**, R = CH$_3$, k_w = 2 x 10^{-4} s^{-1}
11; R = H, k_w = 3 x 10^2 s^{-1} **13**, R = H, k_w = 8 x 10^{-6} s^{-1}

methides would suggest that this stabilization plays less of a role in these systems. One important difference between the two systems is that the esters react directly at the atom bearing the OH or OMe group, while the quinone methides react at the remote methylene carbon in the *para* position. The lack of significant kinetic stabilization by OH in the latter system may mean that the effect on the esters is more related to a modification of the reacting environment by solvation rather than to a specific stabilization effect.

Acknowledgements

Notes and references

† We initially intended to employ the absorbance changes at 495 nm to construct a titration curve to obtain an independent measure of the acidity constant. This however proved not to be possible since the absorbance continued to increase well beyond the point where the kinetics showed saturation. This is likely related to increased quantum efficiency for loss of the OH group associated with an H$^+$-catalyzed reaction in the excited state.[12]

1 M. A. Lewis, D. G. Yoerg, J. L. Bolton and J. A. Thompson, *Chem. Res. Toxicol.*, 1996, **9**, 1368.
2 P. G. McGracken, J. L. Bolton and G. R. J. Thatcher, *J. Org. Chem.*, 1997, **62**, 1820.
3 S. E. Rokita, J. Yang, P. Pande and W. A. Greenberg, *J. Org. Chem.*, 1997, **62**, 3010.
4 P. Pande, J. Shearer, J. Yang, W. A. Greenberg and S. E. Rokita, *J. Am. Chem. Soc.*, 1999, **121**, 6773.
5 J. P. Richard, M. M. Toteva and J. Crugeiras, *J. Am. Chem. Soc.*, 2000, **122**, 1664.
6 Y. Chiang, A. J. Kresge and Y. Zhu, *J. Am. Chem. Soc.*, 2000, **122**, 9854.
7 M. M. Toteva and J. P. Richard, *J. Am. Chem. Soc.*, 2000, **122**, 11073.
8 E. Modica, R. Zanaketti, M. Freccero and M. Mella, *J. Org. Chem.*, 2001, **66**, 41.
9 R. A. McClelland, V. M. Kanagasabapathy and S. Steenken, *J. Am. Chem. Soc.*, 1998, **110**, 6913.
10 R. A. McClelland, V. M. Kanagasabapathy, N. Banait and S. Steenken, *J. Am. Chem. Soc.*, 1989, **111**, 3966.
11 L. Diao, C. Yang and P. Wan, *J. Am. Chem. Soc.*, 1995, **117**, 5369.
12 N. J. Turro and P. Wan, *J. Photochem.*, 1985, **28**, 93.
13 C. A. Bunton and S. K. Huang, *J. Am. Chem. Soc.*, 1972, **94**, 3536.
14 T. H. Lowry and K. S. Richardson, *Mechanism and Theory in Organic Chemistry*, 2nd Edition, Harper and Row, New York, 1981, p. 131.
15 R. A. McClelland, G. H. McGall and G. Patel, *J. Am. Chem. Soc.*, 1985, **107**, 5204.
16 R. A. McClelland, V. M. Kanagasabapathy and S. Steenken, *Can. J. Chem.*, 1990, **68**, 375.

equilibrium with **8**. As a point of consistency, 1 mol dm^{-3} HClO$_4$ results in a 17% decrease in $k_w(\mathbf{6})$ compared to 1 mol dm^{-3} NaClO$_4$. The effect on $k_w(\mathbf{9})$ is 19%, within experimental error the same. It can also be noted that a K_a value of 0.082 has been reported for the *o*-quinone analog of **9**, with a rate constant for hydration of the cation of 4.6×10^5 s^{-1}.[6]

The important conclusion from this study is that $k_w(\mathbf{9})$ is 57% of $k_w(\mathbf{6})$ (and this is independent of acidity). In other words there is little difference between the reactivity of the protonated quinone methide and that of an analogous benzylic carbocation. The small difference is somewhat surprising in light of the σ^+ values for *p*-methoxy (-0.78) and *p*-hydroxy (-0.92),[14] which suggest that the latter should be more stabilizing. It is especially surprising in view of the substantial differences in reactivity seen between methylated and protonated esters.[15] These comparisons are set out in structures **10**–**13**. The α,α-dimethoxybenzyl carbocation **10** has a lifetime in water of 10 μs (verified since ref. 14 by laser flash photolysis).[16] Protonated methyl benzoate (or the α-hydroxy-α-methoxybenzyl carbocation **11**) reacts 300 times more slowly. A 25-fold difference is seen between the dimethoxy-substituted phosphonium ion **12** and the hydroxymethoxy analog **13**, a protonated phosphinate ester. These rather substantial differences between methylated and protonated esters were explained by a hydrogen bonding stabilization in the protonated cation X=O$^+$–H $\cdots$ OH$_2$ (where X = C or P). The much smaller difference seen between the methylated and protonated quinone