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Solvent Effect on Concertedness of the Transition State in the Hydrolysis of *p*-Nitrophenyl Acetate

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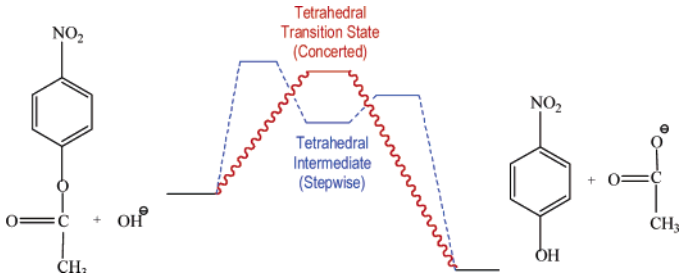
ABSTRACT



The reaction pathway for the alkaline hydrolysis of *p*-nitrophenyl acetate is investigated using density functional theory. It is shown that solvent plays an indispensable role in shaping the concerted transition state. The concertedness of this transition state is supported by good agreement with the measured kinetic isotope effects.

Ester hydrolysis is an important and prevalent reaction in both organic[1] and biological chemistry.[2] The classical mechanism for hydrolysis of esters (and for more general acyl transfer reactions) involves stepwise nucleophilic addition and elimination via a tetrahedral intermediate (TI). However, it has been argued that for good leaving groups such as aryloxides the hydrolysis may be concerted via a tetrahedral transition state.[3] Experimental evidence in support of the concerted mechanism ranges from the Brønsted correlation of the rate constant with the pK_a of the nucleophile[4] to heavy atom kinetic isotope effects (KIEs).[5]

Detailed knowledge of the putative transition state is not only important for mechanistic understanding of the hydrolysis reaction but also essential for designing effective transition-state analogues (haptens) to elicit catalytic antibodies.[6] As pointed out recently,[7] the Brønsted linear free-energy relationship may not be unique in determining the reaction mechanism, and a high-level theoretical understanding is thus necessary. In this Letter, we report a density functional theory (DFT) investigation of the alkaline hydrolysis pathway of *p*-nitrophenyl acetate (PNPA), which has long been a prototypical substrate for studying hydrolysis/acyl transfer reactions in solution phase[4,5] and in enzymes.[8]

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(1) (a) Bender, M. L. *Chem. Rev.* **1960**, *60*, 53. (b) *Ester Formation and Hydrolysis*; Bamford, C. H., Tipper, C. F. H., Eds.; Elsevier: Amsterdam, 1972.
(2) (a) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; Dover: New York, 1986. (b) Williams, A. In *Enzyme Mechanisms*; Page, M. I., Williams, A., Eds.; Burlington: London, 1987. (c) Fersht, A. R. *Enzyme Structure and Mechanism in Protein Science*; Freeman: New York, 1999.
(3) Guthrie, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 3941.
(4) (a) Ba-Saif, S.; Luthra, A. K.; Williams, A. *J. Am. Chem. Soc.* **1987**, *109*, 6362. (b) Ba-Saif, S.; Luthra, A. K.; Williams, A. *J. Am. Chem. Soc.* **1989**, *111*, 2647. (c) Stefanidis, D.; Cho, S.; Dhe-Paganon, S.; Jencks, W. P. *J. Am. Chem. Soc.* **1993**, *115*, 1650.
(5) (a) Hengge, A. C.; Hess, R. A. *J. Am. Chem. Soc.* **1994**, *116*, 11256. (b) Cleland, W. W.; Hengge, A. C. *FASEB J.* **1995**, *9*, 1586.
(6) Lerner, R. A.; Benkovic, S. J.; Schultz, P. G. *Science* **1991**, *252*, 659.
(7) Florian, J.; Warshel, A. *J. Am. Chem. Soc.* **1998**, *120*, 11524.

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Table 1. Calculated and Measured Kinetic Isotope Effects

KIE	$^{16/18}$O(OH$^-$)	$^{16/18}$O(PhO)	$^{12/13}$C(C=O)	$^{16/18}$O(C=O)	$^{14/15}$N(NO$_2$)	3H/D(Me)
calcd[a]		1.0006		1.0079	1.0004	0.9505
calcd[b]	1.0147	0.9982	1.0120	1.0036	1.0001	0.8597
calcd[c]	1.0249	1.0099	1.0404	1.0056	1.0002	0.9711
exptl[d]		1.0135	1.0342	1.0039	1.0002	0.9562

[a] Reference 9. [b] Model I, this study. [c] Model II, this study. [d] Reference 8.

Thanks to the electron-withdrawing nitro (NO_2) group in the *para* position, the *p*-nitrophenoxide is known to be a good leaving group ($pK_a = 7.14$). Despite strong experimental evidence, however, theoretical studies have not yet been able to identify a truly concerted transition state in the alkaline hydrolysis of this and other aryl esters. In the recent work of Tantillo and Houk,[9] for example, a transition state for addition was located in vacuo by geometry optimization at the HF/6-31+G* level. A later DFT study by Kollman group[10] reached the same conclusion. Both attributed the failure in finding the elimination transition state and TI to a concerted mechanism. Although a valid conclusion, it is apparent that a transition state for nucleophilic addition is no substitution for a concerted one, as evidenced by its poor agreement with the measured leaving group $^{16/18}$O KIE (1.0006 vs. 1.0135).[9] As shown below, a more accurate theoretical characterization of the reaction pathway in such systems requires a proper treatment of solvent effects.

In this work, two models were investigated for the alkaline hydrolysis of PNPA. The first model (I) includes only the OH$^-$ nucleophile and PNPA, as shown in Figure 1, whereas

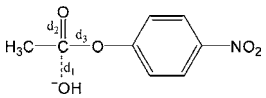

Figure 1. Model for alkaline hydrolysis of PNPA.

seven water molecules were added in the second model (II). The latter supermolecule approach allows explicit solvation of key moieties such as the anionic hydroxide nucleophile, which has been shown to be essential for the accurate determination of the reaction pathway in systems involving charged species.[11] Geometries of stationary points (minima and transition states) were obtained by optimization with the B3LYP functional,[12] as implemented in Gaussian 03,[13] and confirmed by additional frequency calculations. The intrinsic reaction coordinate (IRC) for the transition state was also characterized.[14] The 6-31++G** basis set was employed for model I and for the hydroxide, solvent waters, and acyl moiety of PNPA in model II, whereas the smaller 6-31G* basis set was used for other atoms of PNPA in model II. The inclusion of diffuse functions is essential for anionic species. The KIEs were computed using the Bigeleisen−Mayer theory,[15] and the results are listed in Table 1. The solvent effects for the solution phase reaction were estimated for the stationary points using the polarized continuum model (PCM)[16] with no further geometric optimization, which has been shown[17] to be appropriate for treating the hydrolysis of a small system. The energetics of the stationary points is listed in Table 2.

Table 2. Calculated Energetics (kcal/mol) for the Two Models

model	energetics	reactant complex	transition state	product complex
I	ΔE_{gas}	0.0	2.03	−44.77
	ΔE_{gas} + ZPE	0.0	2.27	−42.82
	ΔG_{gas}	0.0	2.98	−45.20
	ΔE_{sol}(PCM)	0.0	0.46	−40.62
II	ΔE_{gas}	0.0	9.60	−27.32
	ΔE_{gas} + ZPE	0.0	10.98	−24.17
	ΔG_{gas}	0.0	12.79	−22.75
	ΔE_{sol}(PCM)	0.0	15.71	−20.52

A very loose transition state was found for the gas phase alkaline hydrolysis of PNPA (model I), in which the distance between the nucleophile oxygen and the carbonyl carbon (d_1) is rather larger (2.59 Å) while the bond length to the leaving group ($d_3 = 1.41$ Å) is essentially unchanged from that of the reactant complex. This transition state is clearly for the nucleophilic addition step, similar to that obtained by Tantillo and Houk,[9] in which the corresponding distances are 2.28 and 1.37 Å, respectively. A similar transition state was found by Chong et al.[10] at the B3LYP/6-31+G* level, indicating that the electron correlations are not essential for the transition state. As in previous work,[9,10] efforts to locate the TI and the elimination transition state were unsuccessful,

(8) (a) Menger, F. M.; Ladika, M. *J. Am. Chem. Soc.* **1987**, *109*, 3145. (b) Hess, R. A.; Hengge, A. C.; Cleland, W. W. *J. Am. Chem. Soc.* **1998**, *120*, 2703.
(9) Tantillo, D. J.; Houk, K. N. *J. Org. Chem.* **1999**, *64*, 3066.
(10) Chong, L. T.; Bandyopadhyay, P.; Scanlan, T. S.; Kuntz, I. D.; Kollman, P. A. *J. Comput. Chem.* **2003**, *24*, 1371.
(11) (a) Zhan, C.-G.; Landry, D. W.; Ornstein, R. L. *J. Am. Chem. Soc.* **2000**, *122*, 2621. (b) Gregersen, B. A.; Lopez, X.; York, D. M. *J. Am. Chem. Soc.* **2004**, *126*, 7504.
(12) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
(13) Frisch, M. J. et al.; Gaussian, Inc.: Pittsburgh, PA, 2003.
(14) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154.
(15) Bigeleisen, J.; Mayer, M. G. *J. Chem. Phys.* **1947**, *15*, 261.
(16) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027.
(17) Zhan, C.-G.; Landry, D. W.; Ornstein, R. L. *J. Phys. Chem.* **2000**, *A104*, 7672.

which underscores the instability of the potential TI. As shown in Table 1, the KIE for the leaving group oxygen is inverse (0.9982), in poor agreement with the experimental value of 1.0135.[10] The small primary KIE reflects the negligible participation of the PhO−C bond in the reaction coordinate. Its small (2.98 kcal/mol) free energy barrier for nucleophlic addition is rendered negligible (0.46 kcal/mol) by solvation.

The inclusion of the seven water molecules provides a resonably complete solvent shell for the reaction region. Except for the fact that neither TI nor elimination transition state was found, the picture that emerged from model II with seven explicit water molecules is very different. The transition state geometry shown in Figure 2 features a more

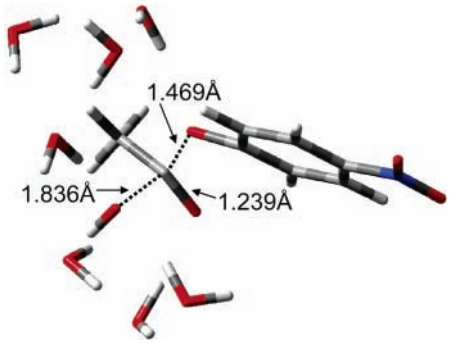

Figure 2. Transition state geometry for the alkaline hydrolysis of PNPA with seven explicit water molecules.

elongated PhO−C bond (d_3 = 1.47 Å) and a much shorter distance between the nucleophilic O and carbonyl C (d_1 = 1.84 Å) than in model I. The analysis of the intrinsic reaction coordinate indicates unmistakenly the involvement of both nucleophilic addition and elimination coordinates, although the larger d_1 implies a somewhat early transition state. Indeed, Table 1 shows that the primary $^{16/18}$O KIE for the leaving group (1.0099) is normal and in quite good agreement with the available experimental value (1.0135), confirming the concerted nature of the transition state. The other primary $^{16/18}$O KIE for the nucleophile is 1.0249, but unfortunately there are no experimental data.

The concerted transition state has a slightly elongated carbonyl bond (d_2 = 1.24 vs. 1.21 Å in the reactant complex), apparently as a result of the weakening of the double bond. This is corroborated by the fact that the negative charge on the carbonyl oxygen is increased from −0.44*e* in the reactant complex to −0.58*e* at the transition state. The involvement of this bond in the reaction coordinate is reflected by the substantial KIEs for the carbonyl oxygen and carbon shown in Table 1, but the exact interpretation of the $^{12/13}$C and $^{16/18}$O KIEs for the C=O group is known to be difficult.[18] On the other hand, the $^{14/15}$N KIE is close to unity, signaling little involvement of the nitro group at the transition state. Finally, the secondary KIE for the β-carbon hydrogens is inverse, also in agreement with experimental data. This KIE measures the change of the C−H bond force constants due to the reduction of hyperconjugation during the nucleophilic attack.[8b]

Comparison of the two models clearly shows that the inclusion of explicit waters alters not only the energy but also the geometry of the transition state. Consequently, stationary points obtained from the unsolvated system may not be trusted for reactions involving ionic species. This important conclusion is not entirely surprising given the involvement of an anionic nucleophile and the loose nature of the transition state. We note in passing that a similar concerted transition state was found in the general base (imidazole)-catalyzed hydrolysis of aryl esters.[19]

The calculated barrier height for the alkaline hydrolysis of PNPA in aqueous solution (15.71 kcal/mol) is in excellent agreement with the experimental activation energy (15.8 kcal/mol).[20] The reaction has a large exothermicity (ΔG = −20.52 kcal/mol). An interesting observation is that the product complex consists of acetic acid and phenoxide (see Supporting Information). The proton transfer from the former to the latter, which is not considered in this work, is expected to further increase the exothermicity.

In conclusion, our DFT results provide strong theoretical evidence for the existence of a concerted transition state for the alkaline hydrolysis of PNPA, as evidenced by both the transition state geometry and the good agreement with experimental KIEs. This conclusion has significant implications for acyl transfer reactions both in solution and in enzymes. In addition, the results underscore the importance of proper treatment of the solvent effects for reactions involving charged species.

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Supporting Information Available: Coordinates, key bond lengths, and energies of the stationary points. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Marlier, J. F. *Acc. Chem. Res.* **2001**, *34*, 283.
(19) Xie, D.; Xu, D.; Zhang, L.; Guo, H. *J. Phys. Chem.* **2005**, *B109*, 5259.
(20) Matta, M. S.; Toenjes, A. A. *J. Am. Chem. Soc.* **1984**, *107*, 7591.