Resolution of Conflicting Mechanistic Observations in Ester Aminolysis. A Warning on the Qualitative Prediction of Isotope Effects for Reactive Intermediates

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Ester aminolysis is a fundamental process in both organic and biological chemistry and its mechanism has long been of great interest. At high pH in water the tetrahedral intermediates T^- and T^0 (Scheme 1) go on to products[1] and the key question is the nature of the rate-limiting general base- or acid-catalyzed formation of these intermediates. Classical mechanistic studies by Jencks and co-workers have supported the intermediacy of $T^\pm$ in the aminolysis of alkyl esters,[1,2,3] and Jencks' observations in these reactions underpin modern comprehension of general acid−base catalysis.[4] Isotope effect studies, however, have not supported this mechanism. In the hydrazinolysis of methyl formate catalyzed by a second molecule of hydrazine, Marlier has recently concluded that T^- is formed by a concerted nucleophilic attack/proton transfer.[5] This would appear to substantially impact the understanding of general catalysis: the concerted formation of T^- would have been expected only with strong bases and when the lifetime of $T^\pm$ would be extremely short.[4] We report here a resolution of the apparently conflicting mechanistic observations in ester aminolyses,[6] resulting from a revised understanding of isotope effects in tetrahedral intermediates. We also suggest a general warning on the modeling of isotope effects for reactive intermediates from isotope effects in analogous stable compounds.

Marlier's key observation was a k_{12C}/k_{13C} of 1.020 for the formyl carbon (Table 1).[5,7] It was argued that if T^- is formed by a stepwise mechanism, the observed kinetic isotope effect (KIE) would approximate the equilibrium isotope effect for formation of $T^\pm$. This equilibrium effect was estimated as 0.979 based on fractionation factors for stable neutral molecules and 0.962 based on a force field generated from stable neutral molecules.[8] Thus the observed KIE of 1.020, typical of primary carbon isotope effects, was judged to be only consistent with the concerted process. The inverse hydrazine ^{15}N KIE was very unusual for a nucleophilic attack[9] but was complicated by averaging of the KIE for the two nitrogens. The substantial inverse ^2H KIE was considered consistent with either full formation of the tetrahedral intermediate or a very late transition state in the concerted mechanism. Overall, the conclusion of a concerted process was

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(2) (a) Cox, M. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1981**, *103*, 572. (b) Cox, M. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1981**, *103*, 580.
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(4) Jencks, W. P. *Chem. Rev.* **1972**, *72*, 705. Jencks, W. P. *J. Am. Chem. Soc.* **1972**, *94*, 4731. Jencks, W. P. *Acc. Chem. Res.* **1976**, *9*, 425.
(5) Marlier, J. F.; Haptonstall, B. A.; Johnson, A. J.; Sacksteder, K. A. *J. Am. Chem. Soc.* **1997**, *119*, 8838.
(6) CAPS buffer ($pK_a = 10.4$) is likely the general base in ref 5 while hydrazine ($pK_a = 8.3$) is the main general base in ref 1. The greater basicity of the CAPS buffer compared to $T^\pm$ with hydrazine ($pK_a \approx 9.6$) would relatively favor a concerted mechanism, as noted by ref 5 and a referee. However, Bronsted studies in refs 1, 2b, and 3 do not support a change in mechanism for buffers moderately more basic than $T^\pm$.
(7) (a) Sawyer, C. B.; Kirsch, J. F. *J. Am. Chem. Soc.* **1973**, *95*, 7375. (b) Bilkadi, Z.; de Lorimier, R.; Kirsch, J. F. *J. Am. Chem. Soc.* **1975**, *97*, 4317.
(8) Hogg, J. L.; Rodgers, J.; Kovach, I.; Schowen, R. L. *J. Am. Chem. Soc.* **1980**, *102*, 79.
(9) Marlier, J. F.; Dopke, N. C.; Johnstone, K. R.; Wirdzig, T. J. *J. Am. Chem. Soc.* **1999**, *121*, 4356.
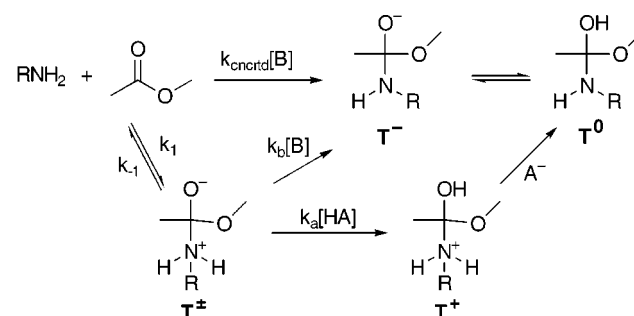
Scheme 1

Table 1. Experimental and Calculated Isotope Effects for Aminolysis of Methyl Formate

	C=O	HC=O	N	C=O	C−OMe
expt:[a] R = NH$_2$	1.020	≈0.72−0.78[b]	0.9917	1.004	1.0048[c]
calculated[d]					
1(6H$_2$O R = NH$_2$)	1.022	0.81	0.989	1.010	1.010
+ implicit solvent[e]	1.021	0.80	0.989	1.009	1.011
2 (8H$_2$O, R = NH$_2$)	1.023	0.80	0.988	1.011	1.009
+ implicit solvent[e]	1.021	0.79	0.988	1.011	1.009
3 (4H$_2$O, R = H)	1.024	0.80			
4 (6H$_2$O, R = H)	1.021	0.79			
5 (8H$_2$O, R = H)	1.018	0.78			
6 (11H$_2$O, R = H)	1.017	0.77			
T$^-$·6H$_2$O, R = NH$_2$	1.015	0.79	0.994	1.014	1.014
T^0·2H$_2$O, R = H	1.008	0.75			

[a] Experimental isotope effects are k_H/k_D, k_{12C}/k_{13C}, k_{16O}/k_{18O}, or k_{14N}/k_{15N}, averaged for the two hydrazine nitrogens, and are taken from refs 5 and 7. [b] Extrapolated in ref 7b from an experimental value of 0.76. [c] Extrapolated in ref 7a from an experimental value of 1.0167. [d] Calculated isotope effects are K_H/K_D, K_{12C}/K_{13C}, K_{16O}/K_{18O}, or K_{14N}/K_{15N}, averaged for the two hydrazine nitrogens. For a more complete set of calculated isotope effects, see Supporting Information. [e] Based on an Onsager model (see ref 12) with $\epsilon = 78.39$ and $a_0 = 4.93$ Å for **1** and 5.31 Å for **2**.

dictated by the ^{13}C KIE. We would emphasize that this is a completely normal and standard interpretation of the observed KIEs.

We hypothesized that a hyperconjugative or anomeric-type effect in $T^\pm$ might reconcile the observed ^{13}C KIE in the hydrazinolysis of methyl formate with a stepwise mechanism. The decreased strength of C−H bonds β to a carbocation is well recognized: this results in the normal ($k_{light}/k_{heavy} > 1$) β-deuterium isotope effect in S_N1 reactions. In carbanions the effect on C−H bonds is similar though smaller.[10] A greater weakening in anions would be expected for β bonds to electronegative atoms that can hyperconjugatively accept a negative charge. This would weaken the C−N and C−OR bonds in $T^\pm$ and favor a normal isotope effect for both atoms involved in the weakened bond.

weakened bonds in reactive intermediates
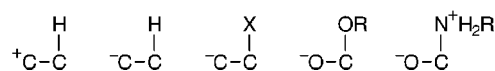
Theoretical calculations were used to test this hypothesis. Predictions of heavy-atom KIEs using high-level calculations have been very successful,[11] but the formation of a zwitterion in water

(10) Davies, M. H. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1018.
(11) See: Meyer, M. P.; DelMonte, A. J.; Singleton, D. A. *J. Am. Chem. Soc.* **1999**, *121*, 10865 and references therein.

presents a special challenge. For the reactions of NH_3 or NH_2-NH_2 with methyl formate, the $T^\pm$ structures **1**−**6** employing 4, 6, 8, and 11 explicit water molecules were fully optimized in Becke3LYP calculations using a 6-31+G** basis set. Structures **1** and **2** were also optimized using an Onsager-type implicit solvation model[12] in combination with the explicit waters. The
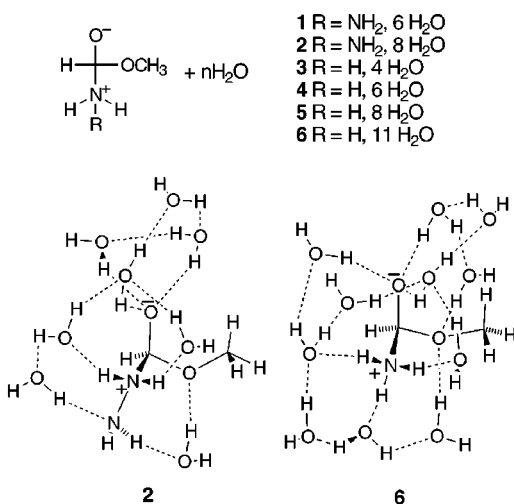

solvation patterns in structures **2** and **6** are shown as examples (complete structures may be found in Supporting Information). The structures studied were generated by design to model minimal expectations for the solvation of $T^\pm$ in bulk water, including the donation of hydrogen bonds to the anionic oxygen and a water oxygen positioned to accept a hydrogen bond from each ammonium N−H bond. Otherwise, the structures are not meant to be realistic and no effort was made to find global minima: the critical assumption in these calculations is that the secondary solvent shell and the detailed choice of solvated structure (among a large ensemble of possibilities) will have little impact on the isotope effects. This assumption is supported in Table 1 by a low variation in the predicted ^{13}C and ^2H isotope effects across the series of model structures and with the inclusion of an implicit solvent model.

The equilibrium isotope effects for the formation of **1**−**6** were calculated from the scaled vibrational frequencies (Table 1).[13] In contrast to the previously expected inverse ^{13}C isotope effect for formation of $T^\pm$, a normal ^{13}C isotope effect near 1.020 is found for **1**−**6**. Each of the structures has a significantly elongated C−N bond (1.67−1.54 Å) compared to that predicted for a hydrated T^0 structure (1.44 Å, see Supporting Information). This supports the idea that the normal isotope effect results from a hyperconjugative bond weakening.

The comparison of the complete set of experimental KIEs with the calculated isotope effects for the hydrazinolysis $T^\pm$ structures

Scheme 2
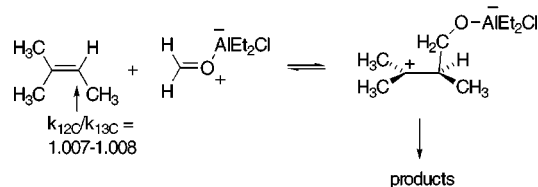
1 and **2** is most striking. Considering the limitations of the calculations, the use of equilibrium isotope effects as an approximation for kinetic isotope effects, and the extrapolations involved in the ^2H and methoxyl ^{18}O experimental values, the agreement of the predicted and experimental isotope effects is excellent. We note that the stepwise mechanism not only explains the ^{13}C isotope effect but also provides a much more intuitively satisfactory explanation of the inverse ^{15}N and large inverse ^2H KIEs. In contrast with their previous interpretation, our conclusion is that the observed isotope effects support the Jencks mechanism.

Other observations suggest a broad admonition on the qualitative interpretation of heavy-atom isotope effects in reactions involving reactive intermediates. From Table 1, the impact of hyperconjugative bond weakening on isotope effects includes not only zwitterionic but also anionic and neutral tetrahedral intermediates. A similar effect appears operative in carbocations. In the Lewis acid-catalyzed ene reaction of formaldehyde with 2-methyl-2-butene, a ^{13}C KIE of 1.007−1.008 observed at an olefinic carbon (Scheme 2) seemed suggestive of rate-limiting C−C bond formation, since an equilibrium isotope effect of 0.989 is expected based on fractionation factors for neutral molecules.[14,15] However, the theoretically predicted equilibrium isotope effect for formation of the carbocation was 1.007 at this carbon, owing to the weakened C−C bond β to the carbocation. Thus, the observed KIE was in fact consistent with other observations indicating a subsequent proton transfer as rate limiting.[14]

The results here underscore the value and importance of theoretical calculations in the interpretation of isotope effects. The observation of a heavy-atom KIE significantly greater than 1.000 has often been taken as indicative of rate-limiting bond formation or breaking at the atom in question. Because bond weakening in reactive intermediates may produce a similar isotope effect, there are a number of circumstances under which such conclusions may be compromised. We are currently investigating the breadth of impact of this idea on mechanistic interpretations in the literature.

Supporting Information Available: Energies and geometries of all calculated structures, and a complete table of calculated isotope effects (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Bigeleisen, J.; Mayer, M. G. *J. Chem. Phys.* **1947**, *15*, 261. Becke3LYP frequencies were scaled by 0.9614.
(14) Singleton, D. A.; Hang, C. *J. Org. Chem.* **2000**, *65*, 895.
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