The Neutral Hydrolysis of Methyl Acetate. Part 2. Is There a Tetrahedral Intermediate?

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The neutral hydrolysis of methyl acetate — Part 2. Is there a tetrahedral intermediate?

Zheng Shi, Yih-huang Hsieh, Noham Weinberg, and Saul Wolfe

Abstract: A computational strategy that reproduces the experimental rates of hydration of formaldehyde, acetaldehyde, acetone, and cyclohexanone and the rates of acetic acid and 2-hydroxypyridine-catalyzed hydration of acetone has been extended to the results of the neutral hydrolysis of methyl acetate reported in Part 1. Calculations have been performed for one-step and two-step mechanisms, with cooperative assistance from one to three additional water molecules in the presence and absence of the acetic acid product. The calculations predict that, for the neutral reaction, a one-step mechanism will be favoured if tetrahedral intermediates have a short lifetime and do not interconvert prior to breakdown (case A), and a two-step mechanism will be operative if tetrahedral intermediates are allowed to interconvert prior to breakdown (case B). The experimental results are consistent with the predictions of case A. In the presence of acetic acid, case A predicts that the acid will contribute only 1.6% to the overall rate, a negligible acceleration over the noncatalytic process, and case B predicts general acid catalysis to be an order of magnitude greater than the experimental result. It is concluded that the neutral hydrolysis of methyl acetate is mainly a cooperative one-step process, and that general acid catalysis by the acetic acid product does not occur.

Key words: cooperative mechanism, one-step mechanism, tetrahedral intermediate.

Résumé : Une stratégie théorique permettant de reproduire les vitesses expérimentales d'hydratation du formaldéhyde, de l'acétaldéhyde, de l'acétone et de la cyclohexanone ainsi que les vitesses d'hydratation de l'acétone catalysée par l'acide acétique et la 2-hydroxypyridine a été étendue aux résultats de l'hydrolyse neutre de l'acétate de méthyle rapportée dans la partie 1. Les calculs ont été effectués pour les mécanismes à une et à deux étapes, avec l'assistance coopérative d'une, deux ou trois molécules d'eau, en présence et en absence d'acide acétique produit. Les calculs permettent de prédire que, pour la réaction neutre, le mécanisme en une étape sera favorisé si les intermédiaires tétraédriques sont de courte vie et qu'ils ne donnent pas lieu à une interconversion avec leur rupture (cas A) et un mécanisme en deux étapes qui opérera si les intermédiaires peuvent subir une interconversion avant leur rupture (cas B). Les résultats expérimentaux sont en accord avec les prédictions du cas A. En présence d'acide acétique, le cas A prédit que l'acide ne contribuera qu'à 1,6% de la vitesse globale, une accélération négligeable par rapport au processus non catalytique; le cas B prédit une catalyse acide générale qui serait d'un ordre de grandeur plus important que le résultat expérimental. On peut donc en conclure que l'hydrolyse neutre de l'acétate de méthyle est principalement en processus coopératif en une étape et que la catalyse par l'acide acétique produit n'a pas lieu.

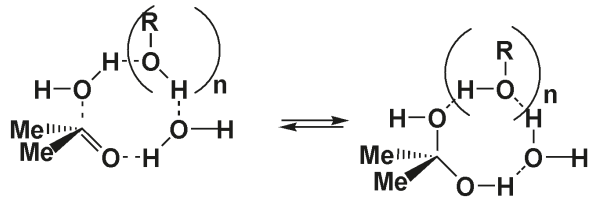
Mots-clés : mécanisme coopératif, mécanisme en une étape, intermédiaire tétraédrique.

[Traduit par la Rédaction]

Introduction

Background

In recent publications, we have discussed the neutral,[1,2] acetic acid-catalyzed,[3] and 2-hydroxypyridine-catalyzed[4] aqueous hydrations of acetone as exemplars of cooperativity, by which we mean that in each case concurrent C–O bond formation and proton transfer to oxygen take place through a bridge of solvent and (or) catalyst molecules (eq [1]). As originally posited by Eigen[5] and by Long and co-workers,[6] the cooperative mechanism offers a preferred neutral alternative to a multistep ionic mechanism in which charged intermediates are subjected to continuous solvation and desolvation as they appear and disappear.

[1] 

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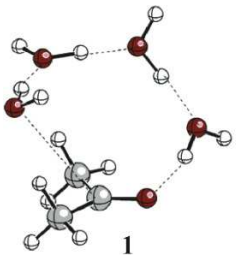
In the work of ref. 1, we found that experimental hydration rates in water solvent can be reproduced by a computational strategy that affords the free energy barriers exhibited by different reaction complexes as well as the concentrations of these complexes. This is achieved by HF/3–21G calculations,[7,8] in conjunction with the self-consistent reaction field (SCRF, Onsager) model[9,10] with a dielectric constant of 78.5. The previously optimized gas-phase structures were used to estimate the radius of the cavity for SCRF calculations. Transition structures were located by the reaction coordinate method.

Free energies of complexes, corrected for loss of translational and rotational degrees of freedom, are calculated using eq. [2].[1,2]

$$[2]\qquad \Delta G = \Delta H - T\Delta S_{\text{vib}} - 6RT\left\{\frac{\hbar\omega/kT}{\exp\left(\hbar\omega/kT\right)-1} - \ln\left[1-\exp\left(-\frac{\hbar\omega}{kT}\right)\right]\right\}$$

The first term on the right-hand side of eq. [2] is the enthalpy change calculated using the 3–21G basis set[8] and augmented by correction for the basis set superposition error (BSSE).[1,11] The second term on the right-hand side accounts for the intramolecular vibration entropy change, and it is also calculated by the Gaussian programme.[8] The third term on the right-hand side refers to the entropy change resulting from the loss of six low-frequency vibration modes representing rotational and translational motions in solution. These vibrations are described by a mass-dependent effective frequency ω, scaled as a root of molecular mass[2] and defined in terms of a single adjustable parameter ω_0, which is estimated numerically for water monomer (m_0 = 18 au) to be 20 cm^{-1}.[1]

At 298 K, the neutral hydration of acetone exhibits k_{obs} = 8.9 × 10^{-6} s^{-1}.[2] The calculated rate is k_{calc} = 19.6 × 10^{-6} s^{-1}, and the principal channel, comprising 97% of the overall reaction, proceeds via the four-water molecule complex **1**, whose free energy barrier and concentration are 11.34 kcal/mol (1 cal = 4.184 J) and 1.63 × 10^{-10} mol/L, respectively.



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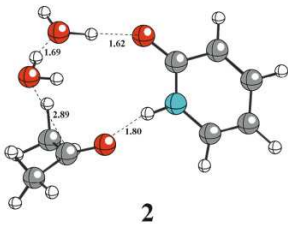


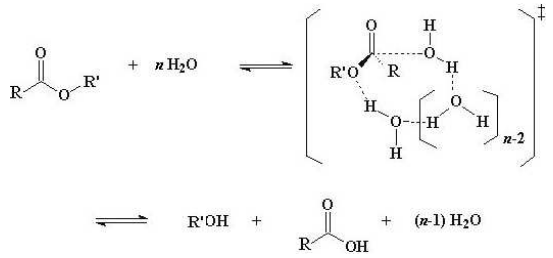
2

Addition of 1 mmol/L 2-hydroxypyridine to a 1 mol/L acetone solution leads to k_{obs} = 1.3 × 10^{-3} s^{-1} at 298 K, a catalytic effect of 150.[4] The calculated rate is k_{calc} = 2.1 × 10^{-3} s^{-1}, and 96% of the reaction, with a free energy barrier of 11.97 kcal/mol, proceeds via the 2-*pyridone* dihydrate **2**, whose concentration of 1.08 × 10^{-7} mol/L is almost 700 times greater than that of **1**. The "bifunctional catalysis"[12] exhibited by 2-hydroxypyridine therefore resides in the exceptional stability of **2**.

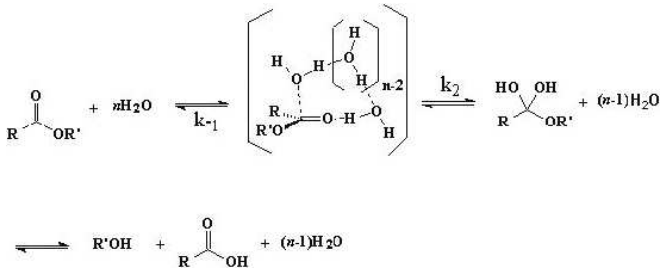
Neutral ester hydrolysis

The present work was undertaken to determine whether an appropriate extension of the cooperative mechanism,

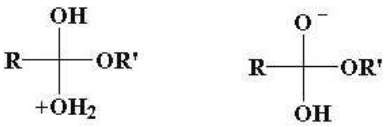
Scheme 1.



Scheme 2.



e.g., Scheme 1 or 2, could be relevant in neutral ester hydrolysis in water solvent. It will be noticed that Scheme 1 suggests the possibility of a one-step process that bypasses the tetrahedral intermediate of Scheme 2,[13] which is well established for acid-catalyzed (**3a**) and base-catalyzed (**3b**) ester hydrolysis.



3a **3b**

In contrast to the extensive literature on acid- and base-catalyzed ester hydrolysis,[13–15] there has been only sporadic interest in neutral hydrolysis (Table 1). At 298 K (Table1, entry 1) the hydrolysis of ethyl acetate proceeds with a first-order rate constant of 2.47 × 10^{-10} s^{-1} ($\Delta G^{\ddagger}$ = 30.6 kcal/mol[21]).

Temperature dependence studies of the hydrolyses of alkyl- and aryl-substituted trifluoroacetates in aqueous acetone lead to rate constants of 1.67–5.67 × 10^{-8} s^{-1} at 25 °C (Table 1, entry 2). For the hydrolysis of chloromethyl chloroacetate (Table 1, entry 3), $\Delta H^{\ddagger}$ = 11.8 kcal/mol and $\Delta S^{\ddagger}$ = –37 cal mol^{-1} K^{-1} at 25 °C. From the rates of hydrolysis of ethyl trifluorothiolacetate in the presence of potassium acetate – acetic acid buffers, and extrapolation to zero buffer concentration, a neutral rate constant of 5.02 × 10^{-3} s^{-1} at 25 °C is obtained (Table 1, entry 4), and proton inventory experiments suggest that there are two to three hydrons in flight. The kinetics and activation parameters for the hydrolysis of ethyl formate in the temperature range 30–50 °C provide a rate constant of 5.0 × 10^{-6} s^{-1} at 298 K (Table 1, entry 5).

The theoretical treatment of neutral ester hydrolysis is even less well-advanced than the limited number of experi-

Table 1. Experimental studies of neutral ester hydrolysis.

Entry	Reactant	Solvent	Rate (s^{-1})[a]	$\Delta H^{\ddagger}$[b] or Ea[b]	$\Delta S^{\ddagger}$[c]	Ref.
1	$MeCO_2Et$	H_2O	2.47×10^{-10}			16
2	CF_3CO_2R	Me_2CO/H_2O				17
	R = C_3H_7		5.67×10^{-8}	9.8	–51.7	
	R = C_4H_9		3.50×10^{-8}	10.9	–49.1	
2	R = C_6H_5		1.67×10^{-8}	6.85	–45.9	
3	$ClCH_2CO_2CH_2Cl$	H_2O	2.29×10^{-5}	11.8	–37	18
4	CF_3COSEt	H_2O	5.02×10^{-3}			19
5	HCO_2Et	H_2O	5.0×10^{-6}[d]	22	–11	20

[a]At 298 K.
[b]In kcal/mol.
[c]In cal mol^{-1} K^{-1}.
[d]Extrapolated value.

mental studies just cited. For the hydrolysis of methyl formate via Schemes 1 and 2, with n = 3, gas-phase B3LYP/6–31G* geometry optimizations, followed by single-point calculations with a polarized continuum model of bulk water, give free energy barriers of 45.66 and 48.05 kcal/mol, respectively, for two-step and one-step mechanisms.[22]

For a two-step gas-phase hydrolysis of ethyl acetate with n = 2 (Scheme 2), 6–31+G* calculations afford a free energy barrier of 64.3 kcal/mol.[21] In the B3LYP/6–31G*/SCRF calculations of Yamabe et al. on the aqueous hydrolysis of ethyl acetate in the presence of different numbers of active water molecules,[23] the concerted (one-step) free energy barrier ranges between 42.9 and 47.9 kcal/mol, much higher than the experimental $\Delta G^{\ddagger}$ of Skrabal and Zahorka.[16] A two-step mechanism with $k_{-1} \approx k_2$ gives free energy barriers close to the experimental $\Delta G^{\ddagger}$, the reaction via a four-water molecule complex being favoured.

Each of the theoretical studies just cited has focused on the magnitudes of calculated barriers. However, as in the hydration studies discussed earlier, we presume that the calculation of hydrolysis *rates* will require that the *concentrations* of reaction complexes also be taken into account.

Present work

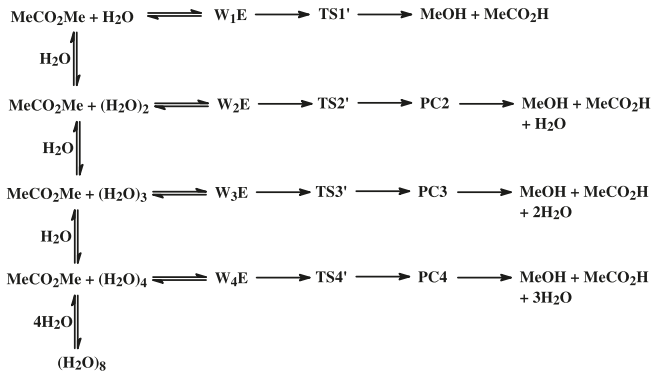
In the present work, of which this is Part 2, we have applied our computational strategy[1,2] to study the neutral hydrolysis of methyl acetate. Since the acetic acid product of hydrolysis catalyzes the reaction,[24] the notion of cooperativity has also been extended to this reaction. The kinetic experiments designed to test the predictions of Part 2 are found in Part 1.[24]

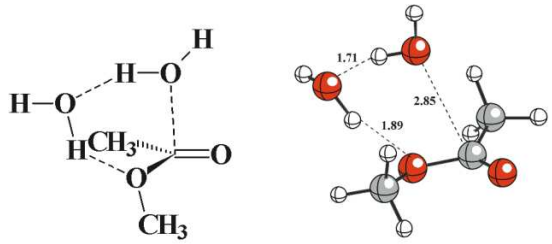
Neutral hydrolysis

One-step mechanism

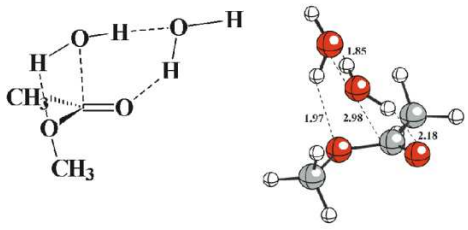
In Scheme 1, the addition of a water molecule to the carbonyl group takes place in concert with proton transfer to the methoxy group. Calculations were performed for n = 1–4 to obtain the free energies of the stationary structures of Scheme 3 in water solvent, where $\mathbf{W}_n\mathbf{E}$ is a cyclic reactant complex of methyl acetate (**E**) with n water molecules (**W**; n = 1–4), **TS***n*′ is a cyclic transition structure derived from $\mathbf{W}_n\mathbf{E}$, and **PC***n* is a product complex of methanol, acetic acid, and (n – 1) water molecules.

Scheme 3.





4b



4c

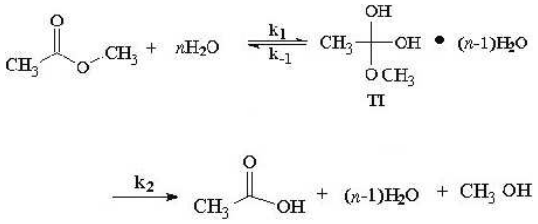
More than one $\mathbf{W}_n\mathbf{E}$ complex is possible when n > 1, e.g., **4b** and **4c** for n = 2. All conceivable topologies of reactant complexes of Scheme 3 were taken into account.

Table 2 lists the ΔG and $\Delta G^{\ddagger}$ calculated at 298 K. Structures **4a**, **4b–4c**, **4d–4f**, and **4g–4k** are, respectively, one-water, two-water, three-water, and four-water $\mathbf{W}_n\mathbf{E}$, and structures **5a–5k** are the **TS***n*′ derived from these complexes. (Structures not shown in the text and full Tables 2–9 are available in the Supplementary data below.)

Table 2. Calculated Gibbs free energies for the neutral hydrolysis of methyl acetate at 298 K via Scheme 3.

Complex	ΔG (kcal/mol)
W_1E 4a	4.04
W_2E 4b	8.57
W_2E 4c	10.27
W_3E 4d	8.28
W_3E 4e	8.31
W_3E 4f	4.74
W_4E 4g	12.06
W_4E 4h	14.35
W_4E 4i	10.94
W_4E 4j	13.83
W_4E 4k	16.33
Transition structure	$\Delta G^{\ddagger}$ (kcal/mol)
TS1′ 5a	47.62
TS2′ 5b	29.31
TS2′ 5c	50.07
TS3′ 5d	22.27
TS3′ 5e	31.20
TS3′ 5f	36.62
TS4′ 5g	15.28
TS4′ 5h	17.43
TS4′ 5i	37.45
TS4′ 5j	37.70
TS4′ 5k	34.33

Scheme 4.



Two-step mechanism

Scheme 4 describes a two-step neutral ester hydrolysis via **TI**, a tetrahedral intermediate. In the network of reactions shown in Scheme 5, the hydrolysis proceeds from the reactant complexes **W_nE**, via a first transition structure **TS*n*″** to the tetrahedral intermediates **TI*n***, and then via a second transition structure **TS*n*‴** to the product complexes **PC*n***. As before, more than one **W_nE** complex is possible for $n > 1$. All conceivable topologies of reactant complexes of Scheme 5 were taken into account.

Tables 3 and 4 list the ΔG and $\Delta G^{\ddagger}$ calculated at 298 K. Structures **6a**, **6b–6c**, **6d–6g**, and **6h–6o** are, respectively, one-water, two-water, three-water, and four-water **W_nE**, structures **7a–7o** refer to **TS*n*″**, the transition structures connecting **W_nE** to the tetrahedral intermediates **8a–8o**, and structures **9a–9o** refer to **TS*n*‴**, the transition structures connecting the tetrahedral intermediates to the products.

The theoretical rate constant

As in our previous works,[1–4] the hydrolysis rate constant can be calculated by taking into account pre-equilibrium

Table 3. Calculated Gibbs free energies of the reactant complexes **W_nE** and transition states **TS*n*″** for the neutral hydrolysis of methyl acetate at 298 K via Scheme 5.

Complex	ΔG (kcal/mol)
W_1E 6a	2.54
W_2E 6b	4.95
W_2E 6c	8.14
W_3E 6d	4.78
W_3E 6e	13.79
W_3E 6f	13.82
W_3E 6g	8.77
W_4E 6h	16.49
W_4E 6i	12.16
W_4E 6j	23.24
W_4E 6k	19.16
W_4E 6l	21.10
W_4E 6m	11.97
W_4E 6n	20.55
W_4E 6o	11.67
TSn″	$\Delta G^{\ddagger}$ (kcal/mol)
TS1″ 7a	48.66
TS2″ 7b	21.64
TS2″ 7c	41.56
TS3″ 7d	14.36
TS3″ 7e	14.95
TS3″ 7f	14.38
TS3″ 7g	38.93
TS4″ 7h	14.34
TS4″ 7i	13.17
TS4″ 7j	8.06
TS4″ 7k	10.30
TS4″ 7l	9.49
TS4″ 7m	34.12
TS4″ 7n	17.87
TS4″ 7o	18.44

Scheme 5.

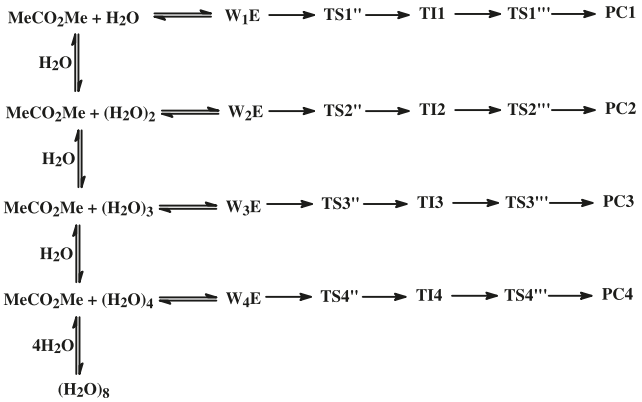
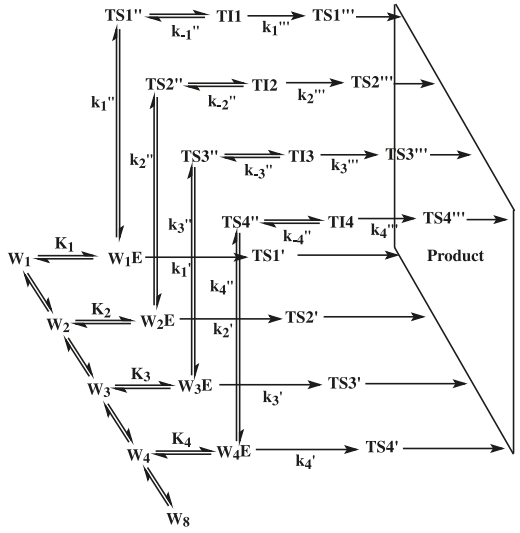


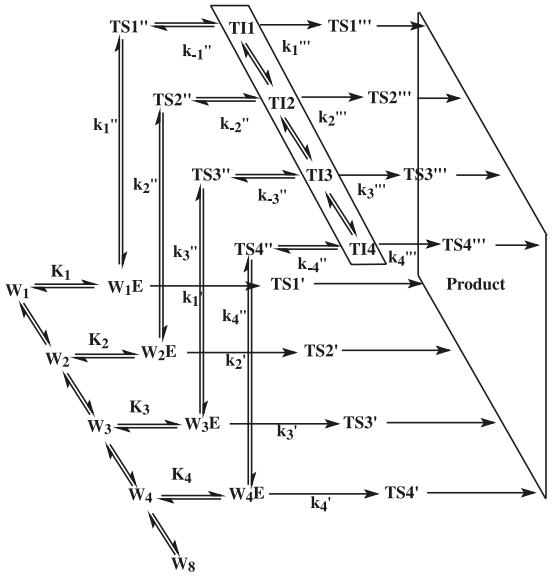
Table 4. Calculated Gibbs free energies of the intermediates **TI*n*** and transition states **TS*n*‴** for the neutral hydrolysis of methyl acetate at 298 K via Scheme 5.

TI*n*	ΔG (kcal/mol)
TI1 8a	5.79
TI2 8b	3.96
TI2 8c	1.03
TI3 8d	9.01
TI3 8e	–2.25
TI3 8f	–3.45
TI3 8g	–1.39
TI4 8h	0.39
TI4 8i	0.11
TI4 8j	–5.11
TI4 8k	–6.16
TI4 8l	–6.97
TI4 8m	–4.56
TI4 8n	–4.15
TI4 8o	4.63
TSn‴	$\Delta G^{\ddagger}$ (kcal/mol)
TS1‴ 9a	46.27
TS2‴ 9a	39.04
TS2‴ 9c	20.56
TS3‴ 9d	34.74
TS3‴ 9e	15.82
TS3‴ 9f	14.95
TS3‴ 9g	14.59
TS4‴ 9h	37.95
TS4‴ 9i	15.77
TS4‴ 9j	11.20
TS4‴ 9k	7.41
TS4‴ 9l	5.82
TS4‴ 9m	12.57
TS4‴ 9n	18.11
TS4‴ 9o	25.94

Scheme 6.



Scheme 7.



among water clusters and reactant complexes, as shown in Scheme 6, combining one- and two-step channels of Schemes 3 and 5. There is, however, an additional complication here because **TI**–water complexes may interconvert. To treat this possibility, two limiting cases were considered: in case (A) the **TI** are short-lived and do not undergo exchange with the solvent (Scheme 6); in case (B) the **TI** are sufficiently stable to allow equilibration among complexes containing different numbers of water molecules (Scheme 7). In either case, $\mathbf{W}_n$ refers to n-mers of water, **E** is the ester, $\mathbf{K}_n$ is the equilibrium constant for the formation of $\mathbf{W}_n\mathbf{E}$, k'_n is the rate constant of a reaction channel of the one-step mechanism, and k''_n, k''_{-n}, and k'''_n are the rate constants of the two-step mechanism.

As already noted, more than one $\mathbf{W}_n\mathbf{E}$ complex is possible for $n > 1$. Those that interconvert through a single step mechanism are labelled $\mathbf{W}_n\mathbf{E}'$, and those that interconvert through a two-step mechanism are labelled $\mathbf{W}_n\mathbf{E}''$. The overall concentration $[\mathbf{W}_n\mathbf{E}]$ is,

$$[\mathrm{W}_n\mathrm{E}] = \sum[\mathrm{W}_n\mathrm{E}'] + \sum[\mathrm{W}_n\mathrm{E}'']$$

and the independent relationships among the concentrations of $\mathbf{W}_n$ and $\mathbf{W}_n\mathbf{E}$ are,

$$[\mathrm{W}_n] = K_n^w[\mathrm{W}_1]^n$$
$$[\mathrm{W}_n\mathrm{E}'] = K'_n[\mathrm{W}_n][\mathrm{E}] = K'_nK_n^w[\mathrm{W}_1]^n[\mathrm{E}]$$
$$[\mathrm{W}_n\mathrm{E}''] = K''_n[\mathrm{W}_n][\mathrm{E}] = K''_nK_n^w[\mathrm{W}_1]^n[\mathrm{E}]$$

In addition, the following two equations of material balance apply to these concentrations,

$$[3] \qquad C_{\mathrm{W}} = \sum_n n[\mathrm{W}_n] + \sum_n n[\mathrm{W}_n\mathrm{E}]$$

$$[4] \qquad C_{\mathrm{E}} = [\mathrm{E}] + \sum_n [\mathrm{W}_n\mathrm{E}]$$

where C_{W} and C_{E} are the analytical concentrations of water (55.5 mol/L) and ester, respectively.

Table 5. Complexes providing major contributions to the rate of hydrolysis of 1.0 mol/L methyl acetate (limiting case A).

Species	Concentration (mol/L)	Rate constant (s^{-1})	Partial rate (mol/L s^{-1})	Contribution (%)[a]
One-step				
W_4E' 4g	1.21×10^{-10}	79.0	9.58×10^{-9}	71.68
All **W_4E'**	—	—	9.58×10^{-9}	71.72
Two-step				
W_4E'' 6i	1.02×10^{-10}	3.42×10	3.48×10^{-9}	26.02
All **W_4E''**	—	—	3.78×10^{-9}	28.28
Total rate (s^{-1})			1.34×10^{-8}	

[a]Contribution to the overall rate of reaction.

Table 6. Complexes providing major contributions to the rate of hydrolysis of 1.0 mol/L methyl acetate (limiting case B).

Species	Concentration (mol/L)	Rate constant (s^{-1})	Partial rate (mol/L s^{-1})	Contribution (%)[a]
One-step				
W_4E' 4g	1.21×10^{-10}	7.90×10	9.58×10^{-9}	2.67
All **W_4E'**	—	—	9.58×10^{-9}	2.67
Two-step: **$W_nE \rightleftharpoons TSn''$**				
W_2E'' 6b	4.61×10^{-5}	1.72×10^{-3}[b]		
		1.36[c]	7.93×10^{-8}	22.70
W_3E'' 6d	2.40×10^{-10}	3.69×10^{2}[b]		
		1.48×10^{9}[c]	4.88×10^{-8}	13.97
W_3E'' 6e	5.99×10^{-17}	1.38×10^{2}[b]		
		3.07[c]	-1.48×10^{-8}[d]	–4.25
W_3E'' 6f	5.67×10^{-17}	3.61×10^{2}[b]		
		1.06[c]	-3.89×10^{-8}[d]	–11.15
W_4E'' 6i	1.02×10^{-10}	2.77×10^{3}[b]		
		3.36×10^{3}[c]	2.82×10^{-7}	80.66
Two-step: **$TIn \rightarrow TSn'''$**				
TI3 8f	3.66×10^{-8}	4.03×10^{-1}	1.47×10^{-8}	4.22
TI3 8g	1.12×10^{-9}	24.1	2.70×10^{-8}	7.72
TI4 8k	1.39×10^{-11}	1.40×10^{3}	1.95×10^{-8}	5.57
TI4 8l	5.41×10^{-11}	5.27×10^{3}	2.85×10^{-7}	81.50
All **TIn**	—	—	3.49×10^{-7}	97.33
Total rate (s^{-1})			35.9×10^{-8}	

[a]Contribution to the overall rate of reaction.
[b]Rate constant for **$W_nE \rightarrow TSn''$**, the forward reaction.
[c]Rate constant for **$TIn \rightarrow TSn''$**, the reverse reaction.
[d]The reverse process dominates.

Limiting case A: No interconversion between TI*n* (Scheme 6)

In this case, all two-step channels are considered to be independent of each other. Application of the steady-state approximation leads to a set of effective rate constants,

$$[5] \qquad k_{\text{eff},\,n} = \frac{k''_n k'''_n}{(k''_{-n} + k'''_n)}$$

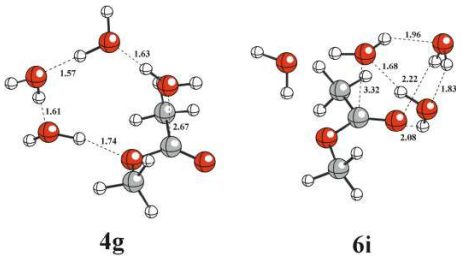
resulting in eqs. [6] and [7] for the overall rate of hydrolysis and its pseudo first-order rate constant k.

$$[6] \qquad v = kC_E = \sum k'_n[W_nE'] + \sum k_{\text{eff},\,n}[W_nE'''] \qquad [7] \qquad k = \frac{\sum k'_n K'_n[W_n] + \sum k''_n K''_n[W_n]}{1 + \sum K'_n[W_n] + \sum K''_n[W_n]}$$

Table 5 summarizes the results for the hydrolysis of a 1.00 mol/L methyl acetate solution at 298 K. According to this analysis, at 298 K the rate of hydrolysis is 1.34×10^{-8} s^{-1}, 72% of the reaction proceeds by a one-step mechanism from the four-water complex **4g** (Fig. 1) and 26% by a two-step mechanism from the four-water complex **6i** (Fig. 2).

Table 7. Calculated Gibbs free energies at 298 K for species involved in the acetic acid-catalyzed hydrolysis of methyl acetate via Scheme 8.

W_nEA'	ΔG (kcal/mol)	$TSAn'$	$\Delta G^{\ddagger}$ (kcal/mol)
W_1EA' 12a	–2.14	**TSA1′ 13a**	22.61
W_1EA' 12b	–4.24	**TSA1′ 13b**	36.78
W_2EA' 12c	32.14	**TSA2′ 13c**	25.12
W_2EA' 12d	34.65	**TSA2′ 13d**	26.74
W_2EA' 12e	29.09	**TSA2′ 13e**	19.95
W_2EA' 12f	33.49	**TSA2′ 13f**	13.51
W_nEA''		**$TSAn''$**	
W_1EA'' 14a	0.57	**TSA1″ 15a**	7.12
W_1EA'' 14b	–7.01	**TSA1″ 15b**	25.28
W_1EA'' 14c	–2.80	**TSA1″ 15c**	40.30
W_1EA'' 14d	5.56	**TSA1″ 15d**	43.35
W_2EA'' 14e	4.09	**TSA2″ 15e**	11.76
W_2EA'' 14f	–1.57	**TSA2″ 15f**	10.29
W_2EA'' 14g	1.18	**TSA2″ 15g**	14.87
W_2EA'' 14h	7.36	**TSA2″ 15h**	6.27
W_2EA'' 14i	8.24	**TSA2″ 15i**	17.79
W_2EA'' 14j	4.72	**TSA2″ 15j**	12.23
W_2EA'' 14k	1.80	**TSA2″ 15k**	39.67
W_2EA'' 14l	–0.08	**TSA2″ 15l**	36.25
W_3EA'' 14m	9.75	**TSA3″ 15m**	4.87
W_3EA'' 14n	7.29	**TSA3″ 15n**	7.48
W_3EA'' 14o	9.90	**TSA3″ 15o**	7.75
W_3EA'' 14p	3.89	**TSA3″ 15p**	5.09
TIA*n*		**$TSAn'''$**	
TIA1 16a	–4.93	**TSA1‴ 17a**	27.81
TIA1 16b	8.20	**TSA1‴ 17b**	40.79
TIA1 16c	–1.85	**TSA1‴ 17c**	10.44
TIA1 16d	–0.41	**TSA1‴ 17d**	12.32
TIA2 16e	–0.92	**TSA2‴ 17e**	31.44
TIA2 16f	–0.67	**TSA2‴ 17f**	36.83
TIA2 16g	1.37	**TSA2‴ 17g**	15.21
TIA2 16h	–6.06	**TSA2‴ 17h**	9.33
TIA2 16i	–0.77	**TSA2‴ 17i**	12.88
TIA2 16j	–5.58	**TSA2‴ 17j**	5.39
TIA2 16k	–0.36	**TSA2‴ 17k**	13.42
TIA2 16l	–4.50	**TSA2‴ 17l**	9.67
TIA3 16m	–6.86	**TSA3‴ 17m**	13.04
TIA3 16n	–8.77	**TSA3‴ 17n**	3.09
TIA3 16o	–8.98	**TSA3‴ 17o**	4.35
TIA3 16p	–7.65	**TSA3‴ 17p**	1.58



Limiting case B: Fast equilibrium among TI*n*

If equilibrium among **TI**′s is taken into account, Scheme 6 is modified to Scheme 7, and the rate of the reversible reac-

Fig. 1. Reaction coordinate of the major hydrolysis channel of limiting case A.

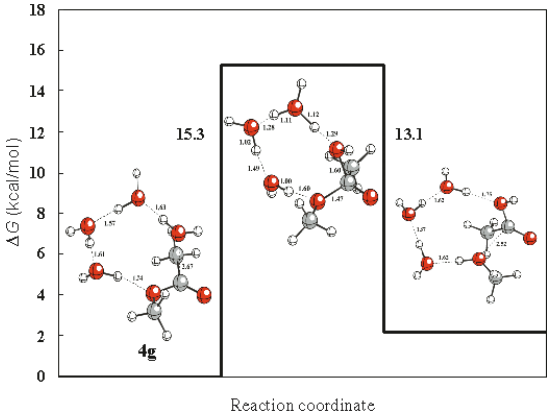
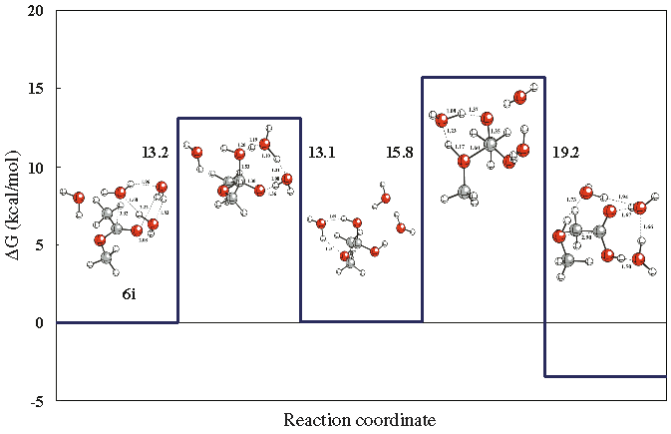


Fig. 2. Reaction coordinate of the minor hydrolysis channel of limiting case A.



Scheme 8.

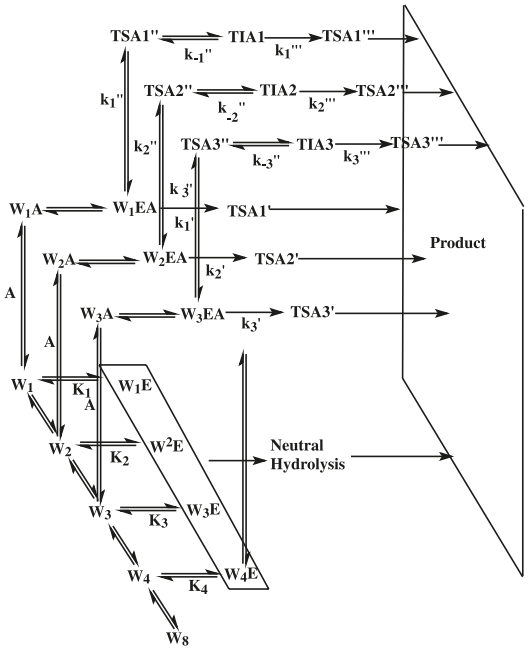


Table 8. Complexes providing major contributions to the rate of hydrolysis of 1.0 mol/L methyl acetate in 1.00 mol/L in acetic acid (limiting case A).

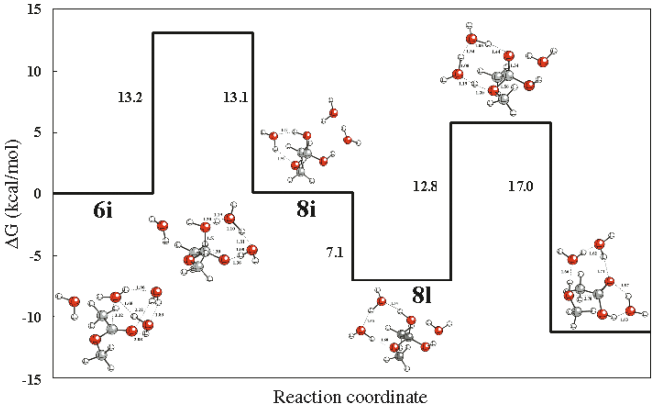
Species	Concentration (mol/L)	Rate constant (s^{-1})	Partial rate (mol/L s^{-1})	Contribution to overall rate (%)
W_4E' 4g	1.19×10^{-10}	79.0	9.40×10^{-9}	70.53
Neutral: 1-step (all **W_nE'**)	—	—	9.41×10^{-9}	70.57
W_4E'' 6i	9.97×10^{-11}	3.42×10	3.41×10^{-9}	25.60
Neutral: 2-step (all **W_nE''**)	—	—	3.71×10^{-9}	27.83
Acetic acid: 1-step (all **W_nEA'**)	—	—	1.43×10^{-14}	0.00
Acetic acid: 2-step (all **W_nEA''**)	—	—	2.14×10^{-10}	1.60
Total rate (s^{-1})			1.34×10^{-8}	
Neutral			1.31×10^{-8}	98.40
Acid			2.14×10^{-10}	1.60

Table 9. Complexes providing major contributions to the rate of hydrolysis of 1.0 mol/L methyl acetate in 1.00 mol/L in acetic acid (limiting case B)

Species	Concentration (mol/L)	Rate constant (s^{-1})	Partial rate (mol/L s^{-1})	Contribution (%)[a]
Neutral: 1-step				
All **W_nE'**	—	—	9.41×10^{-9}	0.00
Neutral, 2-step: **$W_nE \rightleftharpoons TSn''$**				
W_2E'' 6b	4.57×10^{-5}	1.72×10^{-3}[b] 1.36[c]	7.86×10^{-8}	22.88
W_3E'' 6d	2.37×10^{-10}	3.69×10^{2}[b] 1.48×10^{9}[c]	4.81×10^{-8}	13.99
W_3E'' 6e	5.91×10^{-17}	1.38×10^{2}[b] 3.07[c]	-1.47×10^{-8}[d]	–4.27
W_3E'' 6f	5.59×10^{-17}	3.61×10^{2}[b] 1.06[c]	-3.85×10^{-8}[d]	–11.19
W_4E'' 6i	9.97×10^{-11}	2.77×10^{3}[b] 3.36×10^{3}[c]	2.77×10^{-7}	80.53
Neutral, 2-step: **$TIn \rightarrow TSn'''$**				
All **TIn**	—	—	3.44×10^{-7}	0.02
Acid: 1-step				
All **W_nEA'**	—	—	1.43×10^{-14}	0.00
Acid, 2-step: **$W_nEA \rightleftharpoons TSAn''$**				
W_1EA" 14a	4.44×10^{-13}	$7.49\times10^{7}b$ 1.84×10^{4}[c]	3.24×10^{-5}	60.69
W_2EA'' 14f	9.28×10^{-11}	3.59×10^{5}[b] 1.15×10^{5}[c]	3.33×10^{-5}	62.24
W_3EA'' 14m	1.82×10^{-24}	3.34×10^{9}[b] 3.15×10^{4}[c]	-7.09×10^{-6}[d]	–13.26
W_3EA'' 14p	3.63×10^{-20}	2.32×10^{9}[b] 5.71×10^{3}[c]	-4.91×10^{-6}[d]	–9.19
Acid, 2-step: **$TIA \rightarrow TSA'''$**				
TIA				
TIA3 16n	5.69×10^{-9}	2.53×10^{4}	1.44×10^{-4}	7.21
TIA3 16p	8.60×10^{-10}	2.14×10^{6}	1.84×10^{-3}	91.90
Sum	-	-	2.00×10^{-3}	99.98
Total rate (s^{-1})			2.00×10^{-3}	
Neutral			3.53×10^{-7}	0.02
Acid			2.00×10^{-3}	99.98

[a]Contribution to the reaction.
[b]Rate constant for **$W_nE \rightarrow TSn''$**, the forward reaction.
[c]Rate constant for **$TIn \rightarrow TSn''$**, the reverse reaction.
[d]The reverse process dominates.

Fig. 3. Reaction coordinate of the major hydrolysis channel of limiting case B.



tion from $\mathbf{W}_n\mathbf{E}''$ to $\mathbf{TI}n$, given by eq. [8], can be negative if the reverse process dominates.

$$[8] \qquad v''_n = k'_n[\mathrm{W}_n\mathrm{E}''] - k''_{-n}[\mathrm{TI}n]$$

The overall rate of the first step of the two-step process is

$$[9] \qquad v'' = \sum v_n = \sum k''_n[\mathrm{W}_n\mathrm{E}'] - \sum k''_{-n}[\mathrm{TI}n]$$

and the rate of the second step is

$$[10] \qquad v''' = \sum v'''_n = \sum k'''_n[\mathrm{TI}n]$$

Applying the steady-state approximation to the overall concentration of TI gives

$$[11] \qquad \frac{\mathrm{d}[\mathrm{TI}]}{\mathrm{d}t} = \sum k''_n[\mathrm{W}_n\mathrm{E}''] - \sum (k''_{-n} + k'''_n)[\mathrm{TI}n] = 0$$

leading to

$$[12] \qquad \sum k''_n[\mathrm{W}_n\mathrm{E}''] = \sum (k''_{-n} + k'''_n)[\mathrm{TI}n]$$

Since $[\mathrm{TI}n] = K_{\mathrm{TI}n}[\mathrm{TI}_1][\mathrm{W}_1]^{n-1}$ where **TI**1 is unsolvated **TI**, and $K_{\mathrm{TI}n}$ are equilibrium constants relating $[\mathrm{TI}n]$ to [TI1], eq. [12] can be converted to,

$$[13] \qquad \sum k''_n[\mathrm{W}_n\mathrm{E}''] = \{\sum (k''_{-n} + k'''_n)K_{\mathrm{TI}n}[\mathrm{W}_1]^{n-1}\}[\mathrm{TI}1]$$

which gives

$$[14] \qquad [\mathrm{TI}1] = \frac{\sum k''_n[\mathrm{W}_n\mathrm{E}'']}{\sum (k''_{-n} + k'''_n)K_{\mathrm{TI}n}[\mathrm{W}_1]^{n-1}}$$

Since the tetrahedral intermediate hydrates **TI***n* are no longer short-lived, their contributions to C_{W} and C_{E} have to be taken into account comparable to the reactant complexes $\mathbf{W}_n\mathbf{E}$, which expands eqs. [3] and [4] to,

$$[15] \qquad C_{\mathrm{W}} = \sum_n n[\mathrm{W}_n] + \sum_n n[\mathrm{W}_n\mathrm{E}] + \sum_n (n-1)[\mathrm{TI}n]$$

$$[16] \qquad C_{\mathrm{E}} = [\mathrm{E}] + \sum_n [\mathrm{W}_n\mathrm{E}] + \sum_n [\mathrm{TI}n]$$

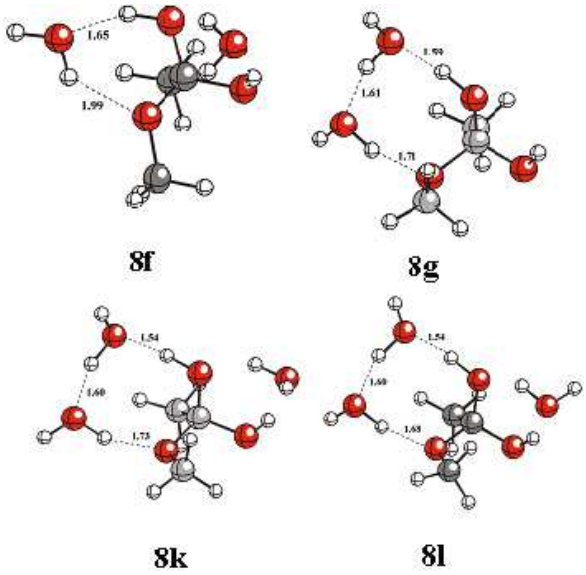
The overall rate of hydrolysis and its pseudo first-order rate constant k can then be found from eqs. [17] and [18].

$$[17] \qquad v = kC_{\mathrm{E}} = \sum k'_n[\mathrm{W}_n\mathrm{E}'] + \sum k'''_n[\mathrm{TI}n]$$

$$[18] \qquad k = \frac{\sum k'_n K'_n[\mathrm{W}_n] + \sum k'''_n[\mathrm{TI}n]}{1 + \sum K'_n[\mathrm{W}_n] + \sum K''_n[\mathrm{W}_n] + \sum [\mathrm{TI}n]}$$

Table 6 summarizes the results for the hydrolysis of a 1.00 mol/L methyl acetate solution at 298 K. In the limiting case B, the rate of hydrolysis is 35.9×10^{-8} s^{-1}, 27 times faster than the rate calculated for the limiting case A, and over 97% of the reaction proceeds by a two–step mechanism via **8f**, **8g**, **8k**, and **8l**, the **TI** having the lowest second-step barrier.

The situation is summarized in the schematic reaction profile of Fig. 3, according to which the four-water complex **6i** is converted to **8i**, which equilibrates with **8l**, which proceeds to the products.

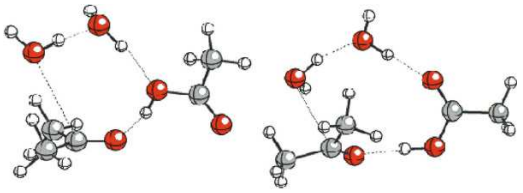


Limiting cases A and B are distinguishable

The calculated reaction rates, 1.34×10^{-8} s^{-1} for case A, in which a one-step four-water mechanism is preferred, and 35.9×10^{-8} s^{-1} for case B, in which a two-step four-water mechanism predominates, would appear to be sufficiently different for the two methods to be distinguishable. The observed rate is 0.17×10^{-8} s^{-1}.[24] It can be concluded that the neutral hydrolysis of methyl acetate mainly proceeds by a one-step cooperative mechanism, as described by limiting case A.

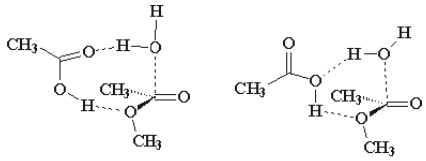
General acid catalysis by acetic acid

Acetic acid provides cooperative *general* acid catalysis of the aqueous hydration of acetone, mainly via complexes **10** and **11**.[3] However, despite the fact that spontaneous hydrolysis of methyl acetate is an autocatalytic process, subject to *specific* acid catalysis by the acetic acid product,[24] no general acid catalysis was experimentally observed in that case. To examine this situation theoretically, we augmented Schemes 6 and 7 by incorporating in them the acetic acid-containing species. The resultant kinetic networks are shown in Schemes 8 and 9 for limiting cases A and B, respectively.



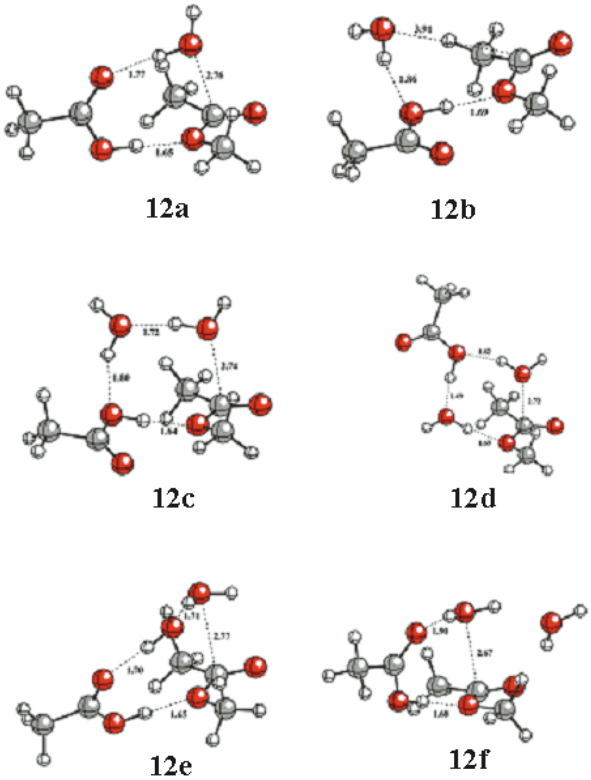
10 11

In these Schemes $\mathbf{W}_n\mathbf{A}$ are complexes of acetic acid with n water molecules and $\mathbf{W}_n\mathbf{EA}$ are cyclic complexes of methyl acetate with one molecule of acetic acid and n water molecules. There is more than one complex for each $\mathbf{W}_n\mathbf{EA}$. For example, **12a** and **12b** are possibilities for n = 1. All conceivable topologies of reactant complexes for n = 1–3 were taken into account.[25]



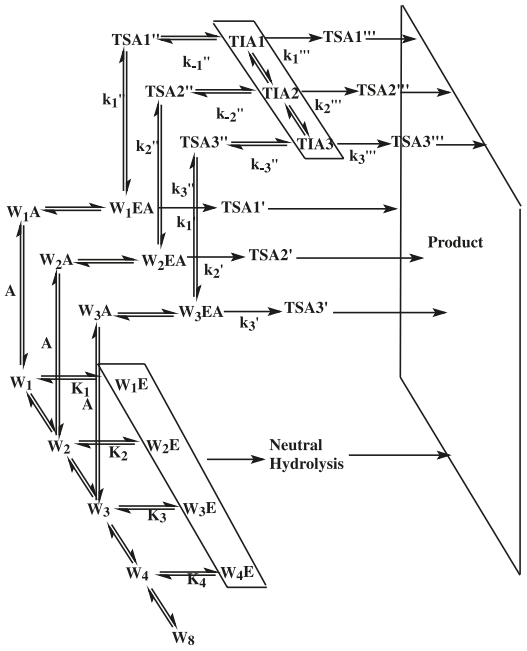
12a 12b

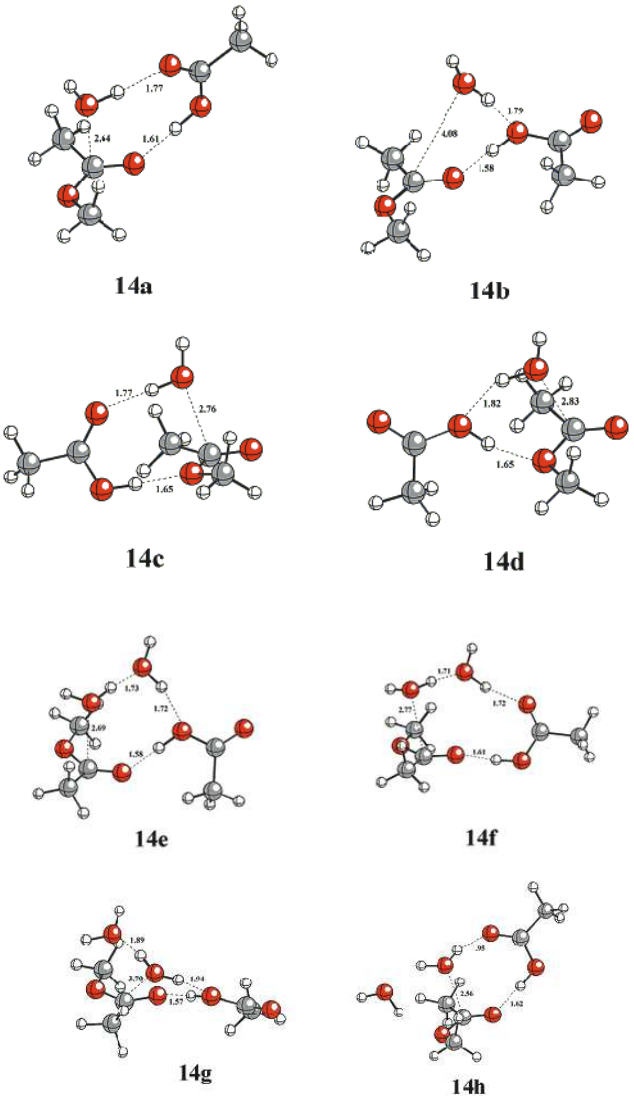
Cyclic transition states **TSA*n***′ (structures **13a**–**13f**) are derived from $\mathbf{W}_n\mathbf{EA}'$ (structures **12a**–**12f**). Tetrahedral intermediates **TIA*n*** (structures **16**) are obtained from $\mathbf{W}_n\mathbf{EA}''$ (structures **14**) via transition states **TSA*n***″ (structures **15**) and further transform into product compexes via transition states **TSA*n***‴ (structures **17**).



12a 12b 12c 12d 12e 12f

Scheme 9.





14a 14b 14c 14d 14e 14f 14g 14h

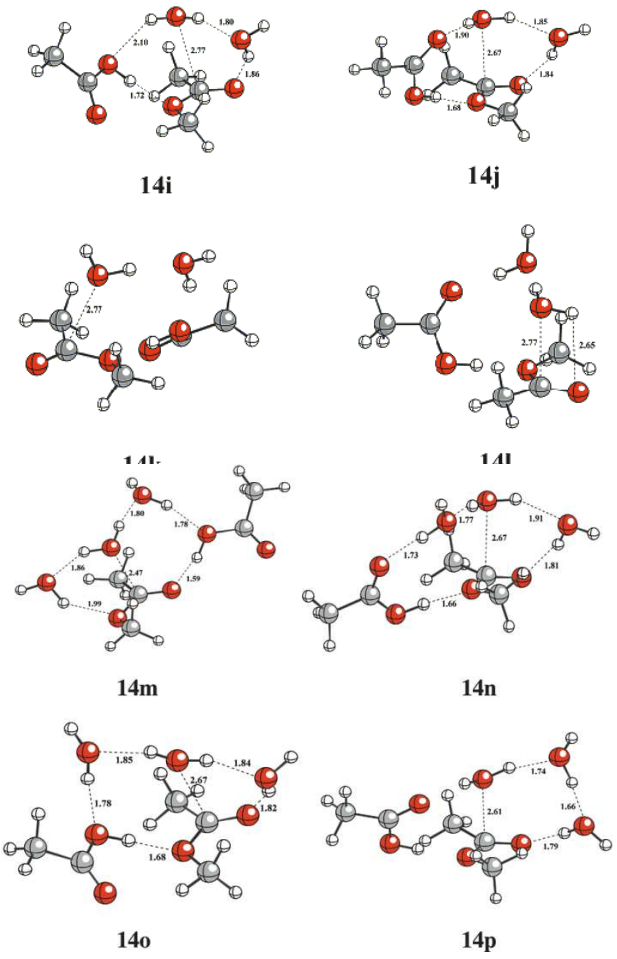


Table 7 lists the ΔG and $\Delta G^{\ddagger}$ at 298 K calculated for species involved in Scheme 8, which were then used to calculate the partial and overall rate constants of hydrolysis of 1 mol/L methyl acetate in the presence of 1 mol/L acetic acid by a trivial extension of the method described in the previous section. The results are summarized in Table 8 (for the limiting case A) and Table 9 (for the limiting case B).

The analysis of these results reveals that on the assumption that tetrahedral intermediates are short-lived and do not interconvert (case A), the acetic-acid-involving channels contribute only 1.6% to the overall rate through non-ionic processes and thus produce a negligible acceleration over the non-catalytic process. This is consistent with the conclusion of Part 1[24] that the catalysis by acetic acid is entirely *specific*.

On the other hand in case B, the computations predict a strong (four orders of magnitude) effect of *general* catalysis by acetic acid, inconsistent with experiment. We therefore conclude that, with and without acetic acid, the non-ionic hydrolysis of methyl acetate predominantly proceeds by a concerted one-step mechanism.

Supplementary data

Supplementary data for this article are available on the journal Web site (canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 3888. For more information on obtaining material refer to cisti-icist.nrc-cnrc.gc.ca/cms/unpub_e.shtml.

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