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Neutral Hydrolysis of Substituted Phenyl Trifluoroacetates in Water–Acetonitrile Mixtures with Low Content of Water

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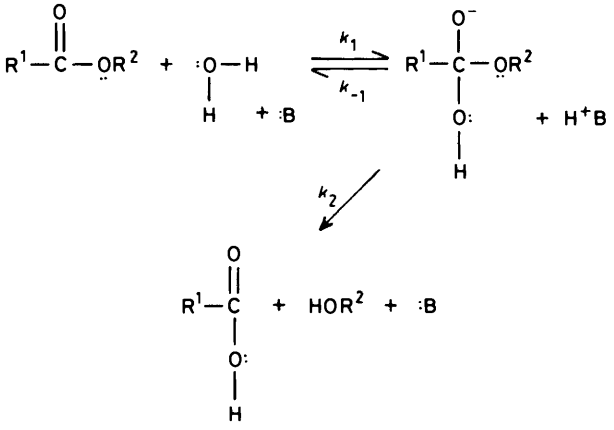
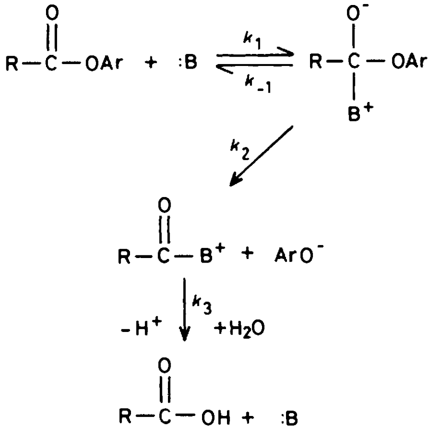
The neutral hydrolysis of substituted phenyl trifluoroacetates has been studied in water–acetonitrile mixtures in the region 0.56—3.89M water. The large solvent deuterium isotope effect (k_{H_2O}/k_{D_2O}) of 2.3 and the thermodynamic activation parameters for the hydrolysis of 4-nitrophenyl and 2,4-dinitrophenyl trifluoroacetates are consistent with a reaction mechanism in which one water molecule acts as a nucleophile and one as a general base. A linear correlation with a slope of 3.4 is found between log k_{obs} and log [H_2O] for the hydrolysis of 4-nitrophenyl trifluoroacetate. This indicates the incorporation of several water molecules in the transition state. The effect of the structure of the leaving group on the rate of the reaction is best explained by a rate-limiting attack on the carbonyl group.

The mechanism preferred for the neutral ester hydrolysis of alkyl carboxylates, $B_{AC}3$, involves a molecule of water acting as a general base :B to assist the addition of a second molecule of water to the ester carbonyl group (Scheme 1).[1–3] The kinetic studies concerning this mechanism have usually involved as substrates halogen-substituted esters like ethyl dichloroacetate and difluoroacetate,[1a] 1,2,2,2-tetrachloroethyl acetate,[4] 1,2-dichloroethyl formate,[4] and chloromethyl chloroacetate.[2a,c] In addition to water, a wide variety of bases, including amines and oxygen anions, can catalyse the hydrolysis of alkyl and halogenoalkyl carboxylates by the $B_{AC}3$ mechanism.[1a,2b,d,3] All these esters possess relatively poor leaving groups. Amines and oxygen anions also catalyse the hydrolysis of esters with good leaving groups, like 4-nitrophenyl acetate and 2,4-dinitrophenyl acetate.[2b,3,5–8] Although the hydrolysis of these esters in the case of weak bases can partially take place as a general base catalysis, nucleophilic catalysis (Scheme 2) is more usual. The mechanism of the neutral hydrolysis of phenyl esters has been investigated to some extent. For the hydrolysis of 4-nitrophenyl acetate, Butler and Gold[9] proposed that a rapid formation of a negatively charged intermediate *via* the addition of the hydroxy group of a water molecule is followed by a rate-limiting proton transfer from H_3O^+ to the oxygen atom of the leaving group, while the expulsion of the leaving group is a rapid step. On the basis of ^{18}O tracer studies, Bunton and Hadwick[10] showed the neutral hydrolysis of phenyl trifluoroacetate to take place by acyl–oxygen fission in 70% dioxane–water. The general base-catalysed attack of water with a transition state like (**1**) was suggested for the hydrolysis of 4-nitrophenyl[11,12] and 4-methoxyphenyl[12] dichloroacetates and 4-methoxyphenyl dichloropropionate[13] in aqueous solution. On the basis of proton-inventory studies, Huskey *et al.*[14] proposed cyclic transition states involving several water molecules for the hydrolysis of 4-nitrophenyl dichloroacetate in water.

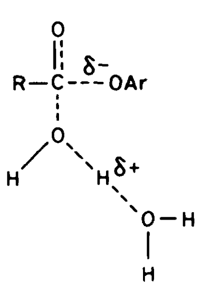


Scheme 1. $k_2, k_{-1} \gg k_1$

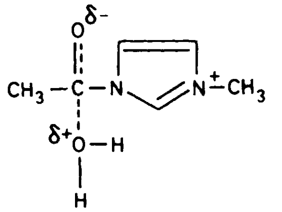


Scheme 2.

In connection with the work concerning the amine-catalysed hydrolysis of phenyl esters, I have studied the neutral hydrolysis of substituted phenyl trifluoroacetates in water–acetonitrile mixtures with low content of water.[15] The high reactivity of these esters toward water limited the study to a narrow range of water concentrations. The electronegative substituents in the acyl group suggest the $B_{AC}3$ mechanism also in this case.[1a,2b,3b] However, the good leaving groups make a nucleophilic-type pathway conceivable for phenyl esters.[1a,2b,3b,6,7] This would mean a mechanism where a water molecule displaces the aryloxy group without catalysis. Although not observed for ester hydrolysis, this kind of mechanism with a transition state like (**2**) was suggested by Gopalakrishnan and Hogg[16] for the hydrolysis of 1-acetyl-3-methylimidazolium ion in water–acetonitrile mixtures at water concentrations < 1M. This mechanism is reasonable in the light of the knowledge that water is monomeric in acetonitrile when [H_2O] < 0.5—1M.[17]



(1)



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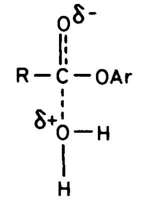

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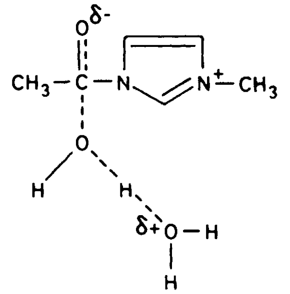

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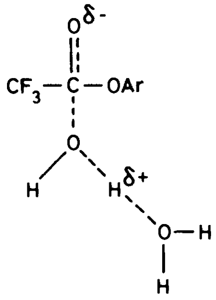

(5)

Table 1. Melting or boiling points and carbonyl group frequencies for substituted phenyl trifluoroacetates

Phenyl substituents	M.p. (or b.p.) (°C) this work	M.p. (or b.p.) (°C) literature	Ref.	ν(C=O)[a]/ cm^{-1}
H	(60 at 28 mmHg)	(123[b])	*c*	1 800
4-Cl	(44—46 at 37 mmHg)	(183[b])	*d*	1 800
		(50 at 5 mmHg)	*c*	
3-Cl	(81—82 at 27 mmHg)	(177—178[b])	*d*	1 802
$3-NO_2$	40.5—41.5	41—41.6	*e*	1 803
	(126.5—127.5 at 22 mmHg)	(92 at 1.2 mmHg)	*e*	
$4-NO_2$	37—38	36—38	*c*	1 806
$2,4-(NO_2)_2$	49	(144—146 at 3 mmHg)	*d*	1 816
	(162.5—163.5 at 13 mmHg)			

[a] The i.r. spectra were obtained for capillary films or KBr discs on a Perkin-Elmer 180 spectrometer. The wavenumbers are considered to be accurate within 5 cm^{-1}. [b] The pressure is not specified. [c] Ref. 18. [d] V. M. Belous, L. A. Alekseeva, and L. M. Yagupol'skii, *Zh. Org. Khim.*, 1975, **11**, 1672. [e] W. A. Sheppard, *J. Org. Chem.*, 1964, **29**, 1.

Experimental

Materials.—Commercial phenyl trifluoroacetate (Pierce Chemical Company) was redistilled before use. The other esters were prepared from trifluoroacetic anhydride and the appropriate phenols according to the procedure used by Sakakibara and Inukai.[18] 4-Nitrophenyl trifluoroacetate was recrystallized from hexane and the other esters were purified by distillation. 3-Nitrophenyl and 2,4-dinitrophenyl trifluoroacetates separated originally as oils but crystallized on standing. The latter was recrystallized from hexane. Table 1 gives the melting or boiling points and carbonyl group wavenumbers for the esters synthesized in this work and for the commercial phenyl trifluoroacetate.

Acetonitrile (Merck; max. H_2O 0.03%) was employed without further purification. The mixtures of acetonitrile and water were prepared from distilled water or from heavy water (Norsk Hydro-elektrisk Kvaelstofaktieselskab; 99.8% D_2O).

Table 2. Rate coefficients of the neutral hydrolysis of substituted phenyl trifluoroacetates in water–acetonitrile mixtures

Phenyl substituents	$[H_2O]$/M	*T*/K	$10^3k_{obs}/s^{-1}$
$2,4-(NO_2)_2$	0.56	298.2	2.514 ± 0.005[a]
$2,4-(NO_2)_2$	0.56	303.2	2.871 ± 0.004
$2,4-(NO_2)_2$	0.56	308.2	3.062 ± 0.011
$2,4-(NO_2)_2$	0.56	313.2	3.511 ± 0.004
$2,4-(NO_2)_2$	0.56	318.2	3.813 ± 0.015
$4-NO_2$	0.56	288.2	0.025 72 ± 0.000 06
$4-NO_2$	0.56	298.2	0.031 92 ± 0.000 11
$4-NO_2$	0.56	308.2	0.037 53 ± 0.000 20
$4-NO_2$	0.56	318.2	0.048 23 ± 0.000 32
$4-NO_2$	1.11	298.2	0.3074 ± 0.0007
$4-NO_2$	1.67	298.2	1.317 ± 0.001
$4-NO_2$	2.22	298.2	3.631 ± 0.004
$4-NO_2$	2.78	298.2	7.725 ± 0.017
$4-NO_2$	3.89	298.2	23.52 ± 0.03
$3-NO_2$	3.89	298.2	11.39 ± 0.04
3-Cl	3.89	298.2	1.885 ± 0.002
4-Cl	3.89	298.2	1.170 ± 0.001
H	3.89	298.2	0.2225 ± 0.0005

[a] Errors shown are standard deviations.

Kinetics.—The rate of phenol release was followed by a Perkin-Elmer 46 or a Perkin-Elmer 550 spectrophotometer at a suitable wavelength (phenol, 270 nm; 4-chlorophenol, 290 nm; 3-chlorophenol, 282 nm; 3-nitrophenol, 333 nm; 4-nitrophenol, 310 nm; 2,4-dinitrophenol, 290 nm). The reaction solution was prethermostatted in the optical cell (3 cm^3) of the thermostatted cell compartment of the spectrophotometer. A portion (1—5 mm^3) of an acetonitrile solution of the ester was added with a Hamilton syringe into the cell to reach a proper concentration, *ca.* 10^{-4}M. The cell was shaken quickly to dissolve the ester and transferred back to the cell compartment. The absorbance changes were recorded with a printer–timer system. The reaction was followed for about six half-lives and the final value was observed after ten half-lives if needed. The cell compartment was thermostatted by circulating water from a thermostat. The temperature of the reaction solution was measured in the optical cell with a calibrated NTC-thermistor. The temperature was constant within ±0.05—0.1 K below 308 K and within ±0.1—0.3 K above that temperature.

The first-order rate coefficients were calculated by the method of Guggenheim.[19] The k_{obs} values were reproducible to within 1—2%. Final values were observed in some cases and the first-order rate coefficients were determined from the linear plots of ln $(A_\infty - A_t)$ *versus* time. Both methods gave essentially the same values.

Results and Discussion

The kinetic data for the hydrolyses of substituted phenyl trifluoroacetates are presented in Table 2. In addition, the rate

Table 3. Activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ at 298.15 K and kinetic solvent deuterium isotope effects at 298.2 K for the neutral hydrolysis of esters CF_3CO_2Ar in water–acetonitrile containing 0.56 mol dm^{-3} of water

Ar	$\Delta H^{\ddagger}$/ kJ mol^{-1}	$-\Delta S^{\ddagger}$/J mol^{-1} K^{-1}	k_{H_2O}/k_{D_2O}
C_6H_4-4-NO_2	13.1 ± 1.1[a]	287 ± 4[a]	2.29 ± 0.02[b]
C_6H_3-2,4-$(NO_2)_2$	13.8 ± 0.9	248 ± 3	2.30 ± 0.01

[a] The errors shown are standard deviations. [b] The error estimates are calculated by the equation $|d(a/b)|/(a/b) \leqq |da|/a + |db|/b$.

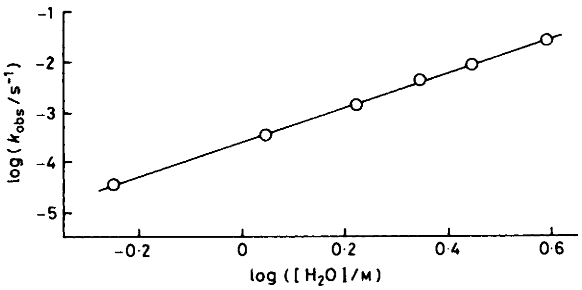

Figure 1. Plot of log k_{obs} *versus* log [H_2O] for the neutral hydrolysis of 4-nitrophenyl trifluoroacetate in water–acetonitrile mixtures at 298.2 K

coefficients (1.395 ± 0.008) × 10^{-5} s^{-1} and (1.094 ± 0.002) × 10^{-3} s^{-1} were determined for 4-nitrophenyl trifluoroacetate and 2,4-dinitrophenyl trifluoroacetate, respectively, in deuterium oxide–acetonitrile containing 0.56 mol dm^{-3} of deuterium oxide.

An appreciable solvent deuterium isotope effect, k_{H_2O}/k_{D_2O} 2.3, was observed in the hydrolyses of both 4-nitrophenyl and 2,4-dinitrophenyl trifluoroacetates (Table 3). This value is comparable with the values 2.93—3.15 observed for the hydrolysis of 4-nitrophenyl dichloroacetate in aqueous solution [11,12,14] and with the values, usually greater than two, found for the neutral hydrolysis of several alkyl carboxylates suggested to take place by the $B_{Ac}3$ mechanism.[1a,2a–c] A value of this size indicates a low proton transfer in the rate-limiting step of the reaction and gives important evidence for a $B_{Ac}3$-like mechanism in the present case. The observed isotope effect is difficult to ascribe to a mechanism like (**3**) since no proton transfer is involved in the rate-limiting step of that reaction.[20]

The entropies of activation of nucleophilically catalysed hydrolyses of esters (Scheme 2) are usually more positive than those of general base-catalysed reactions (Scheme 1) because of the lower order of reaction in the former case,[2b,3b,8,21,22] whereas there is no distinct difference between the enthalpies of activation. Table 3 contains the thermodynamic activation parameters calculated for 4-nitrophenyl and 2,4-dinitrophenyl trifluoroacetates. The values $\Delta H^{\ddagger}$ 26 kJ mol^{-1} and $\Delta S^{\ddagger}$ −192 J mol^{-1} K^{-1} in 70.7% acetone–water [23] and $\Delta H^{\ddagger}$ 32 kJ mol^{-1} and $\Delta S^{\ddagger}$ −170 J mol^{-1} K^{-1} in 70% dioxane–water [10] were obtained for the neutral hydrolysis of phenyl trifluoroacetate. For 4-nitrophenyl and 4-methoxyphenyl dichloroacetates, respectively, the values 38 kJ mol^{-1} and 35 kJ mol^{-1} for $\Delta H^{\ddagger}$ and the values −140 J mol^{-1} K^{-1} and −180 J mol^{-1} K^{-1} for $\Delta S^{\ddagger}$ were found in aqueous solution.[12] The present values of $\Delta H^{\ddagger}$ are smaller than the literature values for phenyl esters [10,12,23] and they also are smaller than the values, typically between 30 and 50 kJ mol^{-1}, observed in aqueous solution for the neutral hydrolysis of alkyl carboxylates taking place by the $B_{Ac}3$ mechanism.[2a,b,3b] The activation entropies (Table 3) also are smaller, *i.e.* more negative, than those usually found for neutral ester hydrolysis.[2a,b,3b,10,12,23] The effect of solvent composition on the thermodynamic activation parameters of chemical reactions and especially on those of solvolysis reactions is, however, known to be noticeable.[24–26] Unfortunately, the numerous investigations of solvent effects on the activation parameters of the neutral ester hydrolysis and related reactions are mainly limited to solvent mixtures rich in water.[24–26] Gopalakrishnan and Hogg [16] determined the thermodynamic activation parameters for the general base-catalysed (*i.e.* water-catalysed) hydrolysis of 1-acetyl-3-methylimidazolium ion at different volume fractions of acetonitrile in water–acetonitrile mixtures. On the basis of proton inventory, the transition state (**4**) was suggested for this reaction.[16] The value of $\Delta H^{\ddagger}$ decreases in this case from 42 to 26 kJ mol^{-1} and that of $\Delta S^{\ddagger}$ from −128 to −218 J mol^{-1} K^{-1} as the solvent composition changes from 0.0 to 0.9 volume fraction of acetonitrile. These changes were explained by solvation changes of the initial and the transition state.[16]

Mechanistic considerations with the aid of entropies of activation are questionable because solvation effects can mask the differences due to different mechanisms. However, consistent with the large solvent deuterium isotope effects, the very negative entropies of activation (Table 3) are more compatible with a general base-catalysed reaction than with a mechanism like (**3**) because of the higher order of reaction in the former case.[3b,8,21,22] Moreover, the entropies of activation indicate a mechanism in which a substantial increase in structuring of the solvent molecules occurs during the activation process. The polar transition state like (**1**) presumably is preferentially solvated by water. On the other hand, the ester probably is preferentially solvated by acetonitrile.[24,27] Thus a reorganization of solvent molecules occurs on going from the initial state to the transition state. Although the transition state obviously is highly solvated relative to the initial state also in aqueous solution,[12] the solvent reorganization undoubtedly is more radical in water–acetonitrile mixtures where water is monomeric. This explains the exceptionally negative entropies of activation in the present case.

The low values of $\Delta H^{\ddagger}$ (Table 3) as compared with those observed in more aqueous reaction solutions for neutral ester hydrolysis [2a,b,3b,10,12,23] can result from the stabilization of the transition state or from the destabilization of the initial state. They possibly reflect the enhanced kinetic basicity of water molecules solvated by acetontrile as compared with mainly water–water hydrogen-bonded water molecules.[24,28] The strongly electron-withdrawing substituents of the esters obviously also contribute to the favourable enthalpies of activation observed in the present study.

Figure 1 shows the dependence of the observed rate coefficient on the water concentration of the solvent mixture for the hydrolysis of 4-nitrophenyl trifluoroacetate. Plots of log k *versus* log [H_2O] have been used to determine the order of reaction in water,[29,30] but the meaning of these plots have been questioned.[31,32] However, the slope of this plot is a kinetic parameter and its high value in the present case, 3.4, illustrates the effect of water concentration on the rate coefficient. Consistent with the very negative entropies of activation (Table 3), several water molecules, not involved in the initial state, are obviously incorporated in the transition state. Values from −27 to −84 J mol^{-1} K^{-1} have been suggested for the entropy change associated with the incorporation of one molecule in the transition state.[22,33,34] Without placing too much emphasis on this subject, there is the interesting possibility that in the present reaction conditions, where water is a solute rather than a solvent, the double-logarithmic plot gives an estimate for the reaction order in water.

The linearity of the plot in Figure 1 suggests a constant hydration difference between the initial state and the transition state and thus a common reaction mechanism over the whole

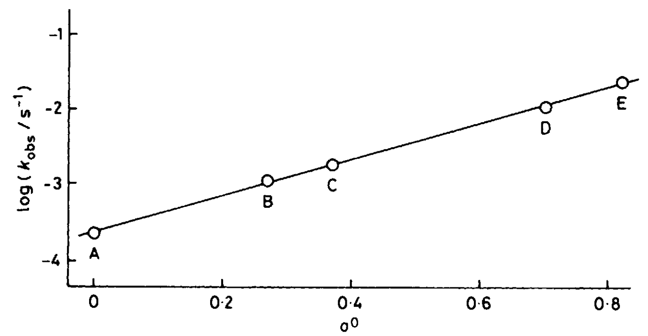

Figure 2. Hammett-type ρσ° plot for the neutral hydrolysis of substituted phenyl trifluoroacetates in water–acetonitrile containing 3.89M-water at 298.2 K: A, phenyl; B, 4-chlorophenyl; C, 3-chlorophenyl; D, 3-nitrophenyl; E, 4-nitrophenyl

range of water concentrations from 0.56 to 3.89M-water in acetonitrile. For the neutral hydrolysis of 1-acetyl-3-methylimidazolium ion in water–acetonitrile mixtures, Gopalakrishnan and Hogg [16] suggested a change in mechanism, from a general base-catalysed nucleophilic reaction of water to a mechanism involving a single nucleophilic water molecule, as the concentration of water decreases below 1M. For that reaction, the slope of the plot of log *k versus* log $[H_2O]$ is 1.86 in the region 2.04—5.65M-water and 0.97 in the region 0.327—0.892M-water. Thus also with higher water concentrations (*i.e* > 1M) the dependence on water concentration is weaker than in the present case although the proposed reaction mechanisms are alike.

The rate coefficients for the neutral hydrolysis of substituted phenyl trifluoroacetates in 3.89M-water in acetonitrile correlate well with the σ° substituent constants [35] (Figure 2), yielding a ρ value of 2.44 ± 0.04. With the σ substituent constants [35] a ρ value of 2.45 ± 0.14 is obtained. The somewhat better correlation with σ° than with σ is probably not significant because the differences between σ° and σ values are small for the electronegative substituents included. It is clear, however, that the σ^- value 1.24 cannot be used for the 4-nitro group.[35] If solvent effects on the substituent constants are not significant, this shows that the 4-nitro group does not stabilize by resonance the transition state more than the initial state. This suggests that the bond breaking between the carbonyl carbon and the phenol oxygen has not proceeded far in the transition state.

The value of ρ, 2.44, observed for phenyl trifluoroacetates in the present study is higher than those found for rate-limiting hydroxide ion attack in alkaline hydrolysis of phenyl esters [36,37] and it is close to those determined for rate-limiting leaving-group expulsion in the reactions between amines and phenyl esters in aqueous solutions.[5b,22,37,38] However, it is considerably lower than the value of ρ, 6.2, observed in acetonitrile for the nucleophilic reaction of pyrrolidine with phenyl acetates, which reaction also involves a rate-limiting departure of the leaving group.[39]

It is well established that there occurs a considerable increase in substituent effects on the pK_a values of phenols on going from aqueous solution to aprotic solvents or to aprotic solvent–water mixtures with low content of water.[40–42] This change is reflected by the higher values of ρ for displacement reactions of phenyl esters in aprotic solvents or solvent mixtures as compared to those determined in aqueous solution. Therefore, in aqueous acetonitrile with low content of water, higher values than the present ρ may be expected for reactions of phenyl esters involving rate-limiting leaving-group expulsion.

There is some evidence in the literature of rate-limiting leaving-group expulsion with a transition state like (**1**) in the neutral hydrolysis of 4-nitrophenyl dichloroacetate in aqueous solution although the occurrence of a tetrahedral intermediate has not been ruled out.[24] However, the present results suggest for phenyl trifluoroacetates a reaction mechanism where the formation of a tetrahedral addition intermediate with a transition state like (**5**) is the rate-limiting step of the reaction. If a concerted process is considered for this reaction, the transition state must be very unsymmetrical with only little C–O bond breaking.

Conclusions.—In spite of the good leaving groups of the esters, the kinetic results for the neutral hydrolysis of substituted phenyl trifluoroacetates in water–acetonitrile mixtures with low content of water cannot be explained by a mechanism involving an uncatalysed nucleophilic attack of water but they suggest a reaction mechanism in which one water molecule acts as a nucleophile and one as a general base. In the transition state of the rate-limiting step of the reaction, the C–O bond-breaking between the phenol oxygen and the carbonyl carbon probably has not proceeded far. Contrary to a related reaction, the neutral hydrolysis of 1-acetyl-3-methylimidazolium ion,[16] the decrease of the water concentration to a range where water exists as monomers does not seem to change the reaction to the nucleophilic mode.

Acknowledgements

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