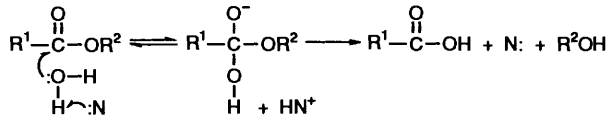
Effect of the acyl group in the reaction of imidazole with acyl-substituted 4-nitrophenyl acetates in acetonitrile and in aqueous acetonitrile with a low water content

Helmi Neuvonen
Department of Chemistry, University of Turku, FIN-20500 Turku, Finland

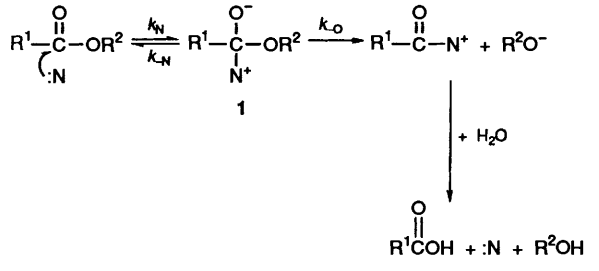
Reactions of imidazole with 4-nitrophenyl chloroacetate and dichloroacetate have been studied in acetonitrile and in 0.56 mol dm^{-3} water in acetonitrile. The second-order dependence, beside the first-order term in imidazole, is observed for all cases. The main interest was to study whether the first-order reaction in imidazole in aqueous acetonitrile is a general base-catalysed hydrolysis or a nucleophilic reaction of imidazole. The water isotope effects, steric effects by the 2-methyl substitution of imidazole, the effect of water in the reaction solution and the thermodynamic activation parameters were determined. Comparison of the results with those found previously for the reactions of imidazole with 4-nitrophenyl acetate and trifluoroacetate suggests that for 4-nitrophenyl chloroacetate and dichloroacetate the reaction first-order in imidazole represents a nucleophilic reaction and the reaction second-order in imidazole the general base-catalysed nucleophilic reaction of the amine. Accordingly, the change in the overall second-order reaction of 4-nitrophenyl acetates from a nucleophilic reaction of imidazole to the general base-catalysed hydrolysis needs a more electron-withdrawing acyl group than the dichloro substituted one.

Weak bases like amines and oxygen anions can catalyse the hydrolysis of carboxylic acid esters by general base catalysis (Scheme 1) or by nucleophilic catalysis (Scheme 2).[1-3] It is well known that usually esters activated by electron-withdrawing substituents in the acyl moiety but possessing a poor leaving group, such as ethyl dichloroacetate and ethyl difluoroacetate, are subject to general base catalysis. On the other hand, esters possessing a good leaving group, such as substituted phenyl acetates, are exposed to nucleophilic reaction.[2] In some cases the two mechanisms may occur concurrently.[4]

In the nucleophilic pathway, the reaction obviously passes through a tetrahedral intermediate (**1**) (Scheme 2). The partitioning of the intermediate in the direction of reactants or products (k_{-N}/k_{-O}) depends on the relative leaving ability of the nucleophile and the leaving group of the ester.[5-7] If a change in the reaction medium, in the structure of the ester, or in that of the catalysing base is accompanied with a sufficiently unfavourable change in the partitioning of the intermediate in the direction of products, there can occur a change in the mechanism from nucleophilic to general base catalysis.[8-11] We have previously detected a change in the reaction mechanism from a nucleophilic reaction to the general base-catalysed hydrolysis in the reaction of imidazole with 4-nitrophenyl esters in aqueous acetonitrile with a low water content (0.56 mol dm^{-3}) when the acyl group is changed from acetyl to trifluoroacetyl group.[12] Electron withdrawal from the acyl carbon is known to favour amine expulsion relative to the negatively charged substituted phenoxide expulsion from a tetrahedral addition intermediate formed in ester aminolysis.[13,14] Accordingly, the change in the reaction mechanism caused by the trifluoro substitution of the acyl group was attributed to the increased electrophilicity of the acyl carbon which affects unfavourably the partitioning ratio of the tetrahedral addition intermediate in the direction of products.[12] The aim of this study was to clarify whether a less electron-withdrawing acyl activation can cause a similar change in the reaction mechanism. Therefore, we have studied the reaction of imidazole with 4-nitrophenyl chloroacetate and 4-nitrophenyl dichloroacetate in acetonitrile and in aqueous acetonitrile with a low content of water.



Scheme 1



Scheme 2

Experimental

Materials

4-Nitrophenyl chloroacetate and dichloroacetate were prepared from 4-nitrophenol and the corresponding acid chlorides, mp 96–97 °C (from hexane) (lit.,[15] 95–97 °C) and 30–30.5 °C (from hexane) (lit.,[16] 30.6 °C), respectively. Imidazole (Schuchardt) and 2-methylimidazole (Fluka AG, *purum*) were recrystallized from benzene. 1-Methylimidazole (Fluka AG, *purum*) was purified by distillation (107 °C/47 mmHg). [*N*-^{2}H]Imidazole was prepared by the method of Garfinkel and Edsall[17] from imidazole by dissolving twice in D_2O and evaporating to dryness. Acetonitrile (Merck; max. H_2O 0.03%) was used as received. Heavy water was from *Norsk Hydro-elektrisk Kvaelstoffaktieselskab* (99.8% D_2O).

Kinetics

Reaction rates were determined by following the formation of 4-nitrophenol at 310 nm. A Perkin-Elmer 550 spectrophotometer with a thermostatted cell compartment was used. The temper-

Table 1 Experimental conditions and first-order rate-coefficients (k_{obs}) for the reactions of imidazoles with 4-nitrophenyl chloroacetate and dichloroacetate[a]

Ester	Amine	Amine/10^{-2} mol dm^{-3}	$k_{obs}/10^{-2}$ s^{-1}	Number of runs
4-Nitrophenyl chloroacetate	Imidazole[b]	2–10	0.595–9.15	5
	Imidazole[c]	2–10	0.36–4.93	5
	Imidazole	2–10	0.55–6.72	5
	Imidazole[d]	2–10	0.33–3.98	5
	Imidazole[e]	2–10	0.49–5.47	5
	[N-^{2}H]Imidazole[f]	2–10	0.45–4.79	13
	2-Methylimidazole	2–10	0.545–5.53	5
4-Nitrophenyl dichloroacetate				
	Imidazole[b]	0.2–1	0.23–5.55	5
	Imidazole[c]	0.2–1	0.15–3.45	5
	Imidazole	0.2–1	0.17–3.58	5
	Imidazole[d]	0.2–1	0.19–3.68	5
	Imidazole[e]	0.2–1	0.21–3.80	5
	[N-^{2}H]Imidazole[f]	0.2–1	0.12–2.31	12
	2-Methylimidazole	0.2–1	0.26–3.92	5

[a] In 0.56 mol dm^{-3} water in acetonitrile and at 298.2 K unless otherwise stated. [b] In acetonitrile. [c] At 288.2 K. [d] At 308.2 K. [e] At 318.2 K. [f] In 0.56 mol dm^{-3} D_2O in acetonitrile.

Table 2 Second- and third-order rate-coefficients (k_1 and k_2) for the reactions of imidazoles with 4-nitrophenyl chloroacetate and dichloroacetate[a,b]

Ester	Amine	T/K	$k_1/10^{-1}$ dm^3 mol^{-1} s^{-1}	k_2/dm^6 mol^{-2} s^{-1}
4-Nitrophenyl chloroacetate	Imidazole[c]	298.2	1.54 ± 0.11	7.66 ± 0.16
	Imidazole	288.2	1.02 ± 0.03	3.92 ± 0.05
	Imidazole	298.2	1.77 ± 0.05	4.99 ± 0.08
	Imidazole	308.2	2.77 ± 0.05	6.51 ± 0.13
	Imidazole	318.2	4.22 ± 0.10	8.23 ± 0.27
	[N-^{2}H]Imidazole[d]	298.2	1.64 ± 0.04	3.07 ± 0.07
	2-Methylimidazole	298.2	2.04 ± 0.04	3.46 ± 0.06
4-Nitrophenyl dichloroacetate	Imidazole[c]	298.2	1.19 ± 0.46	544 ± 7
	Imidazole	288.2	0.96 ± 0.39	332 ± 6
	Imidazole	298.2	1.37 ± 0.09	343 ± 1
	Imidazole	308.2	2.42 ± 0.24	346 ± 4
	Imidazole	318.2	3.48 ± 0.17	344 ± 3
	[N-^{2}H]Imidazole[d]	298.2	1.64 ± 0.20	218 ± 3
	2-Methylimidazole	298.2	7.1 ± 0.8	322 ± 12

[a] In 0.56 mol dm^{-3} water in acetonitrile unless otherwise stated. [b] Errors shown are standard deviations. [c] In acetonitrile. [d] In 0.56 mol dm^{-3} D_2O in acetonitrile.

atures of the reaction solutions were measured in the optical cell with a calibrated NTC-thermistor. The temperature was accurate to 0.05–0.1 K below 308 K and 0.1–0.3 K above that temperature. The absorbance changes were recorded with a printer. The reactions were followed for six half-lives and the final value was observed after 10 half-lives if needed. The ester concentrations in the kinetic solutions were *ca.* 4–7 × 10^{-5} mol dm^{-3}. The reactions were studied under first-order conditions with amine in excess over the ester and the rate coefficients k_{obs} were calculated by Guggenheim's method.[18] The standard deviations of the rate coefficients were in general 0.1–0.3%, but could be in some cases up to 0.7%. The rate coefficients were reproducible to within ± 1–3%. It was checked that the linear plots of $\ln(A_\infty - A_t)$ *vs.* time gave essentially the same values as Guggenheim's method.

Results

Table 1 summarizes the experimental conditions and the range of the first-order rate coefficients determined. The neutral hydrolysis of the ester was insignificant in all cases and the reactions followed the rate-law (1). The calculated second- and third-order rate coefficients are given in Table 2.

$$k_{obs} = k_1[\text{Imidazole}] + k_2[\text{Imidazole}]^2 \quad (1)$$

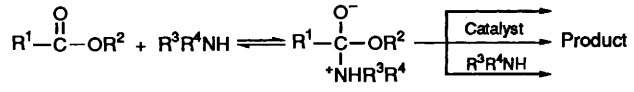
Reactions of imidazole and 2-methylimidazole gave good reproducibility and regular first-order kinetics. On the contrary, deviations from first-order behaviour were observed for the reactions of 1-methylimidazole. The deviations were more significant for 4-nitrophenyl chloroacetate than for 4-nitrophenyl dichloroacetate. The observed rate coefficient was smaller the larger the ester concentration was. Further, the rate coefficient calculated by eqn. (2) decreased markedly during the reaction

$$k_t = (1/t)\ln(A_\infty - A_0)/(A_\infty - A_t) \quad (2)$$

although the first-order reaction conditions prevailed. These observations (rate coefficients for reactions of 1-methylimidazole are not included in Table 1) were attributed to the back-reaction of the liberated 4-nitrophenol with the 1-acyl-3-methylimidazolium ion and could be taken as the first indication of an at least partial nucleophilic mechanism. A transient reaction product possessing an absorption maximum in the region 225–240 nm was observed by the UV scans in the reaction of imidazole with 4-nitrophenyl dichloroacetate in 0.56 mol dm^{-3} water in acetonitrile. The similarity to the λ_{max} value of 1-acetylimidazole (245 nm in water)[19] supports the hypothesis of 1-dichloroacetylimidazole as an intermediate.

Discussion

In acetonitrile and in aqueous acetonitrile with a low content of water both the uncatalysed and the general base-catalysed nucleophilic reaction of imidazole with 4-nitrophenyl acetate have been detected.[12,20] On the other hand, as noted above in the introduction, in aqueous acetonitrile the general base-catalysed hydrolysis of 4-nitrophenyl trifluoroacetate by imidazole (Scheme 1) is observed beside the imidazole-catalysed nucleophilic reaction of imidazole. The mechanism proposed for the ester aminolysis in aprotic solvents involves rate-limiting decomposition of a zwitterionic tetrahedral intermediate through an uncatalysed or a base-catalysed pathway (Scheme 3).[21-24] On the basis of kinetic results this mechanism was



Scheme 3

also suggested for the reaction of imidazole with 4-nitrophenyl acetate and as regards the reaction second-order in imidazole also for 4-nitrophenyl trifluoroacetate in acetonitrile and in aqueous acetonitrile.[12]

The two kinetically indistinguishable mechanisms, general base and nucleophilic catalysis (Schemes 1 and 2, respectively), may be distinguished, *e.g.* by the facts that in the former case the D_2O solvent isotope effect is higher, no intermediate is formed, steric effects are smaller and the entropy of activation is more negative.[1b,d,e] The solvent isotope effects for the k_1 reactions of both 4-nitrophenyl chloroacetate and dichloroacetate (Table 3) are consistent with a nucleophilic reaction of imidazole and they differ markedly from that observed for the k_1 reaction of 4-nitrophenyl trifluoroacetate. The small D_2O isotope effects indicate a mechanism where a proton transfer does not occur in the rate-limiting step.[1b,d,e,12,25,26a,b,27] The values observed for the k_2 reactions of 4-nitrophenyl chloroacetate and dichloroacetate (Table 3) are in accordance with the values between 1.1–1.8 detected for different types of general base-catalysed aminolyses of esters with a second molecule of amine acting as the catalyst.[12,25,26]

The rate coefficient k_1 is affected only slightly by the absence of water in the reaction solution in the case of both 4-nitrophenyl chloroacetate and dichloroacetate (Table 4). The effect is of the same size as that observed for the nucleophilic k_1 reaction of 4-nitrophenyl acetate. On the contrary, a remarkable decrease in the rate coefficient is observed in the general base-catalysed hydrolysis of 4-nitrophenyl trifluoroacetate involving a water molecule in the rate-limiting step of the reaction. The effect of water on the terms k_2 in the reactions of the three least activated esters under consideration is also very similar (Table 4) indicating the general base-catalysed nucleophilic reaction of imidazole in all cases. In spite of the somewhat greater effect of water on the k_2 term for the reaction of imidazole with 4-nitrophenyl trifluoroacetate, the same mechanism has earlier been proposed for that ester on the basis of other kinetic data.[12]

For nucleophilic reactions, methyl substituents adjacent to the attacking nitrogen are known to decrease the reactivity of amines significantly while the steric effects are less meaningful in the general base-catalysed reactions.[1b,d,28-30] The steric effect of the 2-methyl substitution of imidazole on the k_2 terms in the reactions of 4-nitrophenyl chloroacetate and dichloroacetate are smaller than in the case of 4-nitrophenyl acetate and trifluoroacetate, but they are consistent with the general base-catalysed nucleophilic reaction of imidazole (Table 5).[12] However, the steric effects on the k_1 terms are puzzling. The detection of an unstable intermediate during the reaction (*cf.* Results) as well as the kinetic data discussed above indicate a nucleophilic mechanism for the k_1 reactions. However, the effect of the 2-methyl substitution of imidazole does not support this hypothesis.[12,28,29] If the attack of imidazole were rate-limiting in its nucleophilic reaction toward the 4-nitrophenyl acetates, the decreased sensitivity of the k_1 term to steric effects in the case of 4-nitrophenyl chloroacetate and dichloroacetate could be ascribed to the increased reactivity and an earlier transition state when the activation of the acyl group is increased. However, this is not the case.[12] At this moment, the decreased susceptibility to steric effects is unexplained.

The reactivities of imidazole and 1-methylimidazole, possessing the same aqueous basicities,[31] are very different toward the esters investigated (*cf.* Results). This indicates the significance of a proton transfer form the attacking amine molecule during the reaction or from the reaction product to stabilize it. The 1-acetylimidazolium ion is a much stronger acid in water than the imidazolium ion, and it has been proposed that the same is valid also in diethyl ether.[32] If the first reaction product, the 1-acylimidazolium ion, is rapidly transformed to the less reactive 1-acylimidazole, the back-reaction with the other reaction product, 4-nitrophenol, is prevented. For the 1-acyl-3-methylimidazolium ion this reaction pathway is not possible and inhibition by 4-nitrophenol occurs. The hydrolysis of the acylated imidazolium ion, which could also disturb the back-reaction, is obviously not rapid enough in the present reaction conditions.

The mechanistic conclusions drawn above are supported by the activation parameters (Table 6). For the reactions of amines with esters, the general base-catalysed nucleophilic reactions typically exhibit lower enthalpies of activation than the un-

Table 3 Water isotope effects for the reactions of imidazole with esters RCO_2–C_6H_4–NO_2 in 0.56 mol dm^{-3} water in acetonitrile at 298.2 K[a]

R	$k_1{}^b{}_{H_2O}/k_1{}^c{}_{D_2O}$	$k_2{}^b{}_{H_2O}/k_2{}^c{}_{D_2O}$	Ref.
CH_3	1.03 ± 0.06	1.35 ± 0.07	12
CH_2Cl	1.08 ± 0.06	1.63 ± 0.06	This work
$CHCl_2$	0.84 ± 0.16	1.57 ± 0.03	This work
CF_3	1.93 ± 0.16	1.13 ± 0.05	12

[a] The error estimates are calculated with the aid of the standard deviations of the rate coefficients. [b] Rate coefficients in 0.56 mol dm^{-3} water in acetonitrile. [c] Rate coefficients in 0.56 mol dm^{-3} D_2O in acetonitrile.

Table 4 The effect of water in the reaction medium in the reactions of imidazole with esters RCO_2–C_6H_4–NO_2 at 298.2 K[a]

R	$k_1{}^b{}_{H_2O\text{-}AN}/k_1{}^c{}_{AN}$	$k_2{}^b{}_{H_2O\text{-}AN}/k_2{}^c{}_{AN}$	Ref.
CH_3	1.1 ± 0.1	0.71 ± 0.03	12
CH_2Cl	1.1 ± 0.5	0.65 ± 0.02	This work
$CHCl_2$	1.2 ± 0.5	0.63 ± 0.01	This work
CF_3	12 ± 3	2.3 ± 0.1	12

[a] The error estimates are calculated with the aid of the standard deviations of the rate coefficients. [b] Rate coefficients in 0.56 mol dm^{-3} water in acetonitrile. [c] Rate coefficients in acetonitrile.

Table 5 Steric effects for the reactions of imidazole with esters RCO_2–C_6H_4–NO_2 in 0.56 mol dm^{-3} water in acetonitrile at 298.2 K[a]

R	$k_1{}^b{}_{Im}/k_1{}^c{}_{2\text{-}MeIm}$	$k_2{}^b{}_{Im}/k_2{}^c{}_{2\text{-}MeIm}$	Ref.
CH_3	1.6 ± 0.1	1.9 ± 0.1	12
CH_2Cl	0.87 ± 0.04	1.44 ± 0.05	This work
$CHCl_2$	0.19 ± 0.03	1.07 ± 0.04	This work
CF_3	0.28 ± 0.01	1.8 ± 0.2	12

[a] The error estimates are calculated with the aid of the standard deviations of the rate coefficients. [b] Rate coefficients for the reaction of imidazole. [c] Rate coefficients for the reaction of 2-methylimidazole.

Table 6 Activation parameters for the reactions of imidazole with esters RCO_2–C_6H_4–NO_2 in 0.56 mol dm^{-3} water in acetonitrile[a]

R	Reaction	$\Delta H^{\#}$/kJ mol^{-1}	$-\Delta S^{\#}$/J mol^{-1} K^{-1}	Ref.
CH_3	k_1	42.3 ± 0.8	155 ± 2	12
CH_2Cl	k_1	33.5 ± 0.9	147 ± 3	This work
$CHCl_2$	k_1	31.3 ± 2.4	156 ± 8	This work
CF_3	k_1	10.7 ± 0.4	192 ± 1	12
CH_3	k_2	32.7 ± 0.4	173 ± 1	12
CH_2Cl	k_2	16.5 ± 0.4	176 ± 1	This work
$CHCl_2$	k_2	−1.6 ± 0.4	202 ± 1	This work
CF_3	k_2	−18.9 ± 0.3	234 ± 1	12

[a] Errors shown are standard deviations, but the real precision probably is 2–4 kJ mol^{-1} for $\Delta H^{\ddagger}$ and 8–10 J mol^{-1} K^{-1} for $\Delta S^{\ddagger}$.

catalysed nucleophilic reactions, but the increase in the reaction order is usually accompanied by a decrease in the entropy of activation.[26b,c] A similar behaviour is seen in the values given in Table 6. Further, a remarkable difference is observed when compared with approximately similar values of the entropy of activation for the k_1 reactions of 4-nitrophenyl acetate, chloroacetate and dichloroacetate with that for the k_1 reaction of 4-nitrophenyl trifluoroacetate. The reaction order increases when the reaction mechanism is changed from the nucleophilic reaction of imidazole to the general base-catalysed hydrolysis by imidazole along with the increased electronegativity of the acyl group. The $\Delta H^{\#}$ values for the k_2 terms decrease with increasing electronegativity of the acyl group. For 4-nitrophenyl dichloroacetate and trifluoroacetate negative values are observed. This indicates an exothermic equilibrium before the product-forming step and is consistent with the mechanism discussed above (Scheme 3).[12,33]

With the present system the acyl group induced change from a nucleophilic reaction of imidazole to the general base-catalysed hydrolysis seems to take place somewhere between the dichloro and the trifluoro substitution of the acyl group. Still, more data is needed to quantify the 'pull' by which an electron-withdrawing acyl group can decrease the leaving ability of the substituted phenoxide ions relative to amines and change the reaction mechanism.

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