JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 7, 431–436 (1994)

KINETICS AND MECHANISM OF THE IMIDAZOLE-CATALYSED HYDROLYSIS OF SUBSTITUTED *N*-BENZOYLIMIDAZOLES

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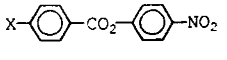
Imidazole (Imz)-catalysed hydrolysis of benzoate esters proceeds via the intermediate formation of *N*-benzoylimidazoles. This paper considers the second step of this reaction, viz., Imz-catalysed hydrolysis of *N*-(4-X-benzoyl)imidazoles, X = CH_3, H, Cl, CN and NO_2, and *N*-(disubstituted benzoyl)imidazoles, 2-chloro-4-nitro, 2,4-dinitro and 3,5-dinitro, in water–acetonitrile mixtures (10% or 14%, v/v, in organic solvent). On the basis of catalytic rate constants and the kinetic solvent isotope effect, it is shown that catalysis by Imz is of the general-base type. Unexpectedly, the hydrolysis of *N*-(2,4-dinitrobenzoyl)imidazole was found to be slower than that of *N*-(4-nitrobenzoyl)imidazole. It is shown that this reactivity order is due to a combination of a steric effect and stabilization of the reactant state due to a donor–acceptor interaction between the Imz moiety and the 2,4-dinitrophenyl ring.

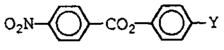
INTRODUCTION

Knowledge of the mechanistic details of a reaction in a reference solvent, e.g. an aqueous organic mixture, is a prerequisite for studying the same reaction in the presence of a surfactant aggregate. In the latter case, micellar catalysis can be rationalized in terms of the transfer of the reaction from a bulk reference solvent to the micellar pseudo-phase.[1-3] We are interested in the mechanism of catalysis by detergent aggregates in organic solvents, i.e. by reversed micelles and water-in-oil microemulsions.[4] As reaction 'media' these aggregates have some peculiar and interesting properties, a fact that has been exploited in several novel applications.[1-6]

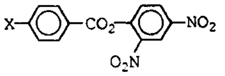
As a first step toward an understanding of the mechanism of reversed micelle-mediated acyl-transfer reactions, we have recently studied details of the imidazole (Imz)-catalysed hydrolyses of the following benzoate esters:

I(a-e) 

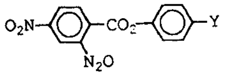
($X = CH_3$, H, Cl, CN, NO_2)

II(a-e) 

($Y = CH_3$, H, Cl, CN, NO_2)

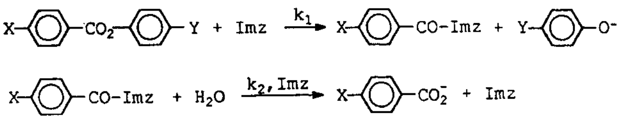
III(a-e) 

($X = CHO_3$, H, Cl, CN, NO_2)

IV(a-e) 

($Y = CH_3$, H, Cl, CN, NO_2)

Proof was given to show that catalysis by Imz is nucleophilic, i.e. the reaction proceeds via the intermediate formation of *N*-acylimidazoles, by way of two consecutive irreversible reactions:[7]



We now report on the step given by the rate constant (k_2), i.e. Imz-catalysed hydrolysis of the intermediate *N*-acylimidazoles (series **V**) which form during the reaction of ester series **I**, **II** and **III**, respectively. Compound **VIa** is that formed during the reaction of ester series **IV**. The remaining members of series **VI** will be used to corroborate a certain mechanistic conclusion.

The results of this study are relevant not only to micellar catalysis, but also to the more complex enzymatic counterpart. In the latter case, acylenzyme intermediates are formed (esterified at serine in the case of serine proteases) and the reaction is completed by the hydrolysis of the acylenzyme, probably via a general base-catalysed route by an imidazole group.[8]

Rate constants, activation parameters, kinetic solvent isotope effects and the Hammet constant (ρ) were determined for series **V** and used to probe certain mechanistic aspects. Unexpectedly, compound **VIa** was

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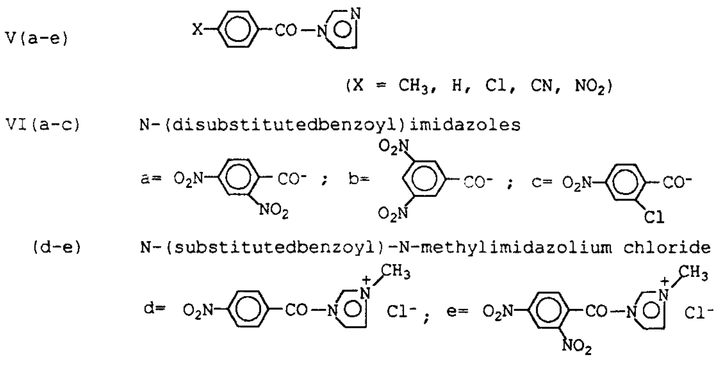
CCC 0894–3230/94/080431–06

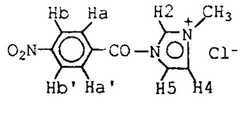
Received 23 November 1993
Revised 11 February 1994



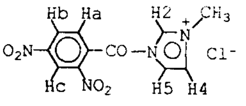
significantly less reactive toward hydrolysis than **Ve**. We show that this effect of structure on reactivity is due to a combination of a steric inhibition of resonance between the carbonyl group and the aromatic moiety and a stabilization of the reactant state by a donor–acceptor interaction between Imz and the 2,4-dinitrophenyl ring. ^{1}H NMR data showed that part of this interaction is due to the presence of the nitro group in an *ortho* position.

EXPERIMENTAL

All reagents for synthesis (Aldrich and Merck) were purified by standard procedures.[9] *N*-Deuterated imidazole (required for the determination of kinetic solvent deuterium isotope effect) was prepared by exchange with D_2O, as given elsewhere.[7] Acyl chlorides were prepared by reacting the appropriate carboxylic acid with excess thionyl chloride, followed by removal of the latter.[10] *N*-Acylimidazoles were prepared by the reaction of the appropriate acyl chloride with two equivalents of Imz in benzene,[11] or in $CHCl_3$,[12] and were purified by crystallization from light petroleum–cyclohexane. The products gave satisfactory melting points,[7,11,12] and showed the expected ^{1}H NMR (Bruker AC-200, 200 MHz, solvent CD_3CN) and IR spectra (Perkin-Elmer FT-1750, KBr). The following are the analytical data for *N*-(2-chloro-4-nitrobenzoyl)imidazole (**VIc**): m.p. 100–102 °C; analysis, calculated for $C_{10}H_6ClN_3O_3$, C 47·73, H 2·40, N 16·70; found C 47·50, H 2·45, N 16·55%; IR 1732 cm^{-1} (ν_{CO}). Compounds **VId** and **VIe** were prepared from the pure, dry reagents under a nitrogen atmosphere (AtomsBag, Aldrich), as follows: to a solution of 1·30 mmol of the appropriate acid chloride in 15 ml of THF was added 1·6 mmol of *N*-methylimidazole. A white precipitate was formed immediately. The mixture was stirred at room temperature for further 15 min, then filtered by using Schlenk-type glassware (Aldrich). After washing the white solid twice with 10 ml portions of THF, it was dried under vacuum and used immediately. The following are the analytical data for these compounds. **VId**: m.p. 155–157 °C; IR, 1718 cm^{-1} (ν_{CO}); ^{1}H NMR (CD_3CN), 3·85 (s, CH_3), 7·34 (d, H5, J_{H4-H5} = 1·2 Hz), 7·39 (d, H4), 8·19 (d, Ha, Ha′, J_{Ha-Hb} = 8·9 Hz), 8·28 (d, Hb, Hb′), 8·56 (s, H2). **VIe**: m.p. 107–109 °C; IR, 1731 cm^{-1} (ν_{CO}); ^{1}H NMR (DMSO-d_6), 3·89 (s, CH_3), 7·61 (d, H5, J_{H4-H5} = 1·2 Hz), 7·71 (d, H4), 7·99 (d, Ha, J_{Ha-Hb} = 8·4 Hz), 8·51 (dd, Hb, J_{Hb-Hc} = 2·2 Hz), 8·65 (d, Hc), 9·21 (s, H2).



VI-d



VI-e

Slow hydrolysis reactions were studied in aqueous solutions containing 10% (v/v) acetonitrile. Fast reactions (i.e. those requiring the use of a stopped-flow spectrophotometer) were studied in 14% (v/v) acetonitrile in water. The pH of the buffers [borate, 2,4,6-trimethylpyridine (hereafter collidine), Imz and *N*-MeImz] were calculated as given elsewhere,[13] and their final values were checked with an Orion 701-A pH meter. The following conditions were used: buffer concentration range, ionic strength (KCl) and pH range: [borate] = 0·02–0·10 M, 0·20, 8·20–9·70; [collidine] = 0·01–0·05 M, 0·07, 7·0; [Imz] = 0·02–0·2 M, 0·07, 7·0–7·85; and *N*-[MeImz] = 0·1–0·5 M, 1·0, 7·02. The spontaneous hydrolysis of **VId** and **VIe** was studied in 0.001 M HCl at an ionic strength of 0·1 (NaCl).

Kinetic runs were carried out with the aid of microcomputer-controlled Zeiss PM6KS and Beckman DU-70 spectrophotometers and Applied Photophysics MV 17F stopped-flow apparatus, as given elsewhere.[7] The decrease in the absorption of the carbonyl group of series **V** compounds was followed as a function of time at wavelengths of 253, 245, 252, 250 and 255 nm for X = CH_3, H, Cl, CN and NO_2, respectively. The corresponding wavelengths used to follow the reaction of the other substrates were 242, 239, 250, 294, 258, 298 and 315 nm for **VIa**, **VIb**, **VIc**, **VId**, **VIe**, 4-nitrobenzoyl chloride and 2,4-dinitrobenzoyl chloride, respectively. Reactions were carried out under pseudo-first-order conditions with all reagents, except the acylimidazole, in excess. Slow reactions were initiated by injecting 3–5 μl of an acetonitrile solution of the latter compound into the thermally equilibrated buffer solution. For fast reactions the reagents were introduced in the mixing chamber with the aid of Accudil syringes (Hamilton) of unequal volumes (0·1 and 2 ml, respectively). The final substrate concentration was in the range 1×10^{-5}–3×10^{-5} M. Use of acylimidazole concentration higher than 5×10^{-5} M resulted in irreproducible rate constants owing to limited substrate solubility in the solvent mixture. All runs were carried out in triplicate. The log (absorbance) vs time plots were rigorously linear over more than five half-lives. Observed first-order rate constants (k_{obs}) were determined from the slopes of the above plots and were reproducible to within ±0·5%. Second-order (catalytic) rate constants, k_c, were obtained from plots of k_{obs} versus [catalyst]. The relative standard deviations in k_c, i.e. (standard deviation/k_c) × 100, were <2%.

RESULTS AND DISCUSSION

The dependence of the observed rate constants for the hydrolysis of series **V** on the concentration of Imz present as a free base was strictly linear, the slopes of these plots giving the catalytic rate constants (k_c) shown in Table 1. The corresponding results for compound **VIa**, the intermediate for ester series **IV**, are given in Table 2. Because of the limited pH range used, no attempt was made to determine rate constants for the spontaneous and OH^--catalysed hydrolyses from the intercepts of these plots.

Regarding Imz-catalysed hydrolyses of the present acylimidazoles and the data in Tables 1 and 2, the following aspects are important:

(a) Catalysis by the buffer is of the general base type because the catalyst and the leaving group are the same, viz. Imz. Accordingly, the reaction is expected to be associated with a relatively large kinetic solvent isotope effect,[8] in agreement with the ratios of k_c (H_2O)/k_c(D_2O), which we determined for series **V** at 25 °C, of 2·94, 2·67, 2·53 and 2·43 for compounds **Vb**, **Vc**, **Vd** and **Ve**, respectively. Our value for **Ve** agrees with that reported for general base-catalysed hydrolysis of both **Ve** (2·38)[14a] and *N*-acetylImz (2·6).[15a] It is interesting to note the decrease in the magnitude of the isotope effect as a function of increasing reactivity of the acylimidazole, probably owing to a variation in the structure of the transition state (which becomes more reagent like) in the same direction.

Table 1. Catalytic rate constants (k_c) for the imidazole-catalysed hydrolysis of *N*-4-X-benzoylimidazoles (X = CH_3, H, Cl, CN, NO_2)[a]

T (°C)	**Va** CH_3	**Vb** H	**Vc** Cl	**Vd** CN	**Ve** NO_2
25	1·21	1·76	3·53	15·62	20·60
30	1·68	2·32	4·68	19·45	25·36
35	2·18	3·14	6·05	24·87	31·43
40	2·88	4·23	7·88	31·33	39·83
45	3·88	5·37	10·22	40·06	50·42
50	5·20	6·85	12·95	49·15	60·92
$\Delta H^{\neq}$	10·4	9·9	9·4	8·3	7·9
$\Delta S^{\neq}$	−36·9	−37·8	−38·3	−39·0	−40·0
$\Delta G^{\neq}$	21·4	21·2	20·8	19·9	19·8

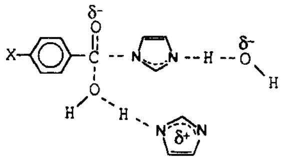
[a] Conditions: 10% (v/v) acetonitrile in water; ionic strength = 0·07 M (KCl). Activation parameters are given in kcal mol^{-1} ($\Delta H^{\neq}$ and $\Delta G^{\neq}$) and cal k^{-1}mol^{-1} ($\Delta S^{\neq}$) (1 kcal = 4·184 kJ). The errors are ±0·1 kcal mol^{-1} ($\Delta H^{\neq}$ and $\Delta G^{\neq}$) and 0·5 e.u. ($\Delta S^{\neq}$).

Table 2. Catalytic rate constants (k_c) for the hydrolysis of acylimidazoles[a]

T (°C)	**VIa**	**VIb**	**VIc**	**VId**	**VIe**
15	—	—	—	1·20	6·93
20	—	—	—	1·65	9·12
25	0·08	13·60	0·51	2·26	12·08
30	0·12	16·40	0·71	2·96	15·65
35	0·18	19·00	0·99	4·10	20·36
40	0·26	21·88	1·32	—	—
45	0·37	26·60	1·81	—	—
50	0·50	30·37	2·45	—	—
$\Delta H^{\neq}$	13·5	5·5	11·4	10·1	8·9
$\Delta S^{\neq}$	−27·2	−43·9	−30·9	−32·1	−32·8
$\Delta G^{\neq}$	21·7	18·6	20·6	19·7	18·7

[a] Conditions: in acetonitrile–water mixtures, 10% (v/v) for **VIa**–**VIc** and 14% (v/v) for **VId** and **VIe**; ionic strength, 0·07 M (KCl or NaCl). The reaction of **VIa**–**VIc** is Imz-catalysed hydrolysis, whereas that for **VId** and **VIe** is a spontaneous hydrolysis. For an estimation of errors in the activation parameters, see footnote to Table 1.

(b) Catalytic rate constants, k_c, that were obtained by following either the disappearance of reactants or the appearance of products were in excellent agreement. For example, the values of $10^2\ k_c$ (l mol^{-1} s^{-1}) for **VIa** at 40 °C and for **VIb** and **VIc** at 35 °C measured by following reactant disappearance were 0·255, 19·00 and 0·993, respectively, and the corresponding values measured by following product appearance were 0·256, 19·09 and 0·975, respectively. Additionally, sharp isosbestic points were observed at 275, 268, 256 and 270 nm during the hydrolyses of **Ve**, **VIa**, **VIb** and **VIc**, respectively. Both results indicate that no species accumulate between reactants and products. Based on this, and on literature data on hydrolyses of acylimidazoles under a variety of conditions,[15–18] we suggest the following structure for the reaction transition state:



without taking a position as to whether a metastable tetrahedral addition intermediate is formed along the reaction path. Note that the ease of the C—N bond breaking is likely to be enhanced by hydrogen bonding of water to N-3 of Imz.[15b,15c,16a,17b]

(c) The Hammett ρ value for series **V** was found to be 1·25 ± 0·02, which is in excellent agreement with the value obtained for the same reaction in water (1·24 ± 0·03).[14a]

(d) The difference in reactivity on going from **Va** to **Ve** is due to a decrease in the enthalpy of activation, not compensated for by a decrease in the $T\Delta S^{\neq}$ term. To our knowledge, the only other activation parameters reported in the literature refer to acid-catalysed hydrolysis of benzoylimidazole[14b] and imidazole buffer-catalysed hydrolyses of aliphatic acylimidazoles.[15a,16a]

Tables 1 and 2 show that **Ve** reacts between 25·8 to 12·2 times faster that **VIa**. This behaviour is not restricted, however, to the Imz-mediated reaction, but was also observed in hydrolyses catalysed by other bases. Thus, at 25 °C, we obtained ratios for k_c (**Ve**)/k_c (**VIa**) of 18·8, 25·7 and 19·1 for catalyses by borate buffer, collidine buffer and OH^- ion, respectively.

What are the possible reasons for this unexpected effect of structure on reactivity? First, we consider steric factors. The presence of the nitro group in the *ortho* position of **VIa** can, in principle, decrease reactivity toward hydrolysis by two mechanisms: hindrance to the attack of the water–Imz complex[16] and steric inhibition of resonance between the CO group and the 2,4-dinitrophenyl ring. Both effects originate from steric crowding at the reaction centre which forces both the *o*-nitro and the CO groups out of plane of the benzene ring. We are unaware of x-ray diffraction studies on *ortho*-substituted benzoylimidazoles, but the results for the precursor 2,4-dinitrobenzoic acid showed that the *o*-nitro and the carboxyl group are 54·7° and 23·4°, respectively, out of plane with the benzene ring.[19] Additionally, physico-chemical properties and spectroscopic data of solutions of acylimidazoles also indicate a lack of coplanarity. Thus, measurements of dipole moments,[20a] ^1H and ^{13}C NMR chemical shifts[20b,c,d] and IR stretching vibrations of the C=O and C—N bonds,[20d] indicate a lack of coplanarity between the CO group and the Imz ring in aliphatic acylimidazoles and between the former group and the benzene ring in aromatic acylimidazoles.

The effect of steric factors on reactivity agrees with the results reported in Table 2 for *N*-(3,5-dinitrobenzoyl)imidazole (**VIb**) and *N*-(2-chloro-4-nitrobenzoyl)imidazole (**VIc**). The former compound, which carries no substituent in the *ortho* position of the benzene ring, reacts between 170 and 61 times faster than **VIa**. Based only on Taft's σ^* constants for Cl and NO_2 in *ortho* positions (0·2 and 0·8, respectively),[21] one would expect **VIa** to react faster than **VIc**. The contrary was observed, however, probably because of less crowding in the latter compound, in agreement with x-ray diffraction results of the precursor *o*-chlorobenzoic acid which showed that the angle between the plane of the carboxyl group and that of the benzene ring is 13·7°.[22]

The preceding discussion raises the question of whether steric factors are the only ones responsible for the observed order of reactivity. The following shows that this is not the case. Additionally, we present evidence to demonstrate that stabilization of the reactant state by an intramolecular electron donor–acceptor interaction between the diazole ring and the electron-deficient aromatic ring (including the *o*-nitro group) also plays a role.

(a) Considering only steric factors, other compounds having a carbon skeleton similar to the above-mentioned acylimidazoles are expected to show the same order of reactivity. However the following rate constants show that collidine-catalysed hydrolysis of 2,4-dinitrobenzoyl chloride is slightly faster than the corresponding reaction of 4-nitrobenzoyl chloride: k_c ($l\,mol^{-1}\,s^{-1}$) for 2,4-dinitrobenzoyl chloride = 68·6, 81·9, 100·3, 125·8 and 148·1 and k_c ($l\,mol^{-1}\,s^{-1}$) for 4-nitrobenzoyl chloride = 62·1, 74·4, 92·2, 113·3 and 131·1 for the reaction at 16, 20, 25, 30 and 35 °C, respectively. Benzoate esters also behave differently from the present *N*-benzoylimidazoles. Thus the catalytic rate constants for the Imz-catalysed hydrolysis of ester series **II** (precursor of **Ve**) and **IV** (precursor of **VIa**) have comparable values.[7] Additionally, the rate constant for the hydroxide ion-catalysed hydrolysis of methyl 2,4-dinitrobenzoate is 1·86 times larger than the corresponding value for methyl 4-nitrobenzoate.[23]

(b) Introduction of alkyl groups in the α-position of aliphatic *N*-acylimidazoles (which induces steric crowding) either does not affect or slightly enhances the rate of hydrolysis of these compounds.[16,17]

The higher $\Delta H^{\neq}$ value for **VIa** may be due to stabilization of the reactant state, destabilization of the transition state or both. Regarding stabilization of the former state, one can envisage an intramolecular electron donor–acceptor interaction between the heterocycle (donor) and the electron-deficient aromatic ring (acceptor). The strength of this interaction is expected to decrease in the order **VIa** > **VIb** > **VIc** > **Ve**; for **VIa** the *o*-nitro group is also probably involved. Such intramolecular interaction is similar to that between the *o*-nitro group of one ring and the opposite aromatic ring in diphenyl ethers, diphenyl thioethers, benzophenones, benzanilides and diphenyl sulphoxides.[24] Additionally, the formation of intermolecular complexes between Imz and aromatic substrates, e.g. pyridoxal[25a] and methyl *trans*-cinnamate,[25b] has been shown. In the case of the latter compound, the complex formation resulted in a small but real decrease in the reaction rate.

Regarding *N*-acylimidazoles, theoretical calculations indicated that the heterocycle is a π-electron donor, and that there exists an intramolecular donor–acceptor interaction between imidazole and electron-withdrawing acyl groups.[26a] Both conclusions are in agreement with observed UV–visible spectra of solutions of acetylimidazole in presence of π-electron acceptors, e.g. iodine and iodine bromide,[26b] and those of *N*-4-substituted benzoylimidazoles.[26c]

We sought experimental evidence for formation of these intramolecular electron donor–acceptor complexes. Theoretical calculations[26a] and IR and ^{1}H NMR spectra[20d] showed that H-2 of imidazole is most affected by electron donation by the heterocycle. Therefore, we measured ^{1}H NMR chemical shift differences ($\Delta\delta$) between the protons of **Ve** and those of **VIa**, **VIb** and **VIc** under the same conditions (0·05 M in dry CD_3CN). On going from **Ve** to **VIa**, the heterocycle H-2 showed the largest downfield shift, 20·2 Hz. The corresponding (downfield) $\Delta\delta$ values for H-4 and H-5 were 14·1 and 12·0 Hz, respectively. A similar trend was observed for **VIb** and **VIc**, with smaller $\Delta\delta$ values of 11·2, 8·3 and 3·5 Hz for **VIb** and 8·0, 6·2 and 1·0 Hz for **VIc** for the heterocycle H-2, H-4 and H-5, respectively. The downfield shift of the diazole discrete protons indicates electron donation to the aromatic ring, the strength of which depends on the nature and position of the substituent, decreasing in the order **VIa** > **VIb** > **VIc** > **Ve**. The $\Delta\delta$ results for the first two compounds (both are dinitrobenzoylimidazoles) point to a specific interaction between imidazole and the *o*-nitro group.

Regarding the transition state (see above), it is safe to conclude that the importance of such an interaction is much less than that in the reactant state This may be due to a combination of (a) an increase in the distance between the imidazole and the aromatic ring because of partial dissociation of the C—N bond and (b) an attenuation of the electron density of the leaving group because of its hydrogen bonding with water.[15b,15c,17b] In summary, the observed relative reactivities of **Ve** and **VIa** are due to a combination of steric crowding at the reaction centre and intramolecular stabilization of the reactant state.

The activation parameters obtained for **Ve** and **VIa** can now be readily explained. For **VIa** the higher $\Delta H^{\neq}$ value is due to a decreased interaction between the CO group and the 2,4-dinitrobenzene ring (owing to lack of coplanarity) and an extra stabilization of the reactant state, imposed by an intramolecular donor–acceptor interaction. For the same compound, the higher $\Delta S^{\neq}$ is a consequence of smaller loss of degrees of freedom on going from the (more structured) reactant state to the transition state.

The preceding rationale can be tested by examining the effect of inhibition of electron donor–acceptor interactions on relative reactivities, i.e. by examining hydrolyses of compounds **VId** (derived from **Ve**) and **VIe** (derived from **VIa**) in which the heterocycle is positively charged. At the outset, any change in molecular geometry which may result from quaternization of the N-3 atom of imidazole is expected to be similar for **VId** and **VIe**. Using the Hyper-Chem program package (Autodesk), we calculated the effect of quaternization of **Ve** and **VIa** on the geometries of the products as follows: dihedral angles, Φ, between the planes of the different groups of the molecule were taken from solution data for acylimidazoles or from x-ray data for the precursor benzoic acids. The following Φ values were used: Φ_1, between the CO group and the aromatic ring, 3·3° and 23·4° for **Ve** and **VIa**, respectively; Φ_2, between the NO_2 group and the aromatic ring, 54·7° and 0° for *o*- and *p*-nitro, respectively; and Φ_3, between the Imz ring and the CO group, 21·0°.[19,20a,20b,22] The geometry of each molecule was first optimized by the MM2 molecular mechanics program by using the above-mentioned dihedral angles as starting values, but without imposing them as constraints. The 'best' geometry based on the MM2 program was further refined with the AM1 semi-empirical program. On going from **Ve** to **VId** there was a decrease in Φ_1 from 38·6° to 26·2° and an increase in Φ_3 from 9·1° to 30·0°. The same behaviour was observed on going from **VIa** to **VIe**, with Φ_1 decreasing from 55·9° to 47·5° and Φ_3 increasing from 7·8° to 25·8°. Interestingly, the value of Φ_2 remained virtually constant (39·1° and 42·8° for **VIa** and **VIe**, respectively). The results of these calculations indicate that quaternization of the N-3 atom of Imz produces parallel changes in the geometry of **VId** (relative to **Ve**) and **VIe** (relative to **VIa**). Therefore, quaternization of the heterocycle should only increase the values of k_c for both compounds, but should not change their order of reactivity, i.e. one would expect k_c(**VId**) to continue to be greater than k_c(**VIe**). Our results, however, show that this is not the case (see below), in agreement with the idea of donor–acceptor interaction.

We attempted to determine the values of k_c for

MeImz-catalysed hydrolyses of **VId** and **VIe** (hydrolysis in Imz buffer would result in nucleophilic catalysis).[15d] At a constant pH of 7·02, the observed rate constants were rather insensitive to [MeImz] in the concentration range 0·04–0·16 M. The use of concentrated buffer solutions (0·1–0·5 M, ionic strength 1·0) resulted in plots of k_{obs} vs [MeImz] which were visibly curved. Although no reliable k_c values could be determined, all k_{obs} values for **VIe** were greater than the corresponding values for **VId**, indicating that quaternization produced an inversion of reactivity.

We determined the pH–rate profiles for spontaneous (i.e. water catalysed) hydrolyses for **VId** and **VIe** and the values of k_{obs} were found to be independent of the solution pH in the range 1·6–4·0, in agreement with the results for water-catalysed hydrolysis of acetylimidazole.[15,16] The values of k_c reported in Table 2 were obtained by dividing k_{obs} by water concentration (47·3*M*). These results show that **VIe** is more reactive than its 4-nitro counterpart, **VId**. This inversion of reactivity (relative to **Ve** and **VIa**) is due to the absence of intramolecular electron donor–acceptor interactions because of quaternization. Activation parameters for the reaction of **VId** and **VIe** corroborate the preceding discussion. Whereas **Ve** is more reactive than **VIa**, essentially owing to the lower enthalpy of activation, the reverse is true for **VId** and **VIe** because donor–acceptor interactions play no role in hydrolyses of *N*-acyl-*N'*-methylimidazolium chlorides. The small difference between the $\Delta S^{\neq}$ values of **VId** and **VIe** also agrees with our discussion (see above) on the relative importance of steric *ortho* effects.

ACKNOWLEDGEMENTS

We thank the FAPESP and FINEP Foundations for financial support. P. Menegheli thanks the UEL, Londrina, for granting him leave of absence and CAPES for a research fellowship. We thank José B. de Picoli for his technical help.

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