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Substituent effects in the addition of carboxylic acids to arylcarbodiimides †

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Rates of addition in aqueous solution of RCOOH (R = CH_3–, CH_3OCH_2–, $ClCH_2$–, Cl_2CH–) to ArN=C=$NCH_2CH_2CH_2N^+(CH_3)_3$ [Ar = C_6H_5–, 3-ClC_6H_4–, 4-$CH_3OC_6H_4$–, 3,4-$Cl_2C_6H_3$–, 2,4-$(CH_3O)_2C_6H_3$–] yielding a transient *O*-acylisourea, have been measured as a function of pH. Relative activities indicate a reaction mechanism in which a carboxylate anion adds to a mono- or di-protonated arylcarbodiimide, available in minor amounts. Only a weak dependence of reaction velocity upon basicity of carboxylate nucleophile is noted (Brønsted β value of ~0.2). Ease of prefatory protonation of aryl-attached nitrogen within ArN=C=NR′ (as estimated from the basicity of correspondingly substituted quinolines) appears to dominate reactivity, so that the presence of electron-donating ring substituents renders such an arylcarbodiimide significantly more susceptible to addition by carboxylates.

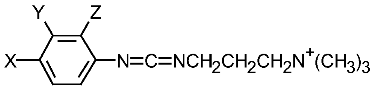
Introduction

Chemical activation of carboxylic acid residues by carbodiimides constitutes a well-established synthetic procedure.[1–3] The *O*-acylisourea resulting from addition of RCOOH across an imino linkage of RN=C=NR′ readily transfers its acyl group to various acceptors, exothermically releasing RNHCONHR′. Certain mechanistic features of the initiatory addition reaction have been examined previously.[4–7] We developed an interest in fine-tuning the process, and have undertaken a systematic investigation of the way in which substituents introduced onto the reactants influence the facility of reaction in the activation of carboxyls.

It has previously been shown that the *O*-acylisourea intermediate produced from addition of AcOH to certain carbodiimides either accumulates prior to subsequent reaction, or further reacts rapidly and irreversibly with acetate to yield acetic anhydride, so that the initial, rate-limiting addition may be followed kinetically.[7] Reaction monitoring is conveniently carried out spectrophotometrically in the case of *N*-arylcarbodiimides, for which the reactant exhibits stronger ultraviolet absorption than do the products. Substrates favorable for examination have the structure X–C_6H_4N=C=$NCH_2CH_2CH_2N^+(CH_3)_3MsO^-$, for which electronic demands exerted upon the carbodiimide functionality may be adjusted by incorporation of different aryl substituents (X). For these substrates water solubility is conferred by the presence of a chemically inert quaternary ammonium ion, allowing for pH control during reaction through employment of an aqueous buffer. In this study addition to such carbodiimide acceptors has been investigated on the part of a series of substituted acetic acids which varies systematically with regard to pK_a.

Results

The substituted-carbodiimide acceptors employed in this investigation are summarized by structures **1a**–**e**, and the nucleophilic carboxy-addends by **2a**–**d**. Kinetic runs for conjoining of these reactants in aqueous solution were conducted under pseudo-first order conditions, employing the acetate component **2** in large excess, so that it functioned also as a buffer holding the pH constant. In kinetic measurements, an exponential decay in the spectral absorption of **1** was recorded subsequent to mixing of reagents, and the trace was fitted to an appropriate mathematical expression by the method of nonlinear least squares. The resulting decay constant was then converted into an apparent second-order rate constant by correction for the bulk concentration of buffer-nucleophile. Each carbodiimide **1** was submitted separately to each substituted acetic acid **2**, with repetition at a variety of [H$^+$] concentrations within the range of pH 1–6. The characteristic pH-dependence for reaction of **1** is shown in Figs. 1–5, for each of **2a**–**d**. The figures show that reaction velocity increases with solution acidity until the pK_a of the substituted acetic acid component is reached, whereupon it levels off in most cases. In accord with previous mechanistic interpretation,[7] this kinetic behavior appears to be a consequence of addition of carboxylate anion to a minor amount of protonated carbodiimide existing at equilibrium in weakly acidic solution [eqn. (1)]. The pH-dependent portion of the curves reflects varying amounts of protonated acceptor available for addition. That acid dependence actually extends into the left-most portion of the curves, but diminishing amounts of available carboxylate nucleophile at pH values below the pK_a of the acetic acid derivative cause the curves to level off; *i.e.*, the acid-activation of substrate carbodiimide becomes compensated by an acid-inhibition of the addend ($RCOO^- \longrightarrow RCOOH$). In several instances, particularly for the chloro-substituted carbodiimides (**1b**, **1d**), the data seem to indicate another increase in apparent rate constant on passing into the range of pH < 2. This is interpreted as due to a concurrent pathway involving di-protonation of substrate [lower loop in eqn. (1)]. While the plausibility of such a mechanistic feature is



R—COOH

1a : X = H, Y = H, Z = H
1b : X = H, Y = Cl, Z = H
1c : X = CH_3O, Y = H, Z = H
1d : X = Cl, Y = Cl, Z = H
1e : X = CH_3O, Y = H, Z = CH_3O

2a : R = CH_3
2b : R = CH_3OCH_2
2c : R = $ClCH_2$
2d : R = Cl_2CH

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† Electronic supplementary information (ESI) available: details on the preparation of substrates and carbodiimide characterization data. See http://www.rsc.org/suppdata/p2/b1/b105867n/

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Table 1 Kinetic rate constants for acid-induced addition of carboxylates to arylcarbodiimides

	Arylcarbodiimide (substituents X, Y, Z)				
	1a (H, H, H)	**1b** (H, Cl, H)	**1c** (CH_3O, H, H)	**1d** (Cl, Cl, H)	**1e** (CH_3O, H, CH_3O)
CH_3COOH (**2a**), pK_a 4.76					
k/K[a]	1570 (± 150)	658 (± 43)	3500 (± 270)	313 (± 24)	2580 (± 400)
$10^{-3}k'/KK'$[b]	18 (± 35)	25 (± 14)	—	174 (± 22)	—
CH_3OCH_2COOH (**2b**), pK_a 3.58					
k/K[a]	1297 (± 80)	352 (± 17)	2490 (± 140)	97 (± 5)	1585 (± 85)
$10^{-3}k'/KK'$[b]	244 (± 56)	22 (± 5)	—	23 (± 2)	—
$ClCH_2COOH$ (**2c**), pK_a 2.85					
k/K[a]	930 (± 106)	183 (± 18)	1460 (± 80)	120 (± 9)	790 (± 70)
$10^{-3}k'/KK'$[b]	—	11 (± 3)	—	10 (± 2)	—
$Cl_2CHCOOH$ (**2d**), pK_a 1.48					
k/K[a]	570 (± 41)	135 (± 5)	470 (± 110)	—	491 (± 29)

[a] $M^{-2}\ s^{-1}$. [b] $M^{-3}\ s^{-1}$.

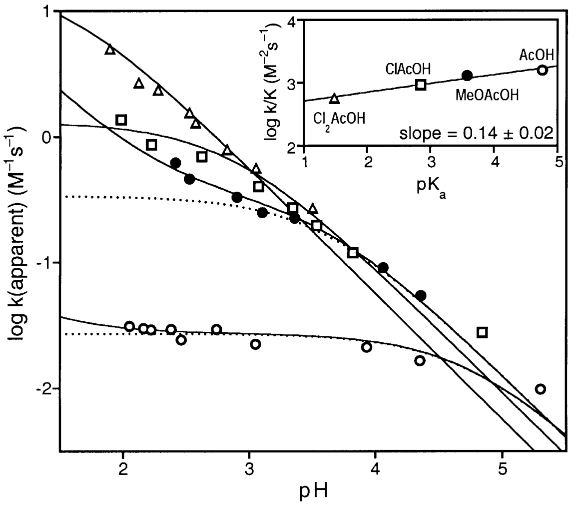

Fig. 1 Plots, for various substituted acetic acids, of log k(apparent) *versus* pH for reaction with $C_6H_5N{=}C{=}NCH_2CH_2CH_2N^+(CH_3)_3$ (**1a** plus RCOOH **2**). Symbols correspond as follows (concentrations given for total carboxyl, RCOOH + $RCOO^-$): open circles, CH_3COOH **2a** (1.0 M); filled circles, CH_3OCH_2COOH **2b** (0.2 M); squares, $ClCH_2COOH$ **2c** (0.05 M); triangles, $Cl_2CHCOOH$ **2d** (0.02 M). Solid-line curves are least-squares fit of second-order kinetic data to the expression for eqn. (1), $\log k(\text{apparent}) = \log \{(k/K + [H^+]k'/KK')[H^+]/(1 + [H^+]/K_a)\}$, in which K_a values are those of the acetic acid addends **2**, with fitted kinetic parameters k/K and k'/KK' listed in Table 1. Dotted curves in multiphasic cases separate out the component kinetic factor arising solely from first-order [H^+] dependence (k only, excluding k' contribution). Inset: replot of log k/K for **1a** *versus* pK_a values of RCOOH (Brønsted plot).

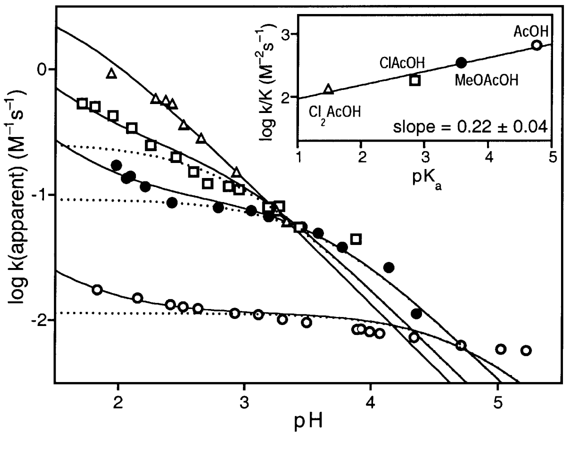

Fig. 2 Plots, for various substituted acetic acids, of log k(apparent) *versus* pH for reaction with $3\text{-}ClC_6H_4N{=}C{=}NCH_2CH_2CH_2N^+(CH_3)_3$ (**1b** plus RCOOH **2**): **2a** (2.0 M), **2b** (0.3 M), **2c** (0.07 M), **2d** (0.04 M). Presentation and curve fitting are as for Fig. 1.

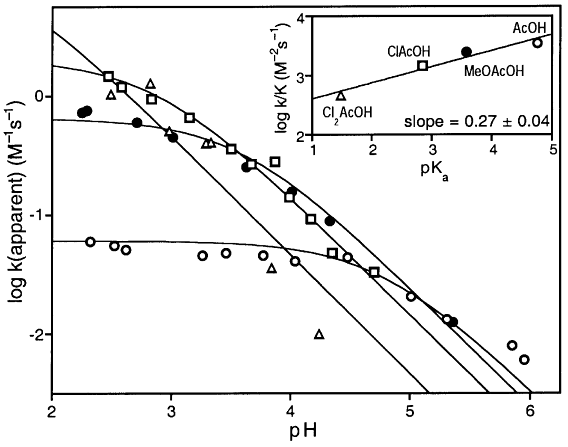

Fig. 3 Plots, for various substituted acetic acids, of log k(apparent) *versus* pH for reaction with $4\text{-}(CH_3O)C_6H_4N{=}C{=}NCH_2CH_2CH_2N^+(CH_3)_3$ (**1c** plus RCOOH **2**): **2a** (1.0 M), **2b** (0.1 M), **2c** (0.05 M), **2d** (0.02 M). Presentation and curve fitting are as for Fig. 1 (k' not required).

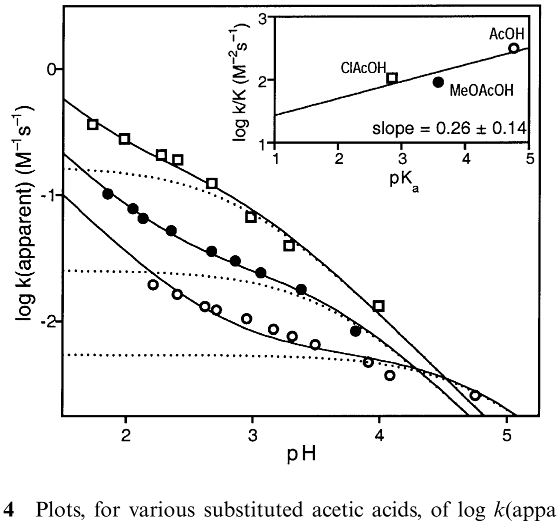

Fig. 4 Plots, for various substituted acetic acids, of log k(apparent) *versus* pH for reaction with $3,4\text{-}Cl_2C_6H_3N{=}C{=}NCH_2CH_2CH_2N^+(CH_3)_3$ (**1d** plus RCOOH **2**): **2a** (2.0 M), **2b** (0.3 M), **2c** (0.07 M). Presentation and curve fitting are as for Fig. 1 (addend $Cl_2CHCOOH$ yields unsatisfactory kinetic data).

open to question, some explanation is required to account for a gradual increase in apparent rate constant realized for those substrates in Figs. 2 and 4. It was shown by appropriate blank reactions that a direct, [H^+]-induced hydration of carbodiimides does not compete significantly with acetate addition. ‡

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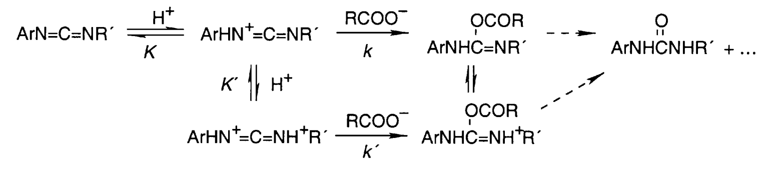
‡ Literature $k_H = 10\ M^{-1}\ s^{-1}$ for **1a** plus H_2O.[8]



(1)

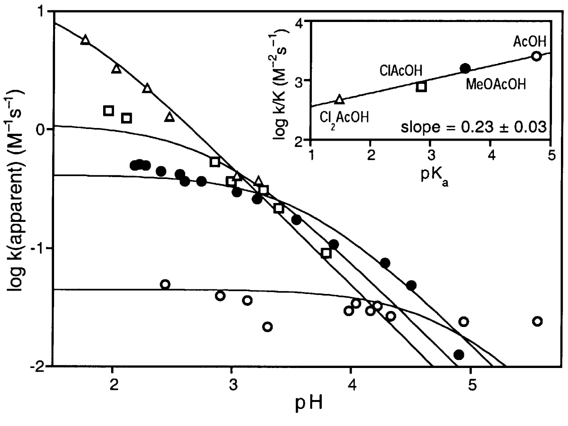


Fig. 5 Plots, for various substituted acetic acids, of log *k*(apparent) *versus* pH for reaction with 2,4-$(CH_3O)_2C_6H_3N{=}C{=}NCH_2CH_2CH_2N^+(CH_3)_3$ (**1e** plus RCOOH **2**): **2a** (0.5 M), **2b** (0.1 M), **2c** (0.05 M), **2d** (0.02 M). Presentation and curve fitting are as for Fig. 1 (k' not required).

Also, the reaction of **1a** was independently shown to exhibit only a first-order variance on buffer-nucleophile (acetate) in the concentration range employed; no evidence for concurrent general acid catalysis by acetic acid[7] could be discerned.

The curves plotted in Figs. 1–5 represent a least-squares fit to a kinetic expression, as given in the legend to Fig. 1, for the chemical mechanism in eqn. (1) (with K and K' being cryptic acid dissociation constants). The primary pathway involves protonation of carbodiimide to $ArHN^+{=}C{=}NR'$ (acid dissociation constant K), with subsequent carboxylate addition (rate k), the ratio of which yields an apparent third-order rate constant. Because the nucleophile is a buffer species, its pH-dependent abundance is designated in the fitting equation by its total concentration adjusted by the denominator term incorporating K_a for **2a**–**d**, the known values of which are provided in Table 1. The additional kinetic term involving acid dissociation K' and rate k' corresponds to the parallel pathway involving diprotonation, as required in some instances. The derived complex third- and fourth-order rate constants reflecting $[H^+]$-dependence (k/K, k'/KK') are provided in Table 1 insofar as kinetic data within the figures allows, for each combination of carbodiimide plus carboxylic acid. A few of the plots show small positive deviations for kinetic data points at pH values of >5. These may reflect a competing base-induced hydration reaction or other consumption of carbodiimide in some instances, which was not accommodated by the curve-fit, in the interest of employing a uniform equation for all nineteen substrate combinations in Figs. 1–5.

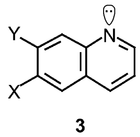
Discussion

The most important generalization from our data is that carbodiimides bearing either indifferent or electron-donating aryl substituents (H, CH_3O) are more reactive as regards acetate addition than those possessing inductively electron-withdrawing substituents (Cl, Cl_2), according to the rate constants in Table 1. Such an observation might initially seem counter-intuitive, for assuredly nucleophilic addition by an anionic carboxylate ought to be enhanced by electron deficiency within the acceptor carbodiimide moiety. This investigation was undertaken in order to explain the phenomenon.

Quantification

To begin, an inset provided for each of Figs. 1–5 displays a Brønsted plot of log k/K (from Table 1) *versus* pK_a values of RCOOH, for the series of carboxylic acids participating in the addition. Since the value of the intrinsic acid dissociation constant K for carbodiimide protonation [eqn. (1)] does not change within the individual figures, each such comparison represents (for $ArHN^+{=}C{=}NR'$) a linear free energy relationship measuring the kinetic sensitivity of the addition reaction to basicity of the carboxylate nucleophile. Any such correlation with respect to k appears tenuous. The values of β (slope) cluster about 0.22, suggesting that bond formation is not far advanced in the transition state for the process of combining carboxylate with carbodiimide cation; *i.e.*, basicity of the nucleophile seems relatively inconsequential. Among the figures no significant trend in the value of β is evident, and since an extrapolation is involved in the determination of k/K in several instances, no conclusion other than a generally low value for β is offered.

A significant quantitative factor, which is not directly measurable, is the proton-accepting capability of the carbodiimide residue [the same equilibrium K in eqn. (1)]. A probable explanation for greater reactivity on the part of the electron-rich substrates is that they are more extensively protonated at a given pH, and consequently they suffer a higher proportion of carbodiimide that has become activated for addition by carboxylate. Ionization constants for the protonated carbodiimide functionality are unknown, and magnitudes are not directly measurable because of chemical reactivity in aqueous solution. However, pK_a values for this deprotonation must all be <2, for within that region of aqueous acidity no break in the plotted curves emerges from Figs. 3 or 5, as this would have suggested incipient saturation with regard to substrate activation (most significantly for these two cases of arylcarbodiimides that are more basic by virtue of possession of electron-donor appendages). In order to derive an estimate of the importance of the protonation factor, we turn to substituted quinolines as models. For quinoline bases, the atomic orbital holding the proton-accepting lone pair of electrons on trigonal nitrogen is obliged to adopt sp^2-hybridization, as should also be the case for carbodiimides. Consequently, 6- or 7-substituted quinolines **3** may serve as chemically stable, iso-structural surrogates for the reactive substrates **1** employed in this study, for the purpose of estimating the effect of aryl-ring substituents upon basicity.



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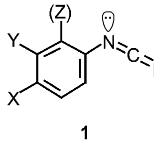


1

Fig. 6 portrays the pK_a values for substituted quinolines plotted *versus* the Hammett σ constants for the respective substituents (left scale, small diamond symbols, solid line). The slope of the regression line is −2.4 ± 0.3, indicating a greater pK_a-dependence on the quinolinium substituent than found for the acidity of 4-substituted benzoic acids, for example. However, the gradient amounts to less than is equivalently observed for pK_a values of 4-substituted anilinium ions, for which a similar plot yields a slope of −3.6. This presumably reflects the coplanar and sp^2-hybridized nature of the proton-accepting lone pair of electrons in quinoline, and justifies a choice of

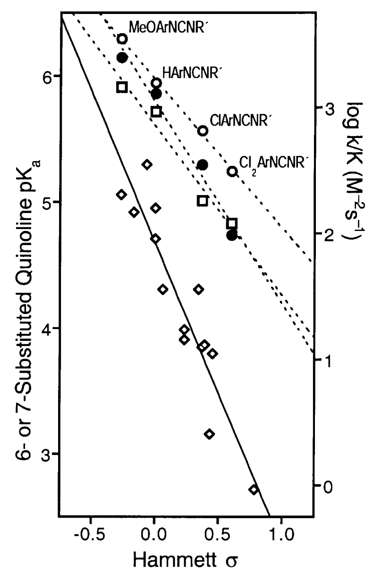


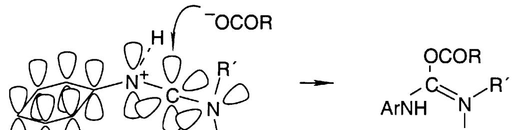
Fig. 6 Plot of pK_a for 6- and 7-substituted quinolinium ions **3** (left scale),[11] and of log k/K for arylcarbodiimides **1a**–**d** (right scale), *versus* Hammett σ value. The linear least-squares fitted slope for quinolines is -2.4 ± 0.3 (small diamonds, solid line). For arylcarbodiimides the slopes (dashed lines, top to bottom) are -1.17 ± 0.05 (for addend CH_3COOH **2a**, open circles), -1.60 ± 0.18 (for addend CH_3OCH_2COOH **2b**, solid circles), and -1.35 ± 0.17 (for addend $ClCH_2COOH$ **2c**, squares). For **1d**, the value for σ is the sum of σ_m and σ_p for Cl; addend **2d** has been excluded as it provided an unsatisfactory linear plot.

conventional σ values rather than σ^n values[9] for the intended correlation. With regard to the kinetic data, the measured variations in addition-velocity for carbodiimides, values of log k/K for **1a**–**d** reacting with **2a**–**c**, have also been plotted in Fig. 6 *versus* the same σ values. Linear fitting yields slopes of -1.2 to -1.6, for common acetates adding to each of the four arylcarbodiimides **1** that do not have an *ortho*-substituent next to the carbodiimide (right scale, previously employed symbols for **2**, dashed line-fit).§ A parallel between the susceptibility of substrates and the basicity of quinolines is apparent. The overall interpretation which follows is that in the case of carboxylate addition to carbodiimides, a comparatively robust inductive effect strongly perturbs pre-equilibrium protonation of substrate (K), with mitigation by a smaller opposing perturbation within the kinetics for the addition reaction itself (k). Ineffectuality in the latter component might be expected from the lesser value of the Brønsted coefficients displayed in Figs. 1–5. However, with present data it is impossible to separate these influences quantitatively for the experimentally observed complex rate constant k/K.

Protonation specificity

This explanation only retains plausibility if the aryl-substituted nitrogen atom of a carbodiimide residue in **1** should be the kinetically significant site of activating protonation, as depicted in eqn. (1). The alternative nitrogen atom of the carbodiimide does not bear an arene, and on that account might loom as potentially more basic. However, protonation at that locus ought not to yield such a potent substituent effect upon the kinetics as is observed. A separate inductive effect arising from the cationic moiety attached to the second nitrogen, $(CH_3)_3N^+CH_2CH_2CH_2$–, should produce an approximate 2 pK-unit suppression of basicity for that atom, according to the difference between first and second acid dissociation constants for propanediamines. That factor is apparently sufficient to outweigh the effects of a benzene substituent, in this situation where the aryl-nitrogen lone pair is not in actual conjugation with the benzene ring, on account of a preferred orbital hybridization for N.

Alternatively, a stereoelectronic effect may dictate the site of protonation, for strictly kinetic reasons [eqn. (2)]. Should the direction of approach of a carboxylate nucleophile toward protonated carbodiimide be focused upon a central-carbon p-orbital having extended conjugative overlap within the acceptor, engaging the benzene ring specifically so as to maximize transition-state delocalization, then the orthogonal nature of bonding within the cumulated carbodiimide linkage suggests that prefatory protonation of a nitrogen adjacent to the arene should prevail. This would transpire in order that the incipient imino linkage of the emerging *O*-acylisourea may experience continuous pi bonding as the central carbon atom of the reacting linkage suffers trigonal rehybridization. In this hypothesis protonation of either carbodiimide nitrogen may be possible, but that shown leads to reaction preferentially.



(2)

Rates for a number of the relatively electron-deficient carbodiimides (especially **1b** and **1d**) appear to exhibit an additional pH dependence in acidic solution (pH ≤ 2), in that the plotted curves do not level off cleanly. Such behavior we tentatively explain by concurrent double-protonation of the carbodiimide [eqn. (1), lower loop, steps involving K' and k'], providing an additional activation pathway. The plausibility of this is open to question from electrostatic considerations. However, it might be noted that the proton-accepting nitrogen orbitals within a carbodiimide are orthogonally oriented [eqn. (2)], minimizing interaction. By way of precedent for such a poly-cationic intermediate, the benzidine rearrangement of diarylhydrazines shows kinetically both first- and second-order terms in $[H^+]$, pointedly indicating the mechanistic feasibility of catalytic diprotonation, for a case of even more intimately connected nitrogen atoms.[10] So long as an increase in rate of addition ($k' \gg k$) matches the difficulty of secondary protonation ($K' \gg K$), the two reaction paths may coexist and compete in the case of carbodiimides. Furthermore, the suggested dual-protonation pathway emerges as kinetically significant only when ring substituents retard reaction by selectively depressing the basicity of the aryl-substituted nitrogen of the carbodiimide (**1b**, **1d**). This fits the previous contention regarding a favored site of initial protonation. As an alternative mechanistic explanation for the extra catalytic $[H^+]$-dependence, a competing addition reaction between the species $ArHN^+{=}C{=}NR'$ and RCOOH is possible, since that entails an identical transition-state stoichiometry as in the k' pathway. The complex rate constants k'/KK' for the secondary path, as also presented in Table 1, are not considered of sufficient reliability to justify any interpretive correlations.

Summation

Regardless of mechanistic explanations, the practical conclusion of this investigation is that carbodiimide reactivity is generally enhanced by the presence of electron-donating substituents. That knowledge may have utility in reagent design.

Experimental

Materials

Previously known 1-phenyl-3-[3-(trimethylammonio)propyl]-carbodiimide iodide, **1a**, was assembled from phenyl isocyanate

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§ Apparent nonlinearity in the data for **2b** (solid circles) probably results from error in the lowest data point, arising from extrapolation within Fig. 4. Were that the case, the actual linear slope would more nearly match that of the other substrates.

and *N*,*N*-dimethyl-1,3-diaminopropane, with dehydration of the resulting urea by toluenesulfonyl chloride and triethylamine in dichloromethane, followed by methylation; mp 163–164 °C.[8] Other carbodiimides **1b**–**e** were prepared analogously, generally as methanesulfonate salts. Characterizations are provided as supplementary data. †

Measurements

Values of pH recorded for kinetic runs are glass-electrode meter readings in aqueous solution buffered by excess carboxylic acid and its carboxylate anion (total concentration 0.02–2 M, as given in the legends to Figs. 1–5), referenced to calibration standards in water. Kinetic runs (entailing 0.1–3 mM substrate) were monitored spectrophotometrically at a suitable wavelength (260–285 nm) at 25.0 °C employing a 2 mm cell, with absorption measurements serially recorded at 1–4 s intervals subsequent to mixing of reactants. Pseudo-first order rate constants obtained by nonlinear least-squares fitting of the resulting exponential decay (over several half-lives) were converted to apparent second order rate constants *via* division with the molar concentration of buffer. Plots of the resulting quantities *versus* pH (Figs. 1–5) were fitted by the method of nonlinear least-squares to an expression governing pH dependence as given in the legend to Fig. 1, yielding complex rate constants recorded in Table 1. Allowance for the proportion of carboxylate present was established by incorporation of the $\mathrm{p}K_\mathrm{a}$ of the carboxylic acid addend into the curve-fitting equation. Throughout, tolerances listed are standard errors from least-squares analysis.

A previous study showed biphasic kinetics in the case of reaction of 1-ethyl-3-(3-(trimethylammonio)propyl)carbodiimide cation with acetic acid, corresponding to the two steps of an initial addition of CH_3COOH, followed by reaction of the *O*-acylisourea with additional acetate to yield acetic anhydride (with a subsequent hydrolysis).[7] For substrates used in the present investigation a single, clean exponential decay in the absorption of carbodiimide-reactant occurs, starting and terminating in values characteristic of the substrate and urea product, respectively. Since the reaction of acetate with **1a** is some 50-fold slower than for the previously cited case, and since comparatively high concentrations of carboxylate were employed, it is likely that the *O*-acylisourea intermediate does not accumulate. Moreover, deacylation of the intermediate ought not to exhibit the aryl substituent effects observed.

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