Amine Catalyzed Intramolecular Imidization of Alkyl and Aryl Phthalamates. Kinetics and Mechanism in Deuteriated Chloroform

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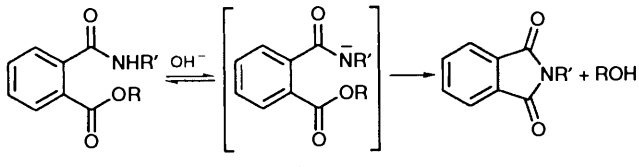
The kinetics of the amine catalyzed intramolecular imidization of alkyl and phenyl phthalamates with a variety of amines were measured in deuteriated chloroform at 40.1 °C. An overall second-order kinetic rate law, rate = $k_{overall}$[amine][phthalamate], was obtained from our experiments. Although pre-association between the amides and the amines through hydrogen-bonding interaction was suggested by proton NMR spectroscopy, the catalytic ability of amines was found to be related to their basicity rather than to their hydrogen-bonding ability or nucleophilicity. This observation implies the involvement of proton transfer from the amide to the amine in the critical transition state. In addition, by changing the leaving group from phenoxy to butoxy group, the reaction rate constants decrease by a factor of 30 to 70. On the basis of these kinetic results, we propose that the intramolecular imidization proceeds through an amine assisted cyclization to a zwitterionic intermediate, followed by the expulsion of the alkoxy or phenoxy group to provide phthalimide and the corresponding alcohol.

The study of catalytic principles has been of great importance in understanding the mechanisms of enzyme action.[1] During the past few decades, numerous model studies about intramolecular catalysis,[2] solvolysis mechanisms,[3] and molecular recognition[4] have been reported. Since most of the physiological reactions happen in a hydroxylic environment, early investigations were mainly concentrated on aqueous phase model studies.[5] However, the actual enzyme catalyzed reactions might occur in the hydrophobic portion of the enzymes. This concept is appealing because impaired ion solvation often leads to very large rate and equilibrium enhancements. In recent years a considerable amount of work has been carried out on hydrogen-bonded interactions,[6] proton transfer processes,[7] and the mechanism of transacylation reactions[8] in organic media. Because of the predominance of amide linkages in proteins, it is reasonable to anticipate that these amido groups also play an important role in enzyme reactivity. Since both neutral amides and their conjugate bases are effective nucleophiles, neighbouring amido groups often facilitate solvolytic and redox reactions.[9] Early work by Hancock and Sondheimer clearly demonstrated that a neighbouring amido group can effectively catalyze the alkaline hydrolysis of the adjacent ester through an imide intermediate.[10] In addition, on the basis of kinetic results, Shafer[11] proposed an amidate (**1**) formation during the imidization process (Scheme 1).



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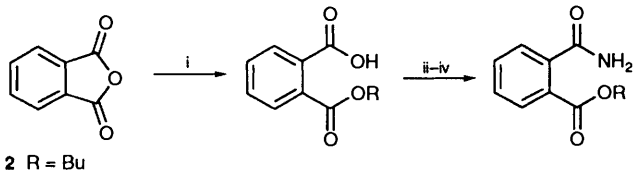
Scheme 1

Our interest in the application of base-catalyzed chemistry to polymer systems has led us to investigate the possibility of using amines as catalysts in intramolecular imidizations.[12] Our ultimate target is the optimization of the design of polyamic acid and polyamic esters[13] in order to facilitate their transformation into polyimides under the influence of base generated photochemically *in situ*.[14] However, the mechanism of this base-catalyzed imidization reaction is not fully understood. Since the basicity of amines is too low for the direct deprotonation of the amido groups, we suspected that the amine-catalyzed imidization proceeds through a different mechanism. In this report, we present our recent progress in the study of the mechanism of the amine-catalyzed intramolecular imidization of alkyl and aryl phthalamates.

Results and Discussion

Amines are versatile reagents that may activate amido-esters through hydrogen-bonding interactions, proton abstraction, or nucleophilic addition to the carbonyl groups. In order to distinguish between these different effects, a wide range of amines having different hydrogen bonding abilities, basicities, and nucleophilicities were selected for this study. Since the intramolecular imidization involves the attack of a neighbouring amido group onto the adjacent ester, the reaction has to proceed through a multi-step process that likely involves several nucleophilic additions and eliminations. In order to ascertain the rate determining step, a variety of leaving groups including phenoxy, 1,1,1-trifluoroethoxy, and butoxy groups were introduced into the substrate. If the rate determining step involves the expulsion of alkoxy or phenoxy group, a significant effect on the imidization rate constants is expected for these different compounds.

Synthesis of Alkyl and Phenyl Phthalamates.—Butyl and 1,1,1-trifluoroethyl phthalamates (**2**) and (**3**) were prepared by a two-step synthetic sequence[15] from phthalic anhydride (Scheme 2). Because of the low conversion of phthalic anhydride



2 R = Bu
3 R = CF_3CH_2

Scheme 2 *Reagents:* i, ROH; ii, $(COCl)_2$; iii, $(TMS)_2NH$; iv, MeOH, H_3O^+

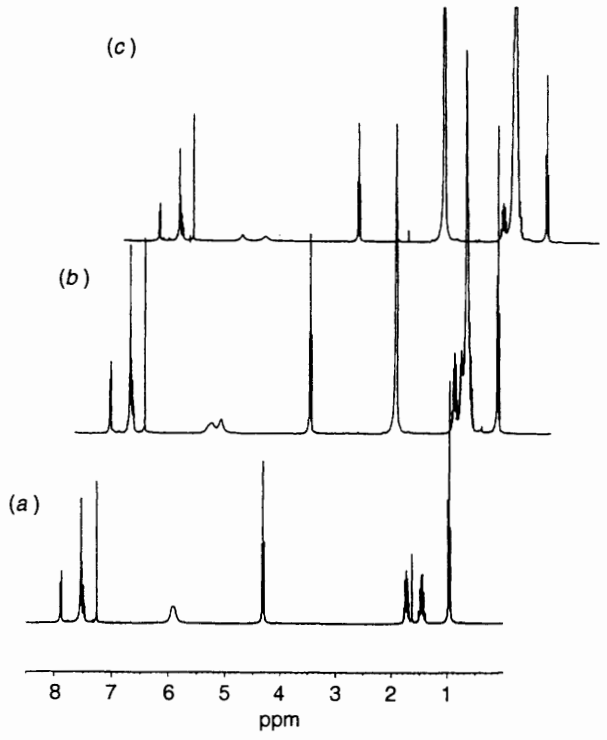
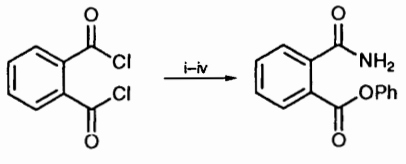


Fig. 1 ^{1}H NMR spectra of butyl phthalamate (3.2×10^{-2} mol dm^{-3}) in $CDCl_3$: (*a*) without piperidine; (*b*) [piperidine] = 9.4×10^{-2} mol dm^{-3}; (*c*) [piperidine] = 1.9×10^{-1} mol dm^{-3}. The broad singlet at 5.9 ppm is assigned to the amide proton. In the presence of piperidine, the broad singlet splits into two smaller signals. The downfield shift signal is assigned to the proton that is hydrogen-bonded to piperidine through type I interaction.

into hydrogen phenyl phthalate, phenyl phthalamate (**4**) was prepared by a one pot synthesis from phthaloyl dichloride as shown in Scheme 3.



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Scheme 3 *Reagents:* i, DMAP, pyridine; ii, phenol; iii, $(TMS)_2NH$; iv, H_3O^+, MeOH

Hydrogen-bonding Complexation.—It has been well documented that amines can be hydrogen-bonded to amides in two different ways (Type I and Type II).[16] In the first case, the amine acts as an acceptor to receive a hydrogen from the amide nitrogen. In the second case, the amine acts as a donor to provide a hydrogen to the amide carbonyl oxygen. In our study, the formation of a hydrogen-bonded complex in deuteriated chloroform is suggested on the basis of ^{1}H NMR observations. The spectrum of butyl phthalamate shows a broad singlet at 5.9 ppm which corresponds to two protons (Fig. 1) and is assigned to the amide protons. In the presence of piperidine, the broad singlet splits into two smaller broad signals, each of which corresponds to one proton. The width of this splitting depends on the piperidine concentration. Similar peak splitting was also observed by addition of 1,4-diazabicyclo[2.2.2]octane, a tertiary amine, to the phthalamate solution. These observations support the formation of hydrogen-bonded complexes between the amines and the amides. Since the amine proton is not a necessary requirement for the signal splitting, we believe that

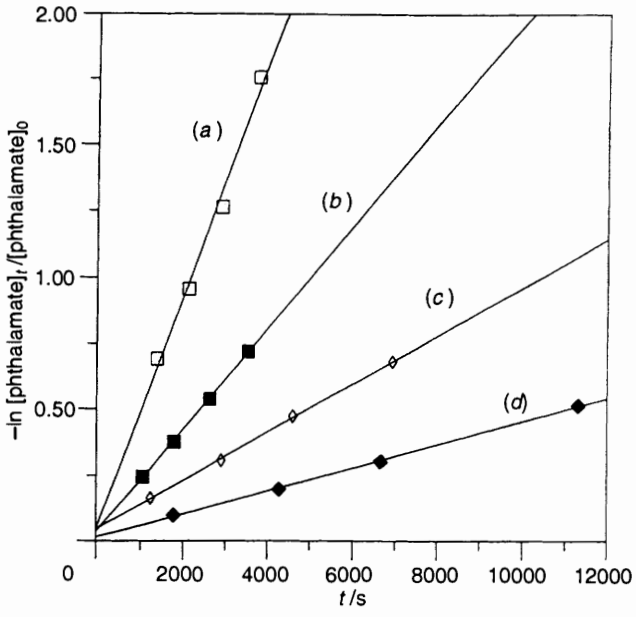
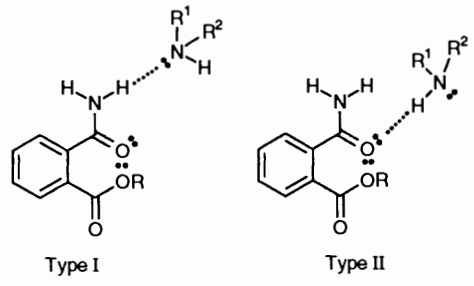


Fig. 2 Plot of $-\ln$ [phthalamate]$_t$/[phthalamate]$_0$ *vs.* reaction time for 1,3-diaminopropane (DAP) catalyzed imidization of phenyl phthalamate at 40.1 °C: (*a*) [DAP] = 1.78×10^{-2} mol dm^{-3}; (*b*) [DAP] = 8.90×10^{-3} mol dm^{-3}; (*c*) [DAP] = 4.45×10^{-3} mol dm^{-3}; (*d*) [DAP] = 2.23×10^{-3} mol dm^{-3}. The solid lines are the least square fits to the points. The linearity of the linear least square fits indicates that the imidization is in pseudo first order to phenyl phthalamate. The pseudo first order rate constants are obtained from the slopes of the solid lines.

type I hydrogen bonding interaction is more significant than type II hydrogen bonding interaction in this case.



Basicity of Amines and Mechanistic Aspects of the Imidization Process.—The kinetics governing the imidization in $CDCl_3$ were determined by ^{1}H NMR spectroscopy. For amines listed in Table 1, the imidization obeys a second-order rate law which was determined under pseudo-first order conditions (Fig. 2). By plotting the pseudo-first order rate constants, k_{pseudo} *vs.* [amine] and measuring the slope of the straight line (Fig. 3), the overall rate constants, $k_{overall}$ were evaluated. The deviation of the intercepts from the origin is within the experimental and least square errors (Fig. 3). The overall kinetic rate law is shown in eqns. (1) and (2).

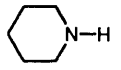
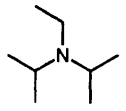
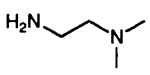
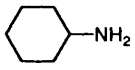
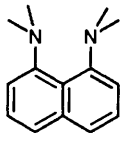
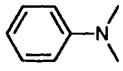
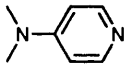
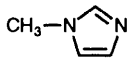
$$\text{Rate} = k_{pseudo}[\text{phthalamate}] \quad (1)$$

where

$$k_{pseudo} = k_{overall}[\text{amine}] \quad (2)$$

Instead of the observations of hydrogen-bonding complex formation, the kinetic data for phenyl phthalamate (Table 1) indicate that the catalytic ability of amines is not correlated to their hydrogen-bonding ability. Strong hydrogen-bonding acceptors[8,17] such as 4-(*N*,*N*-dimethylamino)pyridine (DMAP)

Table 1 Reaction rate constants for the amine-catalysed imidization of phenyl (Ph), 1,1,1-trifluoroethyl (TFE), and butyl (Bu) phthalamates at 40.1 °C in $CDCl_3$

Amine	10^4 k/dm^3 mol^{-1} s^{-1}			
	Ph	TFE	Bu	k(Ph)/k(Bu)
	360 ± 25	250 ± 3	10.8 ± 0.1	33
$H_2N[CH_2]_3NH_2$	260 ± 10	104 ± 10	3.5 ± 0.1	73
	230 ± 7	104 ± 10	0.11 ± 0.002	2100
$H_2N[CH_2]_{10}NH_2$	44 ± 2	—	2.8 ± 0.1	16
	35 ± 1	—	0.98 ± 0.06	47
	32 ± 3	—	—	—
	3.1 ± 0.2	< 1.0	No reaction[a]	—
	No reaction[a]	—	—	—
	—	—	0.21 ± 0.02	—
	—	—	No reaction[b]	—
	—	—	No reaction[b]	—

[a] [amine] = 0.15 mol dm^{-3} for 24 h. [b] [amine] = 0.7 mol dm^{-3} for 24 h.

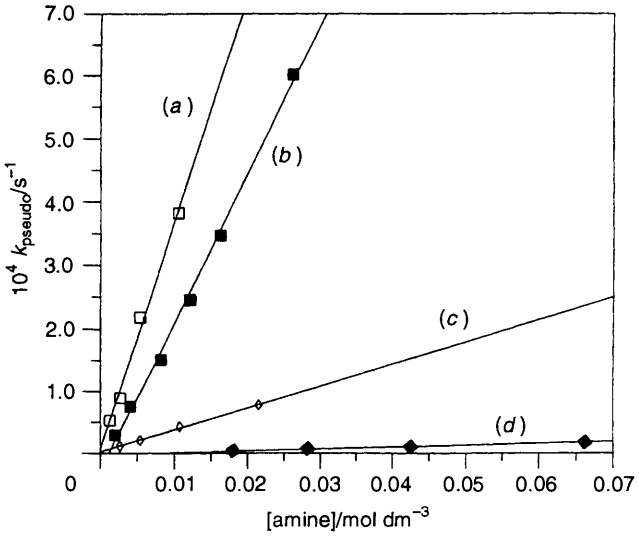


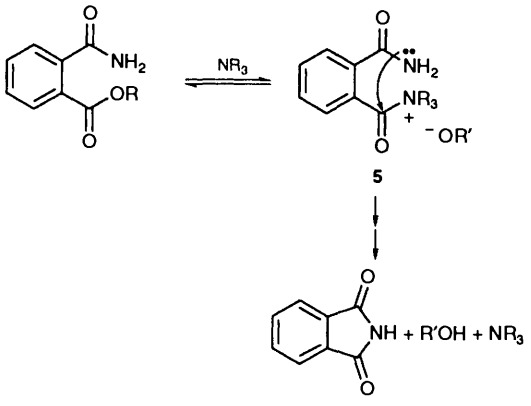
Fig. 3 Plot of k_{pseudo} *vs.* the concentrations of amines for the imidization of phenyl phthalamate: (*a*) piperidine; (*b*) diisopropylethylamine; (*c*) *N*,*N*-dimethyl-1,2-ethylenediamine; (*d*) 1,8-bis(dimethylamino)naphthalene (proton sponge). The linearity of the least square fits indicates that the imidization is in first order to amines.

and *N*-methylimidazole do not facilitate the imidization as effectively as some weaker hydrogen bond acceptors such as primary amines. On the other hand, the catalytic ability of amines follows the trend of their basicity. Rumeau and Balint Novotny reported that the relative basicity of amines in chloroform decreases from the tertiary to the primary ones.[18] Although 1,8-bis(dimethylamino)naphthalene (proton sponge) is a very strong base in aqueous phase, Alder and Benoit reported a dramatic basicity reversal for proton sponge when compared with monoamines in deuteriated dimethylsulfoxide, chloroform, and dichloromethane.[19] These results explain the low catalytic ability of proton sponge in the imidization reaction. Except for sterically hindered diisopropylethylamine, a similar correlation between amine basicities and their catalytic reactivities was also observed for butyl phthalamate. These results strongly suggest that the mechanism involves a large extent of proton transfer from the amide to the amine in the imidization.

Leaving Group Effect.—Phenyl phthalamate cyclizes about 2 times faster than trifluoroethyl phthalamate and about 30–70 times faster than butyl phthalamate. This reactivity order of the leaving groups is consistent with that reported for the alkaline hydrolysis of phenyl *o*-(2-imidazolyl)benzoate,[20] but their rate

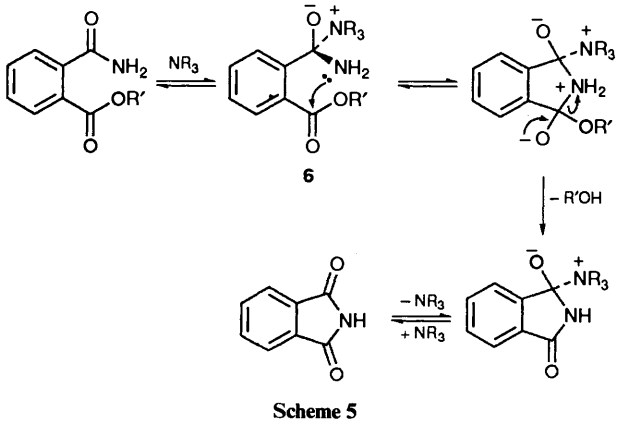
constant differences are two orders of magnitude smaller. The difference in the imidization rate constants implies an influence of the leaving group in the critical transition state. However, the extent of the negative charge located on the oxygen leaving groups may be smaller than that in the hydrolysis of phenyl *o*-(2-imidazolyl)benzoate.

Nucleophilicity and Catalytic Ability.—Amines may act as nucleophiles to attack either the ester carbonyl group or the amide carbonyl group to promote the imidization. For example, tertiary amines and DMAP could conceivably attack the ester group to form an acylium salt intermediate **5**[21] that could further react with the adjacent amide to provide phthalimide (Scheme 4). Nevertheless, generalization of the mechanism to



Scheme 4

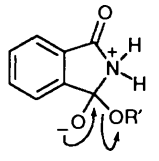
the cases of primary and seconary amines is unlikely because deprotonation of the corresponding acylium salts, which is supposed to be a fast reaction in the basic reaction conditions, would lead to the bis-amides instead of phthalimide as the major products. If the nucleophilic addition of amines to the amide carbonyl group occurred, a zwitterionic tetrahedral intermediate **6** would be generated. In this situation, the lone-pair electrons of the amide nitrogen would no longer be conjugated to the carbonyl group and therefore they would become more nucleophilic. This tetrahedral intermediate would further attack the adjacent ester to induce imidization (Scheme 5). This type of amide activation through a nucleo-



Scheme 5

philic attack was mentioned by Nagasawa and Elberling in the study of the Favorskii rearrangement of α-halolactams.[22] If the nucleophile assisted mechanism operates for the imidization, a correlation between the nucleophilicity of amines and their catalytic ability would be observed. However, our kinetic results are inconsistent with this mechanism. DMAP which shows a very high catalytic activity in nucleophilic acylation reactions[21] is only a moderate catalyst just like the sterically hindered diisopropylethylamine, which is a poor nucleophile and is ineffective in the imidization of butyl phthalamate. In addition, the very poor nucleophile proton sponge shows a higher catalytic ability than the more nucleophilic *N,N*-dimethylaniline in the imidization of phenyl phthalamate.*[,23] These observations are contrary to the predictions based on the nucleophile assisted mechanism. Moreover, this mechanism cannot explain the particularly high catalytic ability of diisopropylethylamine in the imidization of phenyl and trifluoroethyl phthalamate.

Mechanism of Amine Catalyzed Intramolecular Imidization of Alkyl and Phenyl Phthalamates.—Based on all the information obtained from the kinetic studies, a mechanism for the imidization is proposed in Scheme 6. The first step of the reaction involves formation of a hydrogen-bonded complex between the amide and the amine to give intermediate **7**. This assumption is in good agreement with our NMR observations and the results reported in the literature.[24] In general, complex formation results from a fast equilibrium with a low activation energy barrier. The second step involves a reversible intramolecular cyclization during which the lone-pair electrons on the amide nitrogen attack the adjacent ester carbonyl group, along with a simultaneous proton transfer from the amide nitrogen to the hydrogen-bonded amine.[25] The amine molecule in this step functions by removing a proton from the tetrahedral intermediate **8**, thereby avoiding the formation of a high-energy N-protonated amide species **9** during the cyclization. Since the



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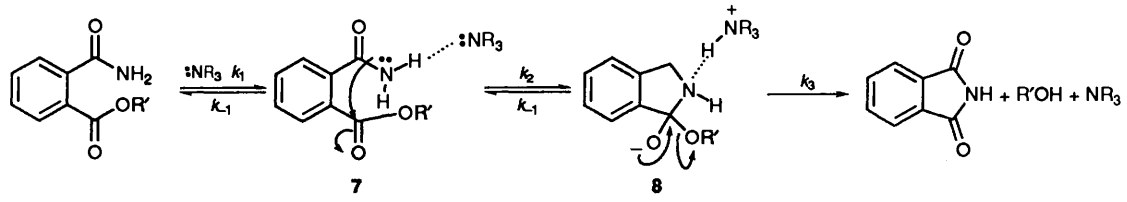
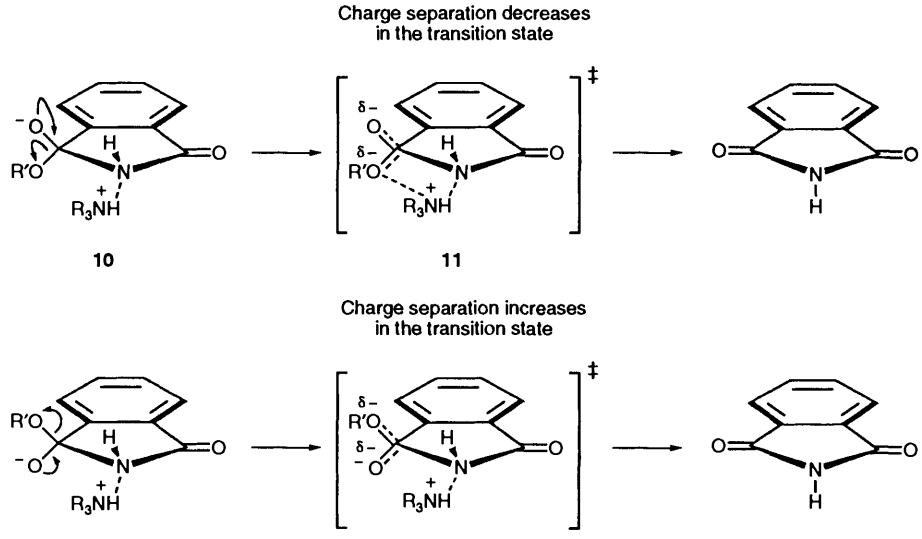
stability of the zwitterionic tetrahedral intermediate **8** is dependent on the extent of proton transfer, this explains the correlation between the amine basicities and their catalytic abilities. An interesting study by Kirby *et al.*[25] on the general base catalysed cyclization of hydantoic esters points out the stereoelectronic problems associated with these cyclizations.

The last step of the reaction sequence involves the expulsion of an oxygen-based leaving group from the tetrahedral intermediate **8**. However, there are two diastereomeric zwitterionic intermediates **10** and **11** that may be formed in the amine assisted cyclization (Scheme 7). Tetrahedral intermediate **10** has the leaving group *syn* to the hydrogen-bonded ammonium ion. When the tetrahedral intermediate collapses, the negative charge localized on the oxygen-based leaving group can be neutralized immediately by the adjacent ammonium ion, and therefore the charge separation involved in the transition state **12** is small. On the other hand, collapse of the *anti* intermediate **11** will inevitably lead to a transient charge separation in the transition state **13**. With relatively good leaving group such as phenolate or trifluoroethoxide, the negative charge localized on the oxygen atom can be stabilized by resonance or by an inductive effect. Therefore, the instability arising from the charge separation is reduced. In both of these cases, both the *syn* and *anti* eliminations, are feasible. However, with a poor leaving group such as butoxy group, the *anti*-

* Because of the steric hindrance, 1,8-bis(dimethylamino)naphthalene (proton sponge) is so poor a nucleophile that it cannot be methylated in normal conditions.



Scheme 6



Scheme 7

elimination that creates a transient charge separation in a nonpolar medium will be highly unfavourable. In this situation, the *syn* elimination through intermediate **10** is expected to be predominant.*,[26] Since the *syn* configuration of **10** is sterically more congested than the *anti* configuration of **11**, its formation would be more sensitive to steric hindrance. For those amines bearing bulky substituents, formation of the *syn* intermediate **10** would be unfavourable and therefore the imidization would be retarded. These considerations explain the exceptionally low catalytic ability of diisopropylethylamine in the imidization of butyl phthalamate.

By applying the steady state conditions to our proposed mechanism, a rate expression for the kinetic law can be deduced and is shown in eqns. (3) and (4). This expression is in good

$$\text{Rate} = k_{\text{overall}}[\text{amine}]\,[\text{phthalamate}] \quad (3)$$

$$k_{\text{overall}} = k_1k_2k_3/(k_{-1}k_3 + k_{-1}k_{-2} + k_2k_3) \quad (4)$$

agreement with our kinetic results which show overall second order kinetics, first order in amines and first order in phthalamates. If the expulsion of the leaving group is the rate determining step, k_3 should be smaller than k_{-2}. Assuming that $k_{-1}k_2 \gg k_3(k_{-1} + k_2)$, eqn. (4) can be simplified to eqn. (5). The

$$k_{\text{overall}} = K'k_3 \quad (5)$$

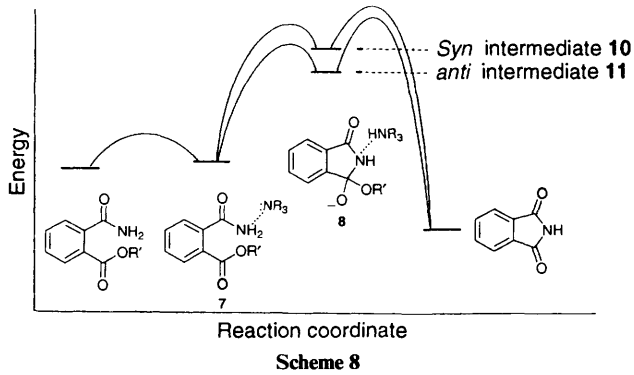
where

$$K' = k_1k_2/k_{-1}k_{-2} = [\mathbf{10} + \mathbf{11}]/[\text{phthalamate}]\,[\text{amine}]$$

term K' is the total equilibrium constant for the formation of the key intermediates **10** and **11**. From this simplified equation, we can understand that the basicity of amines affects the reaction rate by stabilizing the cyclic intermediates **10** and **11** and hence increases the equilibrium constant K'. According to our discussion and hypotheses, a reaction energy profile for the imidization is established in Scheme 8. Since the *anti* intermediate **11** has a smaller charge separation and less steric hindrance, a lower energy is assigned to this intermediate.

Conclusions

Our experimental results demonstrate the importance of amine basicity in the imidization of alkyl or aryl phthalamates. We may be able to elaborate these observations to other organic bases. In particular, in the context of our study of the photochemically induced base-catalyzed preparation of polyimides,[12] we are developing new photoprecursors[14] of bases that are expected to further enhance the imidization step. Similarly, considering the significant roles of carboxylates in enzyme action and their strong basicities in nonpolar sol-



Scheme 8

* A similar *syn* elimination is observed in the amine promoted 1,2-elimination of sulfonylfluoroethanes.[26]

vents,[27] the carboxylate catalyzed intramolecular imidization may be another interesting target to study. Since we predict an involvement of the cyclic zwitterionic intermediate **8** in the reaction, factors governing the equilibrium of ring–chain tautomerism, such as steric assistance effects,[28] may also be pronounced on the imidization reactions. Some of our results concerning these effects will be reported in the near future.

Experimental

General Directions.—M.p.s were measured on a Gallenkamp melting point apparatus. IR spectra were recorded on a Nicolet IR/44 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on solutions in $CDCl_3$, or [$^2H_6$]acetone on an IBM-Bruker AF300 (300 MHz) spectrometer using the solvent proton signal or the solvent carbon signal as an internal standard (J values in Hz). Mass Spectra were obtained on a Hewlett Packard MSD-5971A GC/MS.

Butyl Hydrogen Phthalate.—A mixture of phthalic anhydride (16.9 mmol) and butanol (5 equiv.) was heated at reflux for 4 h, after which the reaction mixture was cooled to room temp., washed with water, extracted with $CHCl_3$, dried (anhyd. Na_2SO_4), and rotary evaporated to dryness to afford a colourless solid in 80% yield (13.5 mmol): m.p. 72–74 °C; ν_{max}/cm^{-1} 3373–2700 (CO_2H), 1716 and 1650 (C=O); δ_H($CDCl_3$) 0.91 (3 H, t, J 7.3), 1.35–1.47 (2 H, m), 1.67–1.74 (2 H, m), 4.31 (2 H, t, J 6.6), 7.40–7.59 (2 H, m), 7.66 (1 H, d, J 7.0), 7.86 (1 H, d, J 7.4) and 11.9 (1 H, br s); δ_C($CDCl_3$) 172.66, 168.12, 133.48, 132.07, 130.64, 129.90, 129.61, 128.62, 65.75, 30.30, 19.05 and 13.55 (Found: C, 65.0; H, 6.4. Calc. for $C_{12}H_{14}O_4$: C, 64.9; H, 6.4; O, 28.8%).

Butyl Phthalamate (**2**)—To a solution of butyl hydrogen phthalate (2.25 mmol) in benzene (10 cm^3) was added a solution of oxalyl chloride (3 equiv.) in benzene (3 cm^3) followed by a few drops of *N*,*N*-dimethylformamide. The reaction mixture was stirred for 2 h, after which the solvent and unreacted oxalyl chloride was removed under reduced pressure. The residue was taken up into benzene (5 cm^3), filtered, and concentrated to provide a crude acid chloride. The crude acid chloride was redissolved in CH_2Cl_2 (10 cm^3) and a solution of 1,1,1,3,3,3-hexamethyldisilazane (3 equiv.) in CH_2Cl_2 (5 cm^3) was added at 0 °C. The mixture was gradually warmed up and stirred at ambient temp. for 8 h after which the mixture was quenched by addition of methanol (20 cm^3) at 0 °C. Stirring was continued for an additional 2 h. The organic phase was washed with dil. H_2SO_4, extracted with ethyl acetate, dried (anhydr. Na_2SO_4), and rotary evaporated to dryness to provide a crude solid. Recrystallization of the crude solid from $CHCl_3$–hexanes gave **2** as colourless crystals in 84% yield (1.89 mmol): m.p. 64–66 °C (lit.,[13] m.p. 64–65 °C); ν_{max}/cm^{-1} 3373, 3175 ($CONH_2$), 1717, 1650 (C=O), 1401, 1259 and 1136; δ_H($CDCl_3$) 0.94 (3 H, t, J 7.4), 1.36–1.49 (2 H, m), 1.65–1.75 (2 H, m), 4.27 (2 H, t, J 6.7), 5.90–5.05 (2 H, br s), 7.43–7.52 (3 H, m) and 7.84 (1 H, d, J 7.2); δ_C($CDCl_3$) 171.78, 167.13, 137.41, 131.78, 129.89, 129.83, 129.74, 127.58, 65.61, 30.52, 19.25 and 13.81 (Found C, 65.3; H, 6.8; N, 6.4. Calc. for $C_{12}H_{15}NO_3$: C, 65.1; H, 6.8; N, 6.3; O, 21.7%).

1,1,1-*Trifluoroethyl Hydrogen Phthalate.*—A mixture of phthalic anhydride (0.1 mol) and 1,1,1-trifluoroethanol (2 equiv.) was heated at reflux for 6 h, after which the mixture was cooled to room temp., taken up into chloroform, and washed twice with water to remove any unreacted trifluoroethanol. The desired acid was extracted into dil. K_2CO_3 solution, separated, and regenerated by acidifying the basic aqueous extracts to provide a white solid. Recrystallization of the white solid from chloroform–hexanes gave 1,1,1-trifluoroethyl hydrogen phthalate in 25% yield (0.025 mol): m.p. 80–82 °C; ν_{max}/cm^{-1} 3300–2400 (CO_2H), 1758 and 1693 (C=O); δ_H($CDCl_3$) 4.68 (2 H, q, J_{HF} 8.4), 7.60–7.71 (3 H, m), 7.93–7.96 (1 H, m) and 10.84 (1 H, br s); δ_C($CDCl_3$) 172.65, 166.66, 132.72, 131.86, 131.73, 130.23, 130.01, 129.09, [128.58, 124.91, 121.24, 117.50 (q, J_{CF} 274)] and [62.33, 61.83, 61.35, 60.86 (q, J_{CF} 37)] (Found: C, 48.6; H, 2.7. Calc. for $C_{10}H_7O_4F_3$: C, 48.4; H, 2.8; O, 25.8; F, 23.0%).

1,1,1-*Trifluoroethyl Phthalamate* (**3**).—Following the procedure for butyl phthalamate (**2**) above, 1,1,1-trifluoroethyl hydrogen phthalate (12.9 mmol) was converted to the corresponding acid chloride, followed by aminolysis with 1,1,1,3,3,3-hexamethyldisilazane (3 equiv.). Since the final phthalamate is sensitive to basic conditions, the reaction mixture was first washed with ice-cooled aq. sulfuric acid before methanolysis. The organic phase was then separated, dried (anhydr. Na_2SO_4) and concentrated under vacuum to provide a viscous oil. The oil was redissolved in methanol (30 cm^3) and allowed to stand at room temp. for 2 h. Rotary evaporation of the methanol gave a white solid which was recrystallized from chloroform to provide **3** as colourless crystals in 73% yield: m.p. 138–140 °C; ν_{max}/cm^{-1} 3374, 3183 (amide NH_2), 1739 and 1650 (C=O); δ_H([$^2H_6$]acetone) 4.74 (2 H, q, J_{HF} 8.8), 6.83 (1 H, br s), 7.39 (1 H, br s), 7.52–7.65 (3 H, m) and 7.75 (1 H, d, J 7.2); δ_C($CDCl_3$) 170.18, 166.77, 138.72, 132.63, 130.72, 130.51, 129.99, 128.50, [130.0 (overlapping with 129.99), 126.32, 122.66, 116.99 (q, J_{CF} 271)] and [62.31, 61.83, 61.36, 60.88 (q, J_{CF} 35)] (Found: C, 48.5; H, 3.0; N, 5.7. Calc. for $C_{10}H_8NO_3F_3$: C, 48.6; H, 3.3; N, 5.7; O, 19.4; F, 23.1%).

Phenyl Phthalamate (**4**).—To a solution of phenol (11.4 mmol) and phthaloyl dichloride (1.2 equiv.) in CH_2Cl_2 (25 cm^3) was added a solution of DMAP (1.2 equiv.) and pyridine (5 cm^3) in CH_2Cl_2 (10 cm^3). The mixture was stirred at room temperature for 3 h after which the mixture was chilled in an ice bath and subsequently added dropwise a solution of 1,1,1,3,3,3-hexamethyldisilazane (3 equiv.) in CH_2Cl_2 (10 cm^3). The reaction mixture was stirred for an additional 6 h and quenched with ice-cooled dil. H_2SO_4 (5%, 100 cm^3). The organic phase was taken up into CH_2Cl_2, washed with saturated aq. NaCl, dried (anhydr. Na_2SO_4) and rotary evaporated to dryness to give a crude oil, which is essentially a silylated amide. The crude oil was then dissolved in MeOH (30 cm^3) and allowed to stand at room temp. for 2 h. Removal of the MeOH under reduced pressure gave a slightly yellowish solid. Flash chromatography of the solid on silica gel, eluting with hexanes–ethyl acetate (1:1.5) led to a white solid. Recrystallization of the solid from chloroform–hexanes (1:2) provided **4** as colourless crystals in 50% yield: m.p. 118–119 °C; ν_{max}/cm^{-1} 3382, 3188 (amide NH_2), 1743 and 1662 (C=O); δ_H($CDCl_3$) 6.09 (1 H, br s), 6.23 (1 H, br s), 7.21–7.24 (3 H, m), 7.35–7.40 (2 H, m), 7.51–7.57 (3 H, m) and 7.98–8.01 (1 H, m); δ_C($CDCl_3$) 171.13, 166.00, 150.96, 137.59, 132.45, 130.53, 130.32, 129.64, 129.36, 127.67, 126.21 and 121.65 (Found: C, 69.5; H, 4.7; N, 5.8. Calc. for $C_{14}H_{11}NO_3$: C, 69.7; H, 4.6; N, 5.8; O, 19.9%).

Kinetic Procedures.—Deuteriated chloroform was stirred over anhydr. potassium carbonate overnight and freshly distilled from P_2O_5 before use. Amines were purified by distillation from CaH_2 or recrystallization from an appropriate solvent according to literature procedures. Kinetics were measured by proton NMR spectroscopy at 40.1 ± 0.05 °C in deuteriated chloroform. In order to avoid any possible interference arising from the reaction between strong amine bases and $CDCl_3$, blank experiments were carried out under similar conditions. These experiments confirmed that under the conditions used for this work no reaction between the amines

and $CDCl_3$ occurred. The rate of decrease of butyl phthalamate was monitored by the disappearance of the triplet at 4.27 ppm (CO_2CH_2–) and the appearance of the triplet at 3.60 ppm ($HOCH_2$–) with the concentrations of amines ranging from 0.05 to 0.5 mol dm^{-3} and the substrate concentration varied from 0.04 to 0.06 mol dm^{-3}. The rate of decrease of phenyl phthalamate was monitored by the disappearance of the multiplet at 7.98–8.01 ppm (ArH of the phthalamate, 1 H) and the appearance of the doublet at 6.79 ppm (*o*-H of phenol, 2 H) with the concentrations of amines ranging from 0.002 to 0.02 mol dm^{-3} and the concentration of the substrate varied from 0.04 to 0.06 mol dm^{-3}. The reaction rate of trifluoroethyl phthalamate was monitored by the disappearance of the quartet at 4.68 ppm ($CO_2CH_2CF_3$) and the appearance of the quarter at 3.90 ppm (CF_3CH_2OH) with the concentrations of amines ranging from 0.005 to 0.02 mol dm^{-3} while the substrate concentration was 0.01 mol dm^{-3}. According to eqn. (6) which is an integral form of eqn. (1), pseudo-first-order rate constants, k_{pseudo}, were obtained from the slope of a plot of $-\ln [\text{phthalamate}]_t/[\text{phthalamate}]_0$ *vs.* reaction time. Second-order rate constants, $k_{overall}$, were obtained from the slope of a plot of k_{pseudo} *vs.* [amine], shown in eqn. (2).

$$-\ln [\text{phthalamate}]_t/[\text{phthalamate}]_0 = k_{pseudo} \times \text{reaction time} \quad (6)$$

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References

1 T. H. Fife, *Adv. Phys. Org. Chem.*, 1975, **11**, 1; F. H. Westheimer, *Adv. Phys. Org. Chem.*, 1985, **21**, 1; J. F. Liebman and A. Greenberg eds., *Mechanistic Principles of Enzyme Activity*, VCH, New York, 1988.
2 A. J. Kirby, *Adv. Phys. Org. Chem.*, 1980, **17**, 183; L. Mandolini, *Adv. Phys. Org. Chem.*, 1986, **22**, 1.
3 B. Capon, M. I. Dosunmu and M. N. M. Sanchez, *Adv. Phys. Org. Chem.*, 1985, **21**, 37; R. Ta-Shma and Z. Rappoport, *Adv. Phys. Org. Chem.*, 1992, **27**, 239.
4 J. F. Liebman and A. Greenberg eds., *Environmental Influences and Recognition in Enzyme Chemistry*, VCH, New York, 1988.
5 W. P. Jencks, *Chem. Rev.*, 1985, **85**, 511; *Chem. Soc. Rev.*, 1981, **10**, 345; *Chem. Rev.*, 1972, **72**, 705; A. Williams and K. T. Douglas, *Chem. Rev.*, 1975, **75**, 627; S. L. Johnson, *Adv. Phys. Org. Chem.*, 1976, **5**, 237; M. L. Bender, *Chem. Rev.*, 1960, **60**, 53.
6 M. D. Joesten and L. J. Schaad, *Hydrogen Bonding*, Marcel Dekker, New York, 1974; M. J. Kamlet, J. L. M. Abbond and R. W. Taft, *Prog. Phys. Org. Chem.*, 1981, **13**, 485; M. Mautner, *Molecular Structure and Energetics*, vol. 4, VCH, 1987, 71; F. Hibbert and J. Emsley, *Adv. Phys. Org. Chem.*, 1990, **26**, 255.
7 E. Caldin and V. Gold, *Proton Transfer Reactions*, Wiley, New York, 1975; F. Hibbert, *Adv. Phys. Org. Chem.*, 1986, **22**, 113.
8 F. M. Menger and J. H. Smith, *J. Am. Chem. Soc.*, 1972, **94**, 3824; C. W. Su and J. W. Watson, *J. Am. Chem. Soc.*, 1974, **96**, 1854; O. B. Nagy, V. Reuliaux, N. Bertrand, A. Van Der Mensbrugghe, J. Leseul, J. B. Nagy, *Bull. Soc. Chim. Belg.*, 1985, **94**, 1055; J. C. Hogan and R. D. Gandour, *J. Org. Chem.*, 1992, **57**, 55 and refs. cited therein.
9 For general reviews, see J. A. Shafer, *The Chemistry of Amides*, ed. J. Zabicky, Wiley Interscience, New York, 1970, p. 685.
10 J. E. H. Hancock and R. P. Linstead, *J. Chem. Soc.*, 1953, 3490; E. Sondheimer and R. W. Holley, *J. Am. Chem. Soc.*, 1953, **76**, 2467.
11 J. A. Shafer and H. Morawetz, *J. Org. Chem.*, 1963, **28**, 1899.
12 J. M. J. Fréchet, J. F. Cameron, C. M. Chung, S. A. Haque and C. G. Willson, *Polym. Bull.*, 1993, **30**, 369.
13 J. F. Cameron and J. M. J. Fréchet, *J. Am. Chem. Soc.*, 1991, **113**, 4303. J. F. Cameron and J. M. J. Fréchet, *J. Org. Chem.*, 1990, **55**, 5919. J. F. Cameron and J. M. J. Fréchet, *J. Photochem. Photobiol. A: Chem.*, 1991, **59**, 105.
14 D. R. McKean, G. M. Walraf, W. Volksen, N. P. Hacker, M. I. Sanchez and J. W. Labadie, *Polym. Mater. Sci. Eng.*, 1992, **66**, 237.
15 R. Pellegata, A. Italia and M. Villa, *Synthesis*, 1985, 517.
16 R. B. Homer and C. D. Johnson, *The Chemistry of Amides*, ed. J. Zabicky, Wiley Interscience, 1970, 187.
17 For references of the hydrogen-bonding ability of amines, see: R. W. Taft, D. Gurka, L. Joris, P. von R. Schleyer and J. W. Rakshy, *J. Am. Chem. Soc.*, 1969, **91**, 4801; D. Gurka and R. W. Taft, *J. Am. Chem. Soc.*, 1969, **91**, 4794; L. Joris, J. Mitsky and R. W. Taft, *J. Am. Chem. Soc.*, 1972, **94**, 3438; E. M. Arnett, E. J. Mitchell and T. S. S. R. Murty, *J. Am. Chem. Soc.*, 1974, **96**, 3875; M. J. Kamlet and R. W. Taft, *J. Am. Chem. Soc.*, 1976, **98**, 377; R. W. Taft, T. Gramstad and M. J. Kamlet, *J. Org. Chem.*, 1982, **47**, 4557.
18 M. Rumeau, *Ann. Chim.*, 1973, **8**, 131; A. Balint Novotny, M. Gracza Lukacs and G. Szasz, *Magy. Kem. Foly.*, 1985, **91**, 44.
19 R. W. Alder, *Chem. Rev.*, 1989, **87**, 1215; R. L. Benoit, D. Lefebvre and M. Fréchette, *Can. J. Chem.*, 1987, **65**, 996.
20 T. H. Fife, R. J. Bambery and B. R. DeMark, *J. Am. Chem. Soc.*, 1978, **100**, 5500; T. H. Fife and B. R. DeMark, *J. Am. Chem. Soc.*, 1979, **101**, 7379.
21 E. F. V. Scriven, *Chem. Soc. Rev.*, 1983, **12**, 129; G. Höfle, W. Steglich and H. Vorbrüggen, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 569.
22 H. T. Nagasawa and J. A. Elberling, *Tetrahedron Lett.*, 1966, 5393.
23 See R. W. Alder, P. S. Bowman, W. R. S. Steele and D. R. Winterman, *J. Chem. Soc., Chem. Commun.*, 1968, 723.
24 I. M. Ginzburg and N. N. Bessonova, *Zh. Obshch. Khim.*, 1974, **44**, 378; J. A. Pullin and R. L. Werner, *Spectrochim. Acta*, 1965, **21**, 1257; F. Takashashi and N. C. Li, *J. Phys. Chem.*, 1965, **69**, 1622, 2950.
25 I. B. Blagoeval, G. Pojarlieff, D. T. Tashev and A. J. Kirby, *J. Chem. Soc., Perkin Trans 2*, 1989, 347.
26 V. Fiandanese, G. Marchese and F. Naso, *J. Chem. Soc., Perkin Trans. 2*, 1973, 1538; *J. Chem. Soc., Chem. Commun.*, 1972, 250.
27 F. M. Menger and A. C. Vitale, *J. Am. Chem. Soc.*, 1973, **95**, 4931 and refs. cited therein.
28 R. E. Valters and W. Flitsch, *Ring–Chain Tautomerism*, Plenum Press, New York, 1985.

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