Effect of Nucleophilicity and Leaving Group Ability on the S_N2 Reactions of Amines with (Acyloxy)alkyl α-Halides: A Product Distribution Study

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The course of the reaction of amines with (acyloxy)alkyl α-halides has been found to depend on the nucleophilicity of the amines and the leaving group ability of the halides. More nucleophilic amines tended to give acylated products **2** from the reaction while less nucleophilic amines gave alkylated products **3**. The use of a better leaving group also tended to favor the formation of a greater amount of alkylated product. These results have been compared to the observations of Westaway on the effect of leaving group ability and nucleophilicity on the bond lengths in the transition state of S_N2 reactions. In addition, secondary amines have been shown to cause the rearrangement of 2-formylbenzamides to 3-amino-1(3*H*)-isobenzofuranones.

The reactions of amines with (acyloxy)alkyl α-halides (**1a** or **9**) lead to unusual results because the halides are ambident electrophiles. A nucleophile such as an amine can react with them at two different electrophilic centers—the carbonyl carbon atom (acylation of the amine) or the halo carbon atom (alkylation of the amine)—to give two different products. Adams[1] has shown that generally the reaction of tertiary amines with (acyloxy)alkyl α-halides gives quaternary salts while the same halide upon reaction with a secondary or primary amine gives the corresponding amides derived from the acyl group. However, Bohme[2] and Volz[3] have shown that (acyloxy)alkyl derivatives of secondary amines can be prepared from the reaction of the (halomethyl)amines with salts of the desired acid, and Wheeler[4] has shown that the reaction of 3-hydroxy-1(3*H*)-isobenzofuranone (**1e**) with secondary amines gives 3-(substituted amino)-1(3*H*)-isobenzofuranones (such as **3c**), so it is clear that the (acyloxy)alkyl derivatives of secondary amines that derive from the reaction of (acyloxy)alkyl α-halides with amines are not too unstable to be isolated but that the reaction conditions that have been used previously were not suitable for their isolation. Since (acyloxy)alkyl derivatives of secondary amines were of interest as a means of latentiating (prodrug) the delivery of drugs containing a carboxylic acid[5] or an amino group, a systematic investigation of the factors influencing the formation of (acyloxy)alkyl derivatives of amines was undertaken to determine which factors favored alkylation of the amine rather than acylation.

The 3-halo-3-substituted and unsubstituted 1(3*H*)-isobenzofuranones were chosen for study as being representative of (acyloxy)alkyl α-halides because the products (**3**) of their reactions with amines were perceived to be more stable[6] and hence easier to isolate and quantitate than their acyclic counterparts. In addition, **3** could be prepared independently by the route mentioned above so their identities could be assured. Finally, although the reactions of aniline,[9-11] methylaniline,[12] and primary amines[11,13] with various 3-halo-1(3*H*)-isobenzofuranones have been reported, the reactions of secondary or tertiary amines[15] with these 3-halophthalides have not been thoroughly investigated.

The amines that were studied in these reactions were chosen to represent as wide a range of nucleophilicities as possible but with as similar steric requirements as could be obtained conveniently. Thus, on the basis of Pearson's n_{CH_3I} values in methanol,[16] we have assumed that the order of nucleophilicity is piperidine (n_{CH_3I} = 7.30) > pyrrolidine (n_{CH_3I} = 7.23) > imidazole (n_{CH_3I} = 4.97). Methylaniline is between pyrrolidine and imidazole based on n_{CH_3I} = 5.70 for aniline and n_{CH_3I} = 5.64 for dimethylaniline while morpholine is only somewhat less nucleophilic than either pyrrolidine or piperidine based on their reactions with 2,4-dinitrochlorobenzene in ethanol (n = 5.29 vs. 5.59 and 5.67, respectively).[17]

The leaving groups in the reactions that have been studied were chloride and iodide. It was felt that they represented sufficiently extreme ends of the leaving group spectrum to give a good idea of how the leaving group effected the product distribution.

Acetone, an aprotic solvent, was chosen as the solvent in which to run the reactions to ensure S_N2-type character in reactions with a substrate that could also undergo S_N1 reactions. The reason for this concern was that it was assumed that if the reaction became more S_N1-like, the resultant intermediate would behave more like a carbenium ion, and MINDO/3 SCF MO calculations[18] on the carbenium ion generated from **1a** indicated that significantly more positive charge resided on the 1-position than on the 3-position in such a carbenium ion.[19] Therefore, if the reaction was more S_N1-like, there would be more acylated and less alkylated products formed because there would be more opportunity for the positive charge being

(1) Ulich, L. H.; Adams, R. *J. Am. Chem. Soc.* **1921**, *43*, 660.
(2) Bohme, H.; Bockhaus, P. *Liebigs Ann. Chem.* **1975**, 1790.
(3) Volz, H.; Ruchti, L. *Liebigs Ann. Chem.* **1977**, 33.
(4) Wheeler, D. D.; Young, D. C.; Erley, D. S. *J. Org. Chem.* **1957**, *22*, 547.
(5) Sloan, K. B. European Patent 81 106 277.7, Dec 1981.
(6) Normal $B_{AC}2$ cleavage of the ester portion of an (acyloxy)alkyl α-amine such as **3c** would generate a nucleophile capable of causing an intramolecular-based recyclization of the ring-opened species similar to that implicated in the ring closure of *o*-(hydroxymethyl)benzoates to phthalide[7] and the hydrolysis of methyl *o*-formylbenzoate to **1e**. Such intramolecular assistance to reversing the hydrolysis reaction is not possible with acyclic systems.
(7) Cain, B. *J. Org. Chem.* **1976**, *41*, 2029.
(8) Bender, M. L.; Reinstein, J. A.; Silver, M. S.; Mikulak, R. *J. Am. Chem. Soc.* **1965**, *87*, 4545.
(9) Halford, J. O.; Weissmann, B. *J. Org. Chem.* **1952**, *17*, 1646.
(10) Pojer, P. M.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1968**, *21*, 1378.
(11) Kubota, Y.; Tatsuno, T. *Chem. Pharm. Bull.* **1971**, *19*, 1226.
(12) Wawzonek, S.; Laitinen, H. A.; Kwiatkowski, S. J. *J. Am. Chem. Soc.* **1944**, *66*, 830.
(13) The reaction of adenine with 5-bromo-4-ethyl-3-methyl-2(5*H*)-furanone[14] should also be considered as a member of this type of reaction in spite of the unusual cyclic product obtained.
(14) Doerr, I. L.; Willetts R. E. *J. Org. Chem.* **1973**, *22*, 3878.
(15) Bodor, N.; Wood, R.; Raper, C.; Kearney, P.; Kaminski, J. J. *J. Med. Chem.* **1980**, *23*, 474.
(16) Pearson, R. G.; Sobel, H.; Songstad, J. *J. Am. Chem. Soc.* **1968**, *90*, 319.
(17) Hall, H. K. *J. Org. Chem.* **1964**, *29*, 3539.
(18) Bingham, R. C.; Dewar, M. J. S.; Lo, D. H. *J. Am. Chem. Soc.* **1975**, *97*, 1285.
(19) Bodor, N., private communication, The University of Florida, Gainesville, FL.

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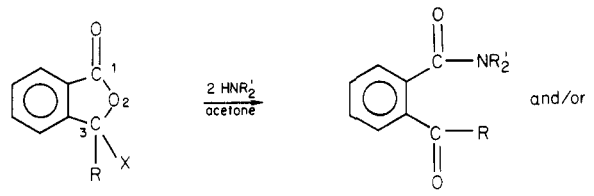
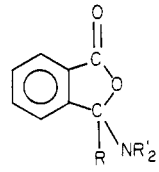
Scheme I

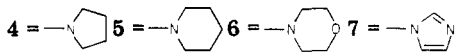


1a, R = H; X = Cl
b, R = C_6H_5; X = Cl
c, R = CH_3; X = Cl
d, R = H; X = I
e, R = H; X = OH
f, R = CH_3; X = OH

2a, R = H; NR'_2 = 4
b, R = H; NR'_2 = 5
c, R = H; NR'_2 = 6
d, R = H; NR'_2 = 7
e, R = H; NR'_2 = $NCH_3C_6H_5$
f, R = C_6H_5; NR'_2 = 6
g, R = CH_3; NR'_2 = 6



3a, R = H; NR'_2 = 4
b, R = H; NR'_2 = 5
c, R = H; NR'_2 = 6
d, R = H; NR'_2 = 7
e, R = H; NR'_2 = $NCH_3C_6H_5$
f, R = C_6H_5; NR'_2 = 7
g, R = CH_3; NR'_2 = 6

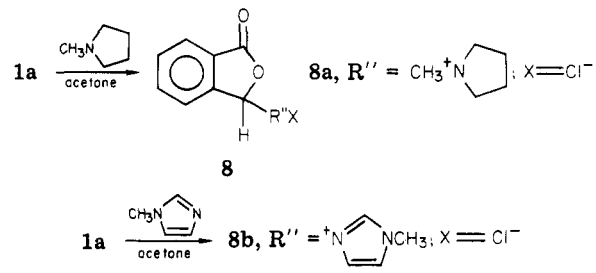


generated at the 3-position to redistribute to the 1-position and hence more opportunity for the amine to react at the 1-position to give acylated products. Thus, it was important to run the reactions under S_N2 conditions to maximize alkylation, and it was assumed that these were S_N2 reactions although the reactions were too fast under the conditions used to determine the order of the reactions. It was also assumed that acetone was not playing a role as a nucleophile in the reactions since acetone is generally considered to be a solvent of relatively low nucleophilicity (N).[20]

Although the n_{CH_3I} and n values were obtained in methanol[16] and ethanol,[17] respectively, it has been assumed that the relative nucleophilicities of the amines have remained constant for the transfer of the reactions to acetone, since Parker[21] has shown that the reactions on which the n_{CH_3I} and n values are based, i.e., N: + RX $\rightleftarrows$ [$^{\delta+}$N–R–X$^{\delta-}$] $\rightleftarrows$ $RN^+ + X^-$, are rather insensitive to protic–dipolar aprotic solvent-transfer effects.

Reaction at the 1-position (acylation, i.e., reaction at a carbonyl) can take place as well as at the 3-position (alkylation). However, the N_+ scale of Ritchie[22] gives a similar rank order for the relative nucleophilicities of the amines from their reactions with ester carbonyl groups in water as does n_{CH_3I} for alkylations. Thus, piperidine (N_+ = 6.11), morpholine (N_+ = 5.25), and imidazole (N_+ = 3.66) fit the trend of n_{CH_3I} and n rank order. Aniline (N_+ = 4.10), on the other hand, behaves more like an α-nucleophile on the basis of the N_+ criteria. Despite the fact that the N_+ scale was developed from reactions in water, the fact that the rank order is the same suggests that the rank order of nucleophilic reaction at electrophilic centers at either the 1- (acylation) or the 3-position (alkylation) should be the same and no unusual reversal of reactivities or preferences for electrophilic sites should obscure the results.

Scheme II



Results and Discussion

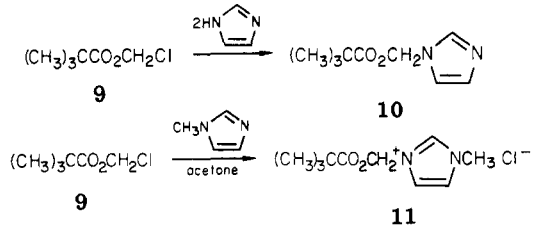
The reactions between hydroxyphthalide **1e** and the secondary amines (Scheme I) all gave the corresponding **3** except for imidazole. The reaction with imidazole gave a salt that tentatively has been assigned as the imidazole salt of 2-formylbenzoic acid. Careful heating of the salt at 50 °C gave a mixture that appeared to contain some **3d** by NMR spectroscopy and TLC, but it could not be isolated. Similarly, the reaction of **1f** with morpholine at room temperature gave a mixture containing an unstable intermediate as a major product (80%) that was neither acylated product (by comparison of its NMR spectrum with that of **2g**) nor alkylated product **3g** on the basis of the chemical shift of its CH_3C absorption (δ 2.47). The minor product (20%) did contain a CH_3C absorption (δ 1.77) that a product such as **3g** might be expected to exhibit. With time (3 days) at room temperature the absorption at δ 1.77 increased to represent 40% of the mixture while the absorption at δ 2.47 decreased accordingly, and a small absorption (<10%) at δ 2.6 (**2g**) appeared. However, when the reaction was heated at 120 °C for 1 h the remaining intermediate was converted to **2g** as determined by comparing the NMR spectrum and the TLC of the mixture with authentic **2g**. The product exhibiting the CH_3C absorption at δ 1.77 was not isolated.

The reactions between the chloride **1a** and the more nucleophilic amines piperidine, pyrrolidine, and morpholine gave only the acylated products **2** while the reaction between **1a** and the less nucleophilic imidazole and methylaniline gave only the alkylated products **3**. The reaction between **1a** and the tertiary amines (Scheme II) gave the expected quaternary salts **8a** and **8b**. The salts exhibited only one well-defined carbonyl absorption in the IR, hence eliminating alternative structures that would arise from acylation of the amines, e.g., **13**. The structure of **8b** was assigned the symmetrical structure as shown on the basis of analogy to the structure of 1,3-dimethylimidazolium iodide.[23] The course of the reaction of methylimidazole and N-methylpyrrolidine with **1a** was followed from t = 1 min to completion by NMR spectroscopy. There was no sign of an aldehyde absorption in the spectra of those reactions. The reaction of the amines with **1a** could also be run in the presence of powdered K_2CO_3 instead of a second equivalent of amine to give essentially the same qualitative results. However, the reaction had to be run for 16 h in order to get complete reaction because the limited solubility of K_2CO_3 in acetone became rate limiting.

The reaction of the acyclic (acyloxy)alkyl α-halide **9** with imidazole and mehthylimidazole (Scheme III) gave **10** and **11**, respectively. The reaction of **9** with pyrrolidine, on the

(20) Schadt, F. L.; Bentley, T. W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1976**, *98*, 7667.
(21) Parker, A. J. *Chem. Rev.* **1969**, *69*, 1.
(22) Ritchie, C. D. *J. Am. Chem. Soc.* **1975**, *97*, 1170.
(23) Overberger, C. G.; Salamone, J. C.; Yaroslavsky, S. *J. Org. Chem.* **1965**, *30*, 3580.

Scheme III



other hand, in keeping with the results of Adams,[1] gave what appeared to be the pivalylamide on the basis of identical chemical shifts of the NCH_2 in this product and **2a**.

The reaction between the amines and the iodide **1d** gave the same results as their reaction with **1a** except for the reactions of **1d** with piperidine and morpholine. In those cases, instead of only the acylated products being formed, mixtures of acylated and alkylated products were obtained with the less nucleophilic amine giving more of the alkylated product (see Experimental Section).

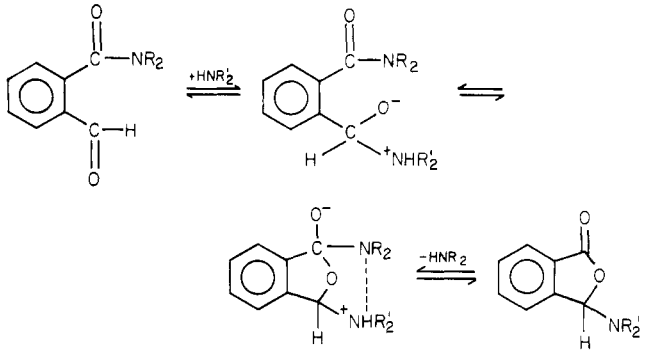
It does not seem reasonable that the difference in the amount of alkylated products obtained from the reaction of these two amines with **1d** can be attributed to differences in steric requirements that might favor the reaction of piperidine at the 1-position and of morpholine at the 3-position, so that the difference must be due to differences in their nucleophilicities. These results were also quite reproducible in terms of the difference in the amount of alkylated product formed from the respective amines although the absolute amounts formed seemed to vary somewhat with the care taken to exclude moisture in any particular series of reactions.

It was not possible to convert the tertiary chlorides **1b** or **1c** to their respective iodides because of the known failure of the Finkelstein exchange reaction to work well with tertiary chlorides. It was not even possible to isolate the iodide when it was run in the presence of $FeCl_3$ in aprotic nonpolar solvents.[24]

In order to establish that the acylated product was not formed first in each reaction of **1d** with amine and that the acylated product then rearranged to the alkylated product, the reactions between **2** and amines were followed by NMR spectroscopy. There was no reaction at all between pyrrolidine and **2a** or piperidine and **2b** except some broadening of the CH=O absorption was observed. However, the reaction between **2c** and 0.1 equiv of morpholine resulted in the conversion of about 4% of the acylated product to alkylated product per day. Integration of the combined CH=O and O–CHN absorptions always accounted for 100% of the integration of the aromatic H absorptions. After 1 month **3c** was isolated in 60% yield from the reaction. On the other hand, when 1 equiv of pyrrolidine was allowed to react with **2c**, an immediate and complete loss of the sharp CH=O absorption was observed followed by the initial appearance of the O–CHN absorption at δ 6.43 due to the formation of **3a**. After 3.5 h the integration of the O–CHN absorption at δ 6.43 suggested that 25% of the mixture was **3a** while the integration of a new peak at δ 6.11 due to the O–CHN absorption of **3c** suggested 5% of the mixture was **3c**. After 3 days a mixture of 65% **3a** and 35% **3c** had formed, which did not change with time. Since an excess of morpholine was not present during the reaction of **1d** with morpholine (certainly less than 0.1 equiv) and the rate of conversion of **2c** to **3c** was slow compared to the time taken to run

(24) Miller, J. A.; Nunn, M. J. *Tetrahedron Lett.* **1975**, 2691.

Scheme IV



the reaction of morpholine with **1d**, we can assume that the product distribution observed from the reaction of **1d** with morpholine was due to the initial reaction and was not an artifact caused by a subsequent fast rearrangement of **2c** to **3c**.

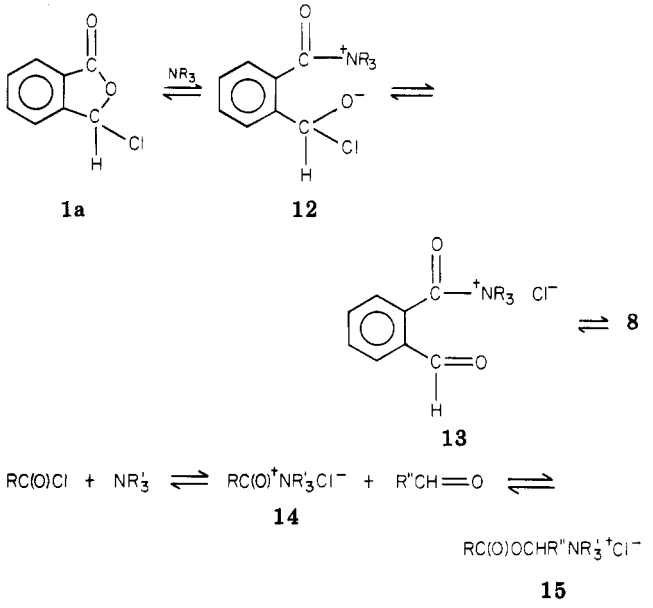
A mechanism for the rearrangement of **2c** to **3c** or **3a** can be envisaged that is similar to the mechanism for formation of **3c** from methyl *o*-formylbenzoate proposed by Bender[8] and for similar reactions investigated by Roedig[25] (see Scheme IV). The fact that the reaction of pyrrolidine with **2c** initially gave only **3a** substantiates the suggestion that an intermolecular attack by an amine is responsible for the rearrangement and that an internal rearrangement apparently does not occur. This represents the first reported instance of an addition compound of an aldehyde functioning as an intramolecular nucleophile in the cleavage of an amide.

Thus, certain qualitative conclusions can be drawn. The reactions of secondary amines with **1a** were dependent on the nucleophilicity of the amine and the leaving group ability of the halide. More nucleophilic amines tended to give acylated products while less nucleophilic amines gave alkylated products. However, even the more nucleophilic amines could be caused to give some alkylated product by changing the leaving group to a better leaving group. The only exception to this trend was pyrrolidine in its reaction with either **1a** or **1d** where products of an unknown composition were formed in addition to **2a**. The reactions of **1b** or **1c** with morpholine and imidazole or **9** with pyrrolidine and imidazole also fit this trend. The more nucleophilic morpholine gave acylated products **2f** and **2g** respectively from its reaction with **1b** and **1c**, while imidazole gave the alkylated product **3f** from its reaction with **1b**. Similarly, the more nucleophilic pyrrolidine gave an acylated product and the less nucleophilic imidazole gave an alkylated product upon their respective reactions with **9**.

It is suggested that the reason that tertiary amines gives only alkylated products regardless of nucleophilicity is that, although both routes of reactions are available to them, the comparable acylated product **12** $\rightleftarrows$ **13** (Scheme V) is not stable compared to **8**. In fact, no aldehyde absorption such as might be exhibited by **13** was observed by NMR spectroscopy during the reaction of **1a** with tertiary amines (Scheme II). In this regard, it should be noted that Adams[26] observed that quaternary salts of acyclic (acyloxy)alkyl α-halides **15** could be prepared by allowing an acid chloride to react with a tertiary amine and then by allowing that product (**14**) to react with the desired aldehyde. Thus, **13** represents the combination of **14** and aldehyde in an intramolecular form, so that even if **13** is

(25) Roedig, A.; Ganns, E. M. *Liebigs Ann. Chem.* **1982**, 406.
(26) French, H. E.; Adams, R. *J. Am. Chem. Soc.* **1921**, *43*, 651.

Scheme V



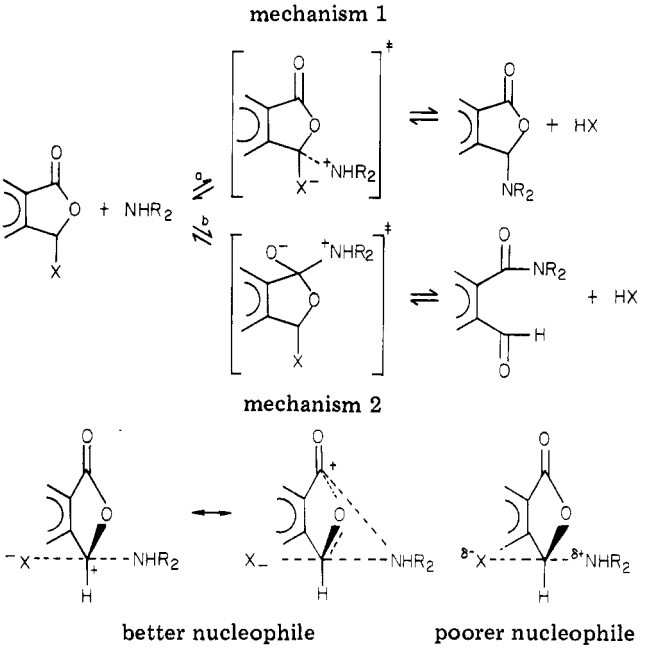
formed transiently, its facile conversion to 8 should be expected.

Assuming that these reactions that have been studied are S_N2 reactions, at least two mechanisms can be drawn to account for the effect of nucleophilicity and nucleofugicity (leaving group ability) on the product distribution that has been observed from the reactions of amines with (acyloxy)alkyl α-halides (Scheme VI). The first mechanism[27] involves amine attack directly at either the 1- (acylation, path b) or the 3-position (alkylation, path a) of the halide in its ground state. Since the distribution of positive charge in the ground state should remain constant for the reaction of each of the amines, this mechanism, in order to rationalize the observed results, implies that less basic amines react faster at the 3-position while more basic amines react faster at the 1-position. It also implies then that the rank order of reactivity of the amines should be different for the different positions, i.e., that imidazole and anilines are better alkyl halide nucleophiles than piperidine and morpholine while the opposite order obtains in their reactions with carbonyls. However, the fact that the rank order of the amines on the N_+ (with carbonyls)[22,27] and the n[17] or n_{CH_3I}[16] scale is the same argues against such a mechanism.

On the other hand, if, as the amine nucleophile approaches the halide molecule, the ground state of the halide is perturbed in some way that is dependent on the nucleophile and the leaving group, then differentiation of the distribution of the positive charge between the 1- and the 3-positions becomes possible. This second mechanism is represented by two transition states (Scheme VI) that would account for the product distribution observed from the reactions. It is suggested that with the better nucleophiles a looser transition state obtains where the positive charge is freer to redistribute (more acylation), whereas with the poorer nucleophiles a tigher transition state results (more alkylation).

If the above qualitative trends are correct, then the usual classification of changes in leaving group ability or nucleophilicity as leading to more reactant- or product-like transition states is not completely satisfactory for these reactions. For instance, if we assume that as the nucleophile approaches **1a** a partial positive charge develops on the 3-carbon and that the positive charge has a certain amount of freedom to redistribute to the 1-carbon (based on the MINDO/3 calculation),[19] then a longer carbon–nucleophile bond (reactant-like) in the transition state would enable the nucleophile to be freer to attack the position carrying the greatest positive charge and, in that case, result in more acylation. Thus, the Hammond postulate,[28] which suggests that changing to a better leaving group in an S_N2 reaction[29] should lead to a more reactant-like transition state with a longer carbon–nucleophile bond and a shorter carbon–leaving group bond, would predict more acylation from the reaction of **1d** with amines on the basis of the above analysis of the consequences of the approach of the nucleophile to **1a**. This is the opposite of what has been observed. It is suggested that, on the basis of the product distribution results, a shorter carbon–nucleophile bond in the transition state must have resulted upon changing to a better leaving group so that less acylation was observed.

Scheme VI



Recently, Westaway[29] has suggested that a change to a better leaving group in S_N2 reactions should actually cause the bond between carbon and nucleophile to be much more fully formed and the bond to the leaving group be essentially unchanged in the transition state. This prediction would fit the trend that we have observed.

Westaway's predictions were partially based on an analysis of the change in Hammett ρ values obtained when leaving group ability was varied. Using that data base, it was possible to generate a complementary set of ρ values[30] for when the nucleophilicity of the attacking group was varied. Analysis of those values suggested that S_N2 reactions with a stronger nucleophile should result in greater carbon–leaving group bond breaking in the transition state than with a weaker nucleophile. It is suggested that applying the above analysis to the present case, a weaker nucleophile, since it causes less advanced carbon–leaving group bond breaking in the transition state, a less free positive charge, and hence less opportunity for positive

(27) Kindly brought to our attention by a reviewer.

(28) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.
(29) Westaway, K. C.; Ali, S. F. *Can. J. Chem.* **1979**, *57*, 1354.
(30) Pross, A.; Shaik, S. S. *J. Am. Chem. Soc.* **1981**, *103*, 3702.

charge redistribution, should undergo significantly more alkylation than acylation compared to its more nucleophilic counterpart. Again, this prediction would fit the trend that we have observed in these S_N2 reactions.

Although it is recognized that the (acyloxy)alkyl α-halide system studied here is not a clean system upon which to base theoretical considerations[29] and the results obtained are qualitative in nature, the interpretation of the results from the reaction of the (acyloxy)alkyl α-halide system with amines is of practical importance not only because of its application to predicting the course of the reaction of other nucleophiles with this system but also because of the possibility of extrapolating this interpretation to predicting the course of reactions of amines and other nucleophiles with similar systems such as those that undergo allylic rearrangement during substitution. Finally, these results provide an independent verification of the predictions of Westaway[29] and Pross and Shaik[30] on the effect of leaving group ability and nucleophilicity on the course of S_N2 reactions in a practical application.

Experimental Section

^1H NMR spectra were recorded on a Varian T-60 instrument and IR spectra on a Beckman Acculab 4 spectrophotometer. Melting points (uncorrected) were determined on a Thomas-Hoover capillary apparatus. Microanalyses were performed by Atlantic Microlab, Inc., of Atlanta, GA. Unless otherwise specified the chemicals were obtained from Aldrich except for the bulk solvents, which were obtained from Fisher. TLC analyses were run on Brinkman Polygram Sil G/UV 254. The amines were freshly redistilled from KOH before use. The anhydrous NaI was stored in a vacuum desiccator until immediately before use, and the acetone was stored over 4A 8–12 mesh molecular sieves before it was used. The silica gel used was Mallinckrodt SilicAR CC-7.

Preparation of the 3-Chloro-1(3*H*)-isobenzofuranones (3-Chlorophthalides): 3-Chloro-1(3*H*)-isobenzofuranone (1a). Typically, 4.0 g (0.0267 mol) of 3-hydroxyphthalide (**1e**) was allowed to react with 10 mL of $SOCl_2$ at 110 °C for 1 h in the presence of 2 mg of $FeCl_3 \cdot 6H_2O$. The $SOCl_2$ was evaporated at reduced pressure and the residue extracted with 80 mL of boiling hexane. The hexane suspension was filtered while hot and the filtrate concentrated to give the desired product as a white solid (80–90% yield): mp 57–59 °C (lit.[31] mp 61 °C); IR (KBr) 1790 cm^{-1} (s, C=O); ^1H NMR ($CDCl_3$) δ 7.07 (s, 1, OCHCl), 8.0–7.35 (m, 4, Ar). The residue from the hexane extraction showed the following: mp 206–213 °C; IR (KBr) 1775 cm^{-1} (s, C=O); ^1H NMR ($CDCl_3$) δ 6.87 (s, 1, OCHO), 8.1–7.55 (m, 4, Ar H).

3-Chloro-3-phenyl-1(3*H*)-isobenzofuranone (1b). The product was obtained from 2-benzoylbenzoic acid as an oil in 73% yield by using the same reaction conditions and extraction procedure as above: IR (KBr) 1790 cm^{-1} (s, C=O); ^1H NMR ($CDCl_3$) δ 8.0–7.2 (m, Ar H). The oil was too unstable to obtain good elemental results and had to be prepared fresh before being used in reactions.

3-Chloro-3-methyl-1(3*H*)-isobenzofuranone (1c). The product was obtained by heating 0.5 g (0.003 mol) of 2-acetylbenzoic acid with 1 mL of $SOCl_2$ at 100 °C until evolution of gas stopped. The hot solution was then triturated with hexane to give 0.45 g (mp 54–58 °C, 82% yield, lit.[10] mp 57–58 °C) of the desired product: IR (KBr) 1730 cm^{-1} (s, C=O); ^1H NMR ($CDCl_3$) δ 8.0–7.4 (m, 4, Ar H), 2.2 (s, 3, CH_3CO), identical with the literature spectrum.

Preparation of 3-Iodo-1(3*H*)-isobenzofuranone (1d). Typically, the chloride **1a** was dissolved in acetone and allowed to react with an equivalent of NaI for 36 h. The suspensions that were obtained were used as they were, although analysis of NMR spectra of such reaction mixtures showed that there were faint absorptions that could be attributed to aldehyde and starting material in addition to the major product the iodide: ^1H NMR (acetone) δ 10.45 (CH=O), 7.41 (OCHCl), 8.15 (OCHI), respectively, relative to acetone at δ 2.07. In one case the iodide was isolated by chromatography as a light yellow solid that very rapidly turned into a brownish-red waxy gum even on storage in a desiccator protected from light.

Reactions between 3-Hydroxy-1(3*H*)-isobenzofuranone (3-Hydroxyphthalide) and Amines. Equal molar amounts of the amine and 3-hydroxyphthalide (**1e**) were mixed without solvent. The exothermic reaction was allowed to cool, and then the solid mass was crystallized to give the following products:

3-(4-Morpholinyl)-1(3*H*)-isobenzofuranone (3c) from hexane to give the product as white crystals (91% yield): mp 125–126.5 °C (lit.[4] mp 127–128 °C); TLC (silica gel, ether) R_f 0.29.

3-(1-Piperidyl)-1(3*H*)-isobenzofuranone (3b) from hexane to give the product as beige crystals (81% yield): mp 97–99 °C; IR (KBr) 1740 cm^{-1} (s, C=O); ^1H NMR ($CDCl_3$) δ 7.9–7.2 (m, 4, Ar H), 6.13 (s, 1, OCHN), 2.83–2.40 (m, 4, CH_2N), 1.73–1.23 (m, 6, CH_2); TLC (silica gel, ether) R_f 0.48.

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.90; H, 6.93; N, 6.42.

3-(1-Pyrrolidyl)-1(3*H*)-isobenzofuranone (3a) from hexane to give the product as white crystals: mp 99–100 °C; TLC (silica gel, ether) R_f 0.40; IR (KBr) 1740 cm^{-1} (s, C=O); ^1H NMR ($CDCl_3$) δ 8.0–7.3 (m, 4, Ar H), 6.43 (s, 1, OCHN), 2.77 (t, 4, J = 6 Hz, CH_2N), 2.0–1.6 (m, 4, CH_2).

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.87; H, 6.48; N, 6.85.

3-(*N*-Methylanilino)-1(3*H*)-isobenzofuranone (3e) from CH_3OH to give the product as white crystals (71% yield): mp 151.5–153 °C (lit.[4] mp 158–159 °C); TLC (silica gel, ether–CH_3OH, 10:1) R_f 0.66; IR (KBr) 1755 cm^{-1} (s, C=O); ^1H NMR ($CDCl_3$) δ 8.0–6.95 (m, 9, Ar H), 6.87 (s, 1, OCHN), 2.63 (s, 3, CH_3N).

Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.29; H, 5.48; N, 5.86. Found: C, 75.32; H, 5.51; N, 5.83.

Imidazole Salt of 2-Formylbenzoic Acid: mp 65–71 °C; IR (KBr) broad acidic OH and NH^+, 1775 (m), 1690 cm^{-1} (s, C=O); ^1H NMR ($CDCl_3$) δ 12.5 (2, NH^+), 9.10 (s, 1, CH=O), 8.03 (s, 1, CHN), 7.85–7.35 (m, 4, Ar H), 7.03 (s, 2, NCH=CHN).

Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.75; H, 4.64; N, 12.60.

Reactions between 3-Chloro-1(3*H*)-isobenzofuranone (3-Chlorophthalide) and Amines. Two equivalents of secondary amine (0.006 mol) in acetone (5 mL) was added to a well-stirred acetone (10 mL) solution of the 3-chlorophthalide (0.003 mol). The reaction was stirred at room temperature for 1 h, diluted with ether, and filtered. The filtrate was concentrated and the concentrate chromatographed on silica gel with ether as the eluent or crystallized directly from the crude reaction mixtures to give the following products:

4-(2-Formylbenzoyl)morpholine (2c) from morpholine by extracting the crude reaction mixture with hexane and concentrating the hexane to give the product as cream-colored crystals (82% yield): mp 79–82 °C; TLC (silica gel, ether) R_f 0.11; IR (KBr) 1705 (s, C=O), 1630 cm^{-1} (s, C=O); ^1H NMR δ 9.97 (s, 1, CH=O), 8.0–7.2 (m, 4, Ar H), 3.8 (s, 4, CH_2O), 3.7–3.37 (m, 2, CH_2NC=O), 3.37–2.93 (m, 2, CH_2NC=O).

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.72; H, 5.97, N, 6.42. Found: C, 65.66; H, 6.03; N, 6.37.

1-(2-Formylbenzoyl)piperidine (2b) from piperidine after chromatography to give the product as a light yellow oil (61% yield): TLC (silica gel, ether) R_f 0.17; IR (neat) 1700 (s, C=O), 1630 cm^{-1} (s, C=O); ^1H NMR ($CDCl_3$) δ 10.0 (s, 1, CH=O), 8.0–7.2 (m, 4, Ar H), 3.93–3.53 (m, 2, CH_2NC=O), 3.3–2.97 (m, 2, CH_2NC=O), 2.15–1.2 (m, 6, CH_2).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.97; H, 6.96; N, 6.43.

1-(2-Formylbenzoyl)pyrrolidine (2a) from pyrrolidine after chromatography to give the product as a light yellow oil (38% yield): TLC (silica gel, ether) R_f 0.09; IR (neat) 1700 (s, C=O), 1635 cm^{-1} (s, C=O); ^1H NMR ($CDCl_3$) δ 10.0 (s, 1, CH=O), 8.0–7.2 (m, 4, Ar H), 3.87–3.4 (m, 2, CH_2NC=O), 3.27–2.87 (m, 2, CH_2NC=O), 2.25–1.55 (m, 4, CH_2).

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.84; H, 6.49; N, 6.80.

3-(1-Imidazolyl)-1(3*H*)-isobenzofuranone (3d) from imidazole by crystallization of the crude reaction mixture from CH_2Cl_2–hexane (2:1) to give the product as light yellow crystals

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(87% yield): mp 110–113 °C; IR (KBr) 1765 cm^{-1} (s, C=O); ^1H NMR ($CDCl_3$) δ 8.15–7.33 (m, 5, Ar H and OCHN), 7.15 (s, 1, NCH), 7.07 (s, 1, NCH), 6.73 (s, 1, NCH); TLC (silica gel, ether–CH_2Cl_2, 1:1) R_f 0.12.

Anal. Calcd for $C_{11}H_8N_2O_2$: C, 65.99; H, 4.03; N, 14.00. Found: C, 66.00; H, 4.08; N, 13.98.

3-(*N*-Methylanilino)-1(3*H*)-isobenzofuranone (3e) from *N*-methylaniline by crystallization of the crude reaction mixture from CH_3OH to give the desired product as white crystals (62% yield), mp 153–155 °C, identical with the product from the reaction between the amine and 3-hydroxy-1(3*H*)-isobenzofuranone by TLC and spectroscopy.

In addition, the reaction of 1 equiv of tertiary amine with 3-chlorophthalide in acetone gave the following products:

3-(1-Methyl-1-pyrrolidinio)-1(3*H*)-isobenzofuranone chloride (8a) from *N*-methylpyrrolidine by crystallization from acetone to give the product as white crystals (96% yield); mp 180–182 °C dec; IR (KBr) 1810 cm^{-1} (s, C=O); ^1H NMR ($CDCl_3$) δ 8.15 (s, 1, $OCHN^+$), 8.2–7.5 (m, 4, Ar H), 5.13–4.5 (m, 1, CH_2N^+), 4.5–4.0 (m, 1, CH_2N^+), 4.0–3.4 (m, 2, CH_2N^+), 2.93 (s, 3, CH_3N^+), 3.0–2.0 (m, 4, CH_2).

Anal. Calcd for $C_{13}H_{16}NO_2Cl·0.75\ H_2O$: C, 58.42; H, 6.60; N, 5.26. Found: C, 58.42; H, 6.67; N, 5.22.

3-(3-Methyl-1-imidazolio)-1(3*H*)-isobenzofuranone chloride (8b) from *N*-methylimidazole by crystallization from acetone to give the product as white crystals (91% yield): mp 220–222 °C; ^1H NMR (Me_2SO-d_6) δ 9.75 (s, 1, $NCH=N^+$), 8.07 (s, 1, $OCHN^+$), 8.2–7.7 (m, 7, Ar H and $NCH=CHN^+$), 3.9 (s, 3, CH_3N^+); IR (KBr) 1795 cm^{-1} (s, C=O).

Anal. Calcd for $C_{12}H_{11}ClN_2O·0.25\ H_2O$: C, 56.47; H, 4.54; N, 10.98. Found: C, 56.58; H, 4.62; N, 10.94.

Reactions between 3-Chloro-3-phenyl-1(3*H*)-isobenzofuranone and Amines. An equivalent amount of the secondary amine was allowed to react with the chlorophthalide in the presence of an equivalent of powdered K_2CO_3 in actone with vigorous stirring for 24 h. The mixture was then filtered and the filtrate concentrated. The concentrated residue was crystallized to give the following products:

4-(2-Benzoylbenzoyl)morpholine (2f) from morpholine by extracting the crude mixture with hexane to give the desired produce as beige crystals (47% yield): mp 76–79° (hexane); TLC (silica gel, ether) R_f 0.12; IR (KBr) 1665, 1630 cm^{-1} (s, C=O); ^1H NMR ($CDCl_3$) δ 7.85–7.15 (m, 9, Ar H), 3.75–3.2 (m, 8, NCH_2CH_2O).

Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.11; H, 5.81; N, 4.72.

3-Phenyl-3-(1-imidazolyl)-1(3*H*)-isobenzofuranone (3f) from imidazole by crystallization from CH_2Cl_2–hexane, 10:40, to give the product as white crystals (73% yield): mp 74–76 °C; TLC (silica gel, ether) R_f 0.06; IR (KBr) 1775 cm^{-1} (s, C=O); ^1H NMR ($CDCl_3$) δ 8.15–7.5 (m, 4, Ar H), 7.43 (s, 6, Ar H and NCH), 7.07 (s, 1, CHN), 6.73 (s, 1, CHN).

Anal. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.66; H, 4.43; N, 10.08.

Reaction between 3-Chloro-3-methyl-1(3*H*)-isobenzofuranone and Morpholine. This reaction was run as above with K_2CO_3 as the acid scavenger to give 4-(2-acetyl)benzoylmorpholine (**2g**) as light yellow crystals (50% yield): mp 121–123 °C; IR (KBr) 1680, 1625 cm^{-1} (s, C=O); ^1H NMR ($CDCl_3$)δ 7.85–7.1 (m, 4, Ar H), 3.83 (s, 4, CH_2O), 4.05–3.4 (m, 2, $CH_2NC=O$), 3.35–3.0 (m, 2, $CH_2NC=O$), 2.6 (s, 3, $CH_3C=O$).

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.69; H, 6.52; N, 5.93.

Reactions between Chloromethyl Pivalate (9) and Amines. Two equivalents of imidazole were allowed to react with the pivalate in acetone at room temperature overnight. The mixture was diluted with ether and filtered. The filtrate was concentrated to give 1-[(pivalyloxy)methyl]imidazole (**10**) as a colorless oil (92% yield): IR (neat) 1740 cm^{-1} (s, C=O); ^1H NMR ($CDCl_3$) δ 7.6 (s, 1, NCH=N), 7.0 (s, 2, NCH=CHN), 5.77 (s, 2, OCH_2N), 1.17 (s, 9, CH_3C).

Anal. Calcd for $C_9H_{14}N_2O_2·0.25\ H_2O$: C, 57.88; H, 7.82; N, 15.01. Found: C, 57.73; H, 7.65; N, 15.32.

When 1 equiv of methylimidazole was allowed to react with the pivalate in acetone at room temperature, a precipitate formed within 10 min. The crystals were filtered to give 3-methyl-1-[(pivalyloxy)methyl]imidazolium chloride (**11**) as white crystals (90% yield): mp 138–142 °C; IR (KBr) 1795 cm^{-1} (s, C=O); ^1H NMR ($CDCl_3$) δ 10.60 (s, 1, $NCHN^+$), 7.93 (s, 1, CHN^+), 7.63 (s, 1, CHN^+), 6.37 (s, 2, OCH_2N^+), 4.2 (s, 3, CH_3N^+), 1.2 (s, 9, CH_3C).

Anal. Calcd for $C_{10}H_{17}N_2O_2Cl·0.5H_2O$: C, 49.68; H, 7.50; N, 11.59. Found: C, 49.68; H, 7.64; N, 11.56.

Reaction of Amines with 3-Iodo-1(3*H*)-isobenzofuranone (1d). Each of the five amines (0.006 mol) that were used in the study were dissolved in 5 mL of acetone and added to an ice-cold well-stirred acetone (10 mL) solution containing the iodide **1d**. The iodide was prepared fresh for each series of reactions by allowing the chloride **1a** (0.003 mol) to react with NaI (0.45 g, 0.003 mol) for 36–48 h at room temperature. The progress of the conversion was followed by NMR spectroscopy and was judged complete when less than 5% of the chloride (OCHCl at δ 7.4) could be seen. Typically, the amount of iodide represented by the integration of the OCHI absorption accounted for 75–80% of the total aromatic H absorption for all species in solution as represented by the integration of the aromatic absorptions. The reaction of amine with the iodide was allowed to proceed for 2 h although it appeared to be complete in 15 min by NMR spectroscopy. The reaction mixture was then processed by diluting it to 150 mL with ether and filtering the suspension. The filtrate was concentrated, weighed, and analyzed by NMR spectroscopy and TLC (silica gel, ether). Initially, all five amines were run in parallel by using the same batch of **1a** to minimize run to run variations as much as possible. However, after the first two runs it was found that imidazole and methylaniline gave only the alkylated products **3d** and **3e**, but in 10–15% lower isolated yields than from their reactions with the chloride **1a**, and that pyrrolidine gave only the aldehyde **2a**, again in somewhat lower yield than from its reaction with the chloride. The reaction of **1d** with piperidine or morpholine, on the other hand, gave mixtures of **2b** and **3b** or **2c** and **3c**, respectively. Thus, a typical result from the reaction with piperidine would be 19% alkylation (**3b**) and 81% acylation (**2b**) while the reaction with morpholine would give 37% alkylation (**3c**) and 53% acylation (**2c**) on the basis of integration of the OCHN and CH=O absorptions contributed by each product. The combined integrations of the OCHN and CH=O absorptions representing alkylated and acylated products, respectively, accounted for 75–100% of the total aromatic H absorption for all species in solution as represented by the integration of the aromatic absorptions; the total yield of crude products from each reaction varied from 85% to 100%. Thus, a reasonable material balance was obtained. TLC analysis of the reactions confirmed that the alkylated and acylated products were the major products. Finally, in order to make sure that the results with morpholine and piperidine were significant, they were run two more times in parallel. Those results were 30 ± 3% alkylation from the piperidine reaction and 46 ± 2% alkylation from the morpholine reaction with the material balance conditions being maintained.

Reaction of 2 with Amines. Solutions (2 mL, $CDCl_3$) of the appropriate **2** were allowed to react with varying amounts of amines. The progress of the reaction, i.e., conversion of **2** to **3**, was followed by NMR spectroscopy by observing the loss of CH=O and the formation of OCHN. In all cases the combined integrations of the OCHN and CH=O absorptions accounted for 90–100% of the total aromatic H absorptions for all species in solution as represented by the integration of the aromatic absorptions.

Registry No. **1a**, 6295-21-2; **1b**, 18852-53-4; **1c**, 19339-65-2; **1d**, 61296-43-3; **1e**, 16859-59-9; **1f**, 1828-76-8; **2a**, 84538-48-7; **2b**, 84538-49-8; **2c**, 84538-50-1; **2d**, 84538-51-2; **2e**, 84538-52-3; **2f**, 31802-10-5; **2g**, 84538-53-4; **3a**, 84538-54-5; **3b**, 84538-55-6; **3c**, 4195-21-5; **3d**, 84538-56-7; **3e**, 84538-57-8; **3f**, 84538-58-9; **3g**, 84538-59-0; **8a**, 84538-60-3; **8b**, 84538-61-4; **9**, 18997-19-8; **10**, 83194-81-4; **11**, 73360-20-0; pyrrolidine, 123-75-1; piperidine, 110-89-4; morpholine, 110-91-8; imidazole, 288-32-4; *N*-methylpyrrolidine, 120-94-5; *N*-methylimidazole, 616-47-7; 2-benzoylbenzoic acid, 85-52-9; 2-acetylbenzoic acid, 577-56-0; sodium iodide, 7681-82-5; 2-formylbenzoic acid imidazole salt, 84538-62-5; *N*-methylaniline, 100-61-8.