4d, 29643-62-7; **4e**, 103386-84-1; **4f**, 1585-06-4; **4g**, 101144-90-5; **4h**, 101144-93-8; **4i**, 124267-89-6; **4j**, 124268-42-4; **4k**, 124267-90-9; **5a**, 576-26-1; **5b**, 1687-64-5; **5c**, 7786-21-2; **5d**, 3520-52-3; **5e**, 36186-96-6; **5f**, 4074-46-8; **5g**, 61783-87-7; **5h**, 31143-55-2; **5i**, 124268-23-1; **5j**, 85244-23-1; **6a**, 2944-49-2; **6b**, 6738-23-4; **6c**, 1706-11-2; **6d**, 1004-66-6; **6e**, 4685-47-6; **6f**, 874-63-5; **6g**, 124268-22-0; **6h**, 79744-78-8; **6i**, 124268-14-0; **6j**, 124268-25-3; **6k**, 124268-16-2; **6l**, 124268-06-0; **6m**, 124268-17-3; **6n**, 124268-27-5; **6o**, 124268-15-1; **6p**, 2944-51-6; **6q**, 124267-88-5; **6r**, 124268-24-2; **6s**, 124268-22-0; **6t**, 124268-19-5; **6u**, 124268-20-8; **6v**, 124268-21-9; **6w**, 124268-26-4; **6x**, 124268-18-4; **6y**, 52489-57-3; **6z**, 124268-28-6; **7a**, 61808-02-4; **7b**, 35338-30-8; **7c**, 26620-08-6; **7d**, 61808-04-6; **7e**, 18102-49-3; **7f**, 124268-03-7; **7g**, 124267-91-0; **7h**, 124267-92-1; **7i**, 124268-40-2; **7j**, 124268-04-8; **7k**, 124267-93-2; **7l**, 18102-07-3; **7m**, 124267-96-5; **7n**, 124268-09-3; **7o**, 124268-01-5; **7p**, 33641-87-1; **7q**, 124267-95-4; **7r**, 124268-08-2; **7s**, 91763-69-8; **7t**, 124268-41-3; **7u**, 124267-98-7; **7v**, 101144-91-6; **7w**, 124268-12-8; **7x**, 124267-99-8; **7y**, 124268-13-9; **7z**, 124268-00-4; **7aa**, 124267-94-3; **7bb**, 124267-97-6; **7cc**, 124268-02-6; **7dd**, 124268-07-1; **7ee**, 124268-11-7; **7ff**, 18102-08-4; **7gg**, 124268-05-9; **8**, 54350-31-1; **9a**, 21573-36-4; **9b**, 4028-66-4; **9c**, 124268-37-7; **9d**, 124268-30-0; **9e**, 124268-29-7; **9f**, 124268-36-6; **9g**, 124268-38-8; **10a**, 61248-63-3; **10b**, 124268-33-3; **10c**, 124268-36-6; **10d**, 124268-31-1; **10e**, 124268-10-6; **10f**, 124268-34-4; **10g**, 124268-32-2; **10h**, 124268-35-5; **10i**, 124268-39-9.

Supplementary Material Available: ^{1}H NMR spectra for new compounds **4–10** (31 pages). Ordering information is given on any current masthead page.

Proximate Charge Effects. 8. Ion Pair Formation as an Assembly Process in Ester Aminolysis[1]

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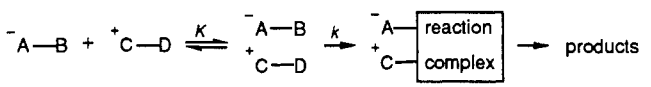
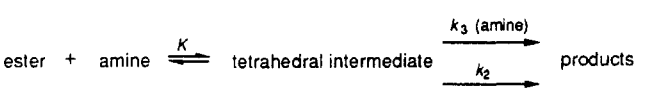
The rate of aminolysis of *p*-nitrophenyl hexanoate by benzylamine in 95.3 mol % dioxane–water was compared to the rate of this reaction when the *n*-pentyl group in the ester was replaced by a $(CH_3)_3{}^+NCH_2CH_2CH_2$ group, and the benzyl group in the amine by a $^-O_3SCH_2CH_2$ group. The second-order rate constant of the first reaction was 4.21×10^{-3} L mol^{-1} s^{-1}, whereas the first-order rate constant for the reacting ion pair was 1.88×10^{-2} s^{-1}, yielding an "effective molarity" of 4.47 mol L^{-1} as the measure of the rate acceleration caused by this preassembly of the reactants by electrostatic attraction. Further evidence for the intermediacy of an ion pair in the reaction between the oppositely charged reactants was the observation of a special salt effect, the addition of an inert salt causing a decrease in the aminolysis rate.

Catalysis by enzymes is generally believed to proceed through the formation of an enzyme–substrate complex, which then reacts further to form products, either directly or by way of one or more intermediates.[2] In this complex the substrate is held in juxtaposition with key functional groups comprising the enzyme. Proximity and orientation of these groups is believed to make a major contribution to the efficiency of the enzyme.[3-6] The importance of this juxtaposition has been examined by studies designed to mimic enzymatic catalysis by means of intramolecular catalysis.[7] Enlightening though many of these studies are, they nevertheless suffer from the difficulty that at best they mimic covalent enzyme–substrate complexes. In general, however, enzyme–substrate complexes are not covalent but involve forces of electrostatic attraction or apolar complexes such as π complexes and inclusion complexes. There are a number of studies of catalysis via apolar complexes.[8] Electrostatic catalysis has been observed in cases of substrate binding to polymeric catalysts[9-12] and to micelles and similar charged aggregates.[13-15]

Scheme I



Scheme II



In a medium of sufficiently low polarity it should be possible to look for the electrostatic assembly of two molecules in solution by the charges proximate to their reaction centers. Thus if A and C are (oppositely) charged inert groups on two molecules, and B and D are reactive sites proximate to A and C, respectively, then the reaction might take the course shown in Scheme I. The work described below endeavors to evaluate the extent to which complex formation via electrostatic attraction (ion pair formation) between reactant molecules in solution will facilitate a subsequent reaction between them.

Results and Discussion

Rates. The reaction selected for study was the aminolysis of an ester in a the nonpolar solvent 95.3 mol % dioxane–water (dielectric constant = 2.53[16]). The active

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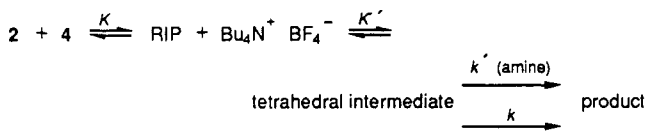
Table I. Rate Constants for the Aminolysis of Ester 1 with Amines 3 and 4 and Ester 2 with Amine 3 in 95.3 mol % Dioxane–Water at 25 °C

ester	amine	k,[a] M^{-1} s^{-1}
p-$NO_2C_6H_4O_2C(CH_2)_4CH_3$, 1	$C_6H_5CH_2NH_2$, 3	0.004212[b]
p-$NO_2C_6H_4O_2C(CH_2)_4CH_3$, 1	$^-O_3SCH_2CH_2N^+H_2$ Bu_4N^+, 4	0.682[c]
p-$NO_2C_6H_4O_2C(CH_2)_3N^+Me_3BF_4^-$, 2	$C_6H_5NH_2$, 3	0.242[d]

[a] Calculated using equation, rate = k(ester)(amine). [b] Standard deviation ±0.00024, amine concentration 0.050–0.0050 M. [c] Standard deviation ±0.024, amine concentration 0.014–0.00153. [d] Standard deviation ±0.008, amine concentration 0.030–0.00252.

Scheme III



RIP = the reacting ion pair, p-nitrophenyl γ-(trimethylammonio)butyrate taurinate

sites of hydrolytic enzymes have been found to contain hydrophobic regions,[17] and hence a nonpolar, water-containing solvent may be a reasonable model for the apolar catalytic site of enzyme-catalyzed nucleophilic reactions of carboxylic acid derivatives.[18] The esters selected for study were p-nitrophenyl hexanoate, 1, and its charged analogue p-nitrophenyl γ-(trimethylammonio)butyrate fluoroborate, 2. The amines used were benzylamine, 3,

$$\underset{1}{CH_3CH_2CH_2CH_2CH_2COOC_6H_4NO_2\text{-}p}$$

$$\underset{2}{BF_4^-\ (CH_3)_3N^+CH_2CH_2CH_2COOC_6H_4NO_2\text{-}p}$$

and its charged analogue tetra-n-butylammonium taurinate, 4. The choice in the latter case was dictated in part

$$\underset{3}{C_6H_5CH_2NH_2} \qquad \underset{4}{Bu_4N^+\ ^-O_3SCH_2CH_2NH_2}$$

by the fact that these two amines have comparable aqueous basicities, the pK_B of benzylamine being 4.65[19] and that of taurinate 4.94.[20]

The aminolysis of esters in aprotic solvents has been shown by Menger and co-workers[21] to proceed via the mechanism shown in Scheme II and to obey a two-term rate law, eq 1. The third-order term in eq 1 represents

$$\text{rate} = k_2(\text{ester})(\text{amine}) + k_3(\text{ester})(\text{amine})^2 \quad (1)$$

a second molecule of amine which assists in proton transfer in the tetrahedral intermediate. This third-order term should vanish in a protic medium; indeed, in 95.3 mol % dioxane–water, at amine concentrations at least 10 times less than the ambient water concentration, the reaction of 3 with 1 or 2 and the reaction of 1 with 4 followed clean second-order kinetics. The rate constants for these three model reactions, listed in Table I, were determined by conventional methods by observing the appearance of p-nitrophenoxide ion. The aminolysis of the charged ester, 2, by the charged amine, 4, was found to be too fast to be measured by conventional methods, and here the rate of appearance of p-nitrophenoxide was followed by the stopped-flow technique.

Table II. First- and Second-Order Rate Constants for the Reaction of 2 with 4 at Low and High Amine Concentrations[a]

[2], M × 10^5	[4], M × 10^3	k_1,[b] s^{-1}	k_2,[c] M^{-1} s^{-1}
1.15	0.0115	0.0190	0.00358
1.62	0.0213	0.0193	0.00170
4.92	2.77	0.131	45.4
4.92	5.53	0.244	44.6

[a] In 95.3 mol % dioxane–water at 25 °C. [b] First-order rate constant calculated using eq 4. [c] Second-order rate constant calculated using eq 5.

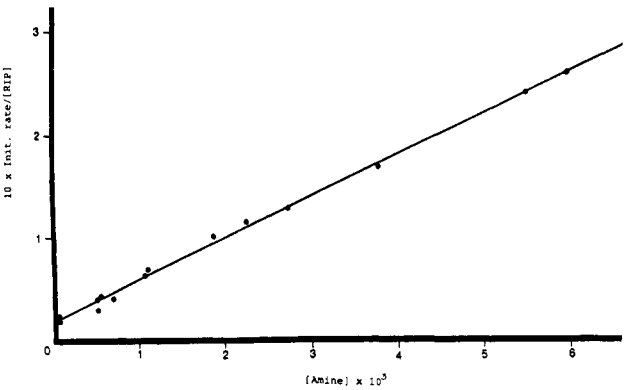


Figure 1. Initial rate/[RIP] = k_2[amine] + k_1 (eq 6) for the reaction of 2 with 4.

The reaction pathway shown in Scheme III, in which breakdown of the tetrahedral intermediate is rate-determining, yields the rate law:

$$\text{rate} = kK[\text{RIP}] + k'K[\text{RIP}][\text{amine}] \quad (2)$$

$$\text{rate} = k_1[\text{RIP}] + k_2[\text{RIP}][\text{amine}] \quad (3)$$

The concentration of the reacting ion pair, [RIP], is governed by the relation:

$$K = \frac{[\text{RIP}]^2}{(\text{C2} - [\text{RIP}])(\text{C4} - [\text{RIP}])}$$

where C2 and C4 are the stoichiometric concentrations of 2 and 4, respectively. At low amine concentrations eq 3 should simplify to

$$\text{rate} = k_1[\text{RIP}] \quad (4)$$

whereas at high amine concentrations eq 3 should become

$$\text{rate} = k_2[\text{RIP}][\text{amine}] \quad (5)$$

That this is so is shown in Table II where first- and second-order rate constants are calculated using eqs 4 and 5, with K = 1.4 to calculate [RIP] (for a justification of the K value, see below). By use of the k_1 and k_2 values thus obtained at low and high amine concentrations, respectively, initial rates at intermediate amine concentrations were calculated using various values for the equilibrium constant K. These calculated rates were compared with experimentally determined rates at these concentrations. It was found that the least discrepancy between calculated and observed rates was found at a value of K = 1.4. A plot of

$$\text{init rate}/[\text{RIP}] = k_2[\text{free amine}] + k_1 \quad (6)$$

over the whole concentration range, shown in Figure 1,

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Table III. Variations in Rate Constants k_1 and k_2 as a Consequence of Using Different Values for K[a]

K	k_1, s^{-1}	k_2, M^{-1} s^{-1}
0.01	3.91	40.8
1.4	1.88	41.2
10.0	1.59	41.5

[a] k_1 and k_2 calculated using the equation: initial rate = k_1[RIP] + k_2[RIP][free amine].

Table IV. Estimate of the Degree of Facilitation of Aminolysis by the Electrostatic Attraction of Reactants

bimolecular analogue	effective molarity[a]	rate enhancement[b]
1 + 3	4.5	10^5–10^6
2 + 3	0.078	10^3–10^4
1 + 4	0.028	5×10^2 to 5×10^3

[a] Effective molarity = k_1/k, the k being the second-order rate constant for the model reaction (Table I) and the k_1 being the first-order rate constant for the reacting ion pair, RIP, $k_1 = 1.88 \times 10^{-2}$ s^{-1}. [b] Rate enhancement = effective molarity/[RIP], the [RIP] values in our experiments ranging from 6×10^{-6} to 5×10^{-5} M.

yielded the following values for the first- and second-order rate constants:

$$k_1 = (1.88 \pm 0.20) \times 10^{-2}\ s^{-1}$$

$$k_2 = 41.2 \pm 0.75\ M^{-1}\ s^{-1}$$

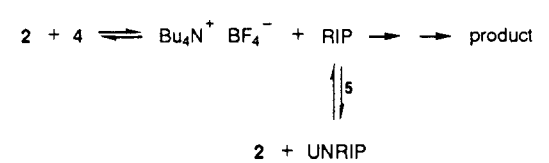
The value obtained for the ion pair exchange equilibrium constant, K, is reasonable when compared to available literature data. In order for this constant to have a value far removed from unity, the ion pair dissociation constants for tetrabutylammonium fluroborate and for *p*-nitrophenyl γ-(trimethylammonio)butyrate taurinate (RIP) would have to be substantially different. Data for these salts in the present solvent are unavailable, but examination of a large number of ion pair dissociation constants in solvents of low polarity[23-31] suggest that dissociation constants vary only slightly with similar changes in the structure of the anion and cation.

To evaluate the effect which a wrong K value would have on the above k_1 and k_2 values, we recalculated these rate constants using some quite extreme K values. As can be seen from the data in Table III the effect on k_2 is negligible, and the effect on k_1, through larger, is too small to affect the conclusions presented below.

Examination of our k_1 and k_2 values reveals that at equimolar initial concentrations of ester and amine the aminolysis proceeds essentially as a first-order reaction of the RIP. Only at a 10-fold excess of amine does about half of the reaction proceed via the second-order pathway. We shall limit our discussion to the process described by the k_1 term.

To assess the effectiveness of ion pair formation in facilitating this reaction one can apply the method of "effective molarity".[32] The EM is obtained by dividing the first-order rate constant of an intramolecular reaction by the second-order rate constant of an analogous bimolecular reaction. This yields the concentration of the reactants in the model bimolecular reaction which would cause it to proceed at the same rate as the intramolecular reaction. This approach would view the reaction within the ion pair as an "intramolecular reaction". Although this is clearly not the case, it is instructive to consider these effective molarities (Table IV). It can be seen that although the numbers obtained differ somewhat depending on the nature of the model reaction (the neutral–neutral model reaction gives a higher EM than the two neutral–ion reactions), the effective molarity is clearly quite large. Dividing this EM by the concentration of the RIP in our reactions then leads to values for the rate enhancement of 10^3 to 10^6 (Table IV). This begins to approach the rate enhancements observed in true intramolecular reactions.[32] Considering the loose association present in the ion pair and therefore the absence of actual proximity of the nucleophile to the electrophilic site, the observed effect is remarkably large.

Scheme IV



UNRIP = unreacting ion pair, *N*-benzyl-γ-(trimethylammonio)-butyramide taurinate

Special Salt Effect. The special salt effect was first observed by Winstein and his students in solvolysis reactions where a solvent-separated ion pair was found to undergo an ion pair exchange reaction with $LiClO_4$.[33] This produced a new ion pair which could not return to reactants, thus causing a steep rate *increase*. If the reacting ion pair in eq 1 were to undergo an ion pair exchange reaction with an added inert salt, then the concentration of the reacting ion pair would be decreased and this would manifest itself by a rate *decrease*.

Addition of a 3.5-fold excess of *N*-benzyl-γ-(trimethylammonio)butyramide fluroborate, **5**, to a 2.0×10^{-5} M

BF_4^- $(CH_3)_3N^+CH_2CH_2CH_2CONHCH_2C_6H_5$
5

solution of **2** and **4** yielded an initial rate that was 36% of the rate observed at this concentration in the absence of the added salt. We interpret this dramatic rate decrease as the manifestation of a new kind of special salt effect, one which causes a rate decrease by diminishing the concentration of the reacting ion pair (Scheme IV).

Product Analysis. The products of the four-ester aminolysis reactions reported in this paper are *N*-benzylhexanamide, **6**, tetrabutylammonium *N*-(2-sulfonatoethyl)hexanamide, **7**, *N*-benzyl-γ-(trimethylammonio)butyramide fluoroborate, **5**, and *N*-(2-sulfonatoethyl)-γ-(trimethylammonio)butyramide, **8**.

$CH_3(CH_2)_4CONHCH_2C_6H_5$ **6**

$CH_3(CH_2)_4CONHCH_2CH_2SO_3^-$ Bu_4N^+ **7**

$(CH_3)_3NCH_2CH_2CH_2CONHCH_2C_6H_5$ BF_4^- **5**

$(CH_3)_3NCH_2CH_2CH_2CONHCH_2CH_2SO_3^-$ **8**

Analysis of representative kinetic runs found quantitative yields of these four expected products.

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Conclusions

Ester aminolysis in a nonpolar medium was found to be substantially accelerated when a nonreacting cationic and anionic moiety was located four bonds away from the reactive site on the ester and the amine, respectively. The effect of this assembly of the reactants by electrostatic attraction was estimated to cause a rate increase of 10^3–10^6-fold compared to model ester aminolyses in which the reactants are not brought together by ion pair formation. A special salt effect was observed when ion pair exchange, caused by addition of an inert salt, decreased the concentration of the reacting ion pair and thus decreased the rate.

Experimental Section

Materials. 1,4-Dioxane (ACS grade) was passed through a column of activated alumina and stored under nitrogen, n^{20}_D 1.4229 (lit.[34] n^{20}_D 1.4224). The 95.3 mol % dioxane–water solvent was then prepared by weight from the above and deionized water. The aqueous dioxane was dearated with CO_2-free nitrogen, stored in the dark, and used within 3 days. Benzylamine was dried over KOH and distilled under nitrogen, n^{20}_D 1.5441 (lit.[35] n^{20}_D 1.5438).

***p*-Nitrophenyl Hexanoate (1).** This ester was prepared from hexanoyl chloride and *p*-nitrophenol, bp 142 °C at 2.4 mm (lit.[36] bp 123 °C at 1 mm), n^{20}_D 1.5185. Spectrophotometric assay of the *p*-nitrophenoxide ion (at 400 nm) produced by hydrolysis with aqueous NaOH gave an equivalent weight of 237.1 (calcd 237.3).

***p*-Nitrophenyl γ-(Trimethylammonio)butyrate Fluoroborate (2).** To a solution of 70 mL (0.92 mol) of γ-butyrolactone in 150 mL of ethanol was added, dropwise, 90 mL (1.125 mol) of thionyl chloride. After the mixture was heated at reflux for 16 h, distilation yielded 110 g (80% yield) of ethyl γ-chlorobutyrate, bp 185 °C (lit.[37] bp 186 °C). This chloro ester, 50 mL (0.357 mol), aqueous trimethylamine (750 mL of a 3.83 M solution, 2.47 mol), and enough acetone to produce a single phase were allowed to stand for 3 days. Removal of the solvent followed by hydrolysis with 1 N HCl yielded 45.4 g (70% yield) of the chloride salt of γ-(trimethylammonio)butyric acid (actinine hydrochloride): mp 208–212 °C (lit.[38] mp 207–210 °C); IR (KBr) 1721 (C=O); ^{1}H NMR (D_2O) δ 2.4 (2 H, m, CH_2), 2.8 (2 H, t, CH_2), 3.4 (9 H, s, CH_3), 3.6 (2 H, t, CH_2). The above carboxylic acid, 6.7 g (0.037 mol), was dissolved in 0.6 mL (0.082 mol) of thionyl chloride. After the mixture was stirred at room temperature for 16 h, the excess thionyl chloride was removed by distillation and the residue was heated with 6.2 g (0.044 mol) of nitrophenol and 2 mL of nitrobenzene at 80 °C for 3.5 h. The nitrobenzene was removed by distillation, and the residue was triturated with ether and then recrystallized from acetone to yield *p*-nitrophenyl γ-(trimethylammonio)butyrate chloride: mp 205–207 °C dec; UV (water) λ_{max} (ε) 270 nm (8569); ^{1}H NMR (D_2O) δ 1.9 (2 H, m, CH_2), 2.5 (2 H, t, CH_2), 2.87 (9 H, s, CH_3), 3.17 (2 H, t, CH_2), 6.9 (2 H, d, arom), 7.8 (2 H, d, arom). Potentiometric chloride titration gave an equivalent weight of 303.0 (calcd 302.8).

The above chloride was converted to the fluoroborate by treating an 8-g sample, dissolved in 130 mL of ethanol, with 9 mL of 48% aqueous fluoboric acid. The resulting precipitate was recrystallized from acetone and then from acetone–ether to yield 4.2 g (45% yield) of *p*-nitrophenyl γ-(trimethylammonio)butyrate fluoroborate, **2**, mp 132–133 °C; UV (water) λ_{max} (ε) 270 nm (8.5×10^4). Spectrophotometric assay of the *p*-nitrophenoxide ion (at 400 nm) produced by hydrolysis with aqueous NaOH gave an equivalent weight of 352 (calcd 354). Anal. Calcd for $C_{13}H_{19}N_2O_4BF_4$: C, 44.10; H, 5.41; N, 7.91. Found: C, 44.35; H, 5.49; N, 7.65.

Tetra-*n*-butylammonium Taurinate (4). To 95 mL of a 0.2024 M aqueous solution of tetra-*n*-butylammonium hydroxide (0.01923 mol) was added 2.456 g of taurine. Evaporation of the water yielded a brown solid, which was dissolved in methylene chloride and decolorized with charcoal to yield a colorless oil. Trituration of this oil with hexane yielded 5.5 g (78% yield) of a white, very hygroscopic solid, mp 116–118 °C. Titration of this salt with HCl to a bromothymol blue endpoint gave an equivalent weight of 377.0 (calcd 366.6).

***N*-Benzyl-γ-(trimethylammonio)butyramide Fluoroborate (5).** Actinine hydrochloride (see above for preparation), 14 g (0.077 mol), 0.9 g of *p*-toluenesulfonic acid, 100 mL of benzene, and 150 mL of ethanol were heated at reflux for 2.5 h in a flask fitted with a Dean–Stark trap. Evaporation of the solvent followed by trituration of the residue with ether and then with acetone yielded 14 g (87% yield) of ethyl γ-(trimethylammonio)butyrate chloride: mp 135–137 °C; IR (KBr) 1738 (C=O); ^{1}H NMR (D_2O) δ 1.4 (3 H, t, CH_3CH_2), 2.3 (2 H, m, CH_2), 2.7 (2 H, t, CH_2), 3.4 (9 H, s, CH_3), 3.6 (2 H, t, CH_2), 4.4 (2 H, q, CH_2CH_3).

This ethyl ester, 11.0 g (0.052 mol), 0.176 g (0.00123 mol) of benzylamine hydrochloride, and 30 mL (0.275 mol) of benzylamine were heated at reflux for 3 h. The excess benzylamine was removed by distillation, and the residue, dissolved in 80 mL of ice cold ethanol, was treated with 20 mL of 48% fluoboric acid. The resulting precipitate, 8 g (48% yield), was collected. Recrystallization from acetone–ether and then from methanol yielded 3.0 g of white crystals: mp 185–186 °C; IR (KBr) 3250 (N—H), 1640 (C=O); ^{1}H NMR (DMSO-d_6) δ 1.8–2.2 (2 H, CH_2), 2.2 (2 H, t, CH_2), 3.15 (9 H, s, CH_3), 3.4 (2 H, t, CH_2), 4.4 (2 H, d, CH_2), 7.4 (5 H, s, arom), 8.5 (1 H, broad, NH). Anal. Calcd for $C_{14}H_{23}ON_2BF_4$: C, 52.20; H, 7.20; N, 8.69. Found: C, 52.48; H, 7.35; N, 8.46.

***N*-Benzylhexanamide (6).** This amide was prepared in the usual way from *n*-hexanoyl chloride and benzylamine. Recrystallization from methanol–water yielded white crystals: mp 54–55 °C (lit.[22] mp 52–52.5 °C); IR (KBr) 3300 (N—H), 1632 (C—O); ^{1}H NMR ($CDCl_3$) δ 0.8–1.9 (9 H, m, $CH_3(CH_2)_3$), 2.2 (2 H, t, CH_2) 4.4 (2 H, d, CH_2NH), 6.5 (1 H, s, NH), 7.4 (5 H, s, arom).

Sodium *N*-(2-Sulfonatoethyl)hexanamide (Na Salt of 7). This amide was prepared from *n*-hexanoyl chloride and sodium taurinate ($Na^+ {}^-O_3SCH_2CH_2NH_2$): mp 249 °C dec; IR (KBr) 3310 (N—H), 1642 (C=O; ^{1}H NMR (D_2O) δ 1.1 (3 H, t, CH_3), 1.3–2.0 (6 H, m, CH_2), 2.5 (2 H, t, CH_2CO), 3.3 (2 H, t, CH_2), 3.8 (2 H, t, CH_2).

***N*-(2-Sulfonatoethyl)-γ-(trimethylammonio)butyramide (8).** Actinine hydrochloride (see above), 3.4 g (0.019 mol), was stirred overnight with 3 mL (0.04 mol) of thionyl chloride. The excess $SOCl_2$ was removed by distillation, and the residue was stirred with 3.0 g (0.02 mol) of sodium taurinate in 5 mL of nitrobenzene at 90 °C for 1 h. The product was triturated with ether and then with acetone and then recrystallized first from methanol and then three times from aqueous methanol. The yield of white crystals was 1.5 g (32% yield): mp 285–287 °C; IR (KBr) 3340 (N—H), 1670 (C=O); ^{1}H NMR (D_2O) δ 2.0–2.8 (4 H, m, CH_2), 3.35 (9 H, s, CH_3), 4.0–3.4 (6 H, m, CH_2). Anal. Calcd for $C_9H_{20}O_4N_2S$: C, 42.84; H, 7.99; N, 11.10. Found: C, 41.80; H, 8.05; N, 11.00.

Kinetic Measurements. The rates of the reactions of esters **1** and **2** with amine **3**, and of ester **1** with amine **4** were measured as follows. A thermostated solution of the ester (about 10^{-4} M) was mixed with a thermostated solution of the amine (about 10^{-3} to 10^{-2} M) and placed in a thermostated cell. The spectrophotometer recorder was then switched on, and a continuous trace of absorbance at 310 nm (*p*-nitrophenol) versus time was recorded. All rates were measured at 25 °C. In converting the absorbance into product concentration, allowance was made for the absorbance of the ester at 310 nm (ϵ_{310} = 1142 M for **1**, ϵ_{310} = 1391 M for **2**, and ϵ_{310} = 10695 M for nitrophenol in 95.3 mol % dioxane–water). Rates were calculated using a PL/C computer program using the standard second-order rate equations, $kt = \ln (A/A - x)$ and $kt = (1/(B - A)) \ln (A(B - x)/B(A - x))$. Rates were run at two different amine concentrations, at least 12 points between 20% and 80% reaction being used. Calculated infininity absorbances were found to be in good agreement with those observed.

The rates of the reaction of ester **2** with amine **4** were found to be too fast to be measured by the above method and were measured by the stopped-flow technique. (Several runs of ester **1** with amine **4** were also measured by this method.) A solution of ester, about 5×10^{-5} M, and a solution of the amine, 5×10^{-3} M to 5×10^{-4} M, were injected into the thermostated value block

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Table V. HPLC Analysis of the Four Amide Products

amide	liquid phase	t_R, s	internal standard (t_R, s)
5	50 vol % CH_3OH-H_2O, 0.1 M NH_4NO_3	269	2-chloro-5-hydroxytoluene (798)
6	66 vol % CH_3OH-H_2O, 0.1 M NH_4NO_3	402	none used
7	20 vol % CH_3OH-H_2O, 0.1 M NH_4NO_3	685	p-$ClC_6H_4SO_3^-$ Na^+ (536)
8	H_2O, 0.1 M NH_4NO_3	319	butyramide (621)

of a Morrow stopped-flow apparatus equiped with a Beckman Model DU quartz spectrometer and a Type 549 storage oscilloscope. The spectrometer was set to read at 400 nm (p-nitrophenoxide ion). A recording of the transmittance vs time trace of the oscilloscope screen was photographed, and the initial rate (d(product)/dt) was determined from the initial slope of the p-nitrophenoxide concentration vs time. No correction had to be made for the absorbance of the ester or the amine at 400 nm, both reactants being transparent at this wavelength. A correction had to be made for the p-nitrophenoxide-p-nitrophenol equilibrium in the presence of the taurinate zwitterion in 95.3 mol % dioxane-water (see ref 1).

Product Analysis Runs. About 50 mg of the ester and an appropriate amount of the amine (same ratios of amine to ester as used in representative kinetic runs) in 50 mL of 95.3 mol % dioxane-water were allowed to stand (with stirring when necessary) at 25 °C for a length of time calculated to allow >99% reaction. The solvent was removed by vacuum distillation at room temperature, and the residue was analyzed by HPLC. Analyses were performed on a Waters Model 6000A chromatograph equiped with a reversed-phase Waters Microbondapak C_{18} column (30 cm × 3.9 cm i.d.). The flow rate was 1 mL/min at a pressure of approximately 1000 psi. The relevant parameters are listed in Table V. The yields ranged from 97% to 100%.

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Registry No. 1, 956-75-2; 2, 109686-78-4; 3, 100-46-9; 4, 91900-05-9; 5, 124563-44-6; 6, 6283-98-3; 7·Na, 124563-45-7; 8, 124563-46-8; $H_3C(CH_2)_4COCl$, 142-61-0; p-$NO_2C_6H_4OH$, 100-02-7; $EtOCO(CH_2)_3Cl$, 3153-36-4; $HO_2C(CH_2)_3N^+(Me)_3\cdot Cl^-$, 6249-56-5; p-$NO_2C_6H_4OCO(CH_2)_3N^+(Me)_3\cdot Cl^-$, 124563-42-4; $NH_2CH_2CH_2SO_3H$, 107-35-7; $EtOCO(CH_2)_3N^+(Me)_3\cdot Cl^-$, 51963-62-3; $NH_2CH_2CH_2SO_3^-\cdot Na^+$, 7347-25-3; γ-butyrolactone, 96-48-0.

Supplementary Material Available: NMR spectra for 4 and 6 (2 pages). Ordering information is given on any current masthead page.

Reactions of 2-Phenylethyl and 3-Phenylpropyl Carbinols with Fluorosulfuric Acid

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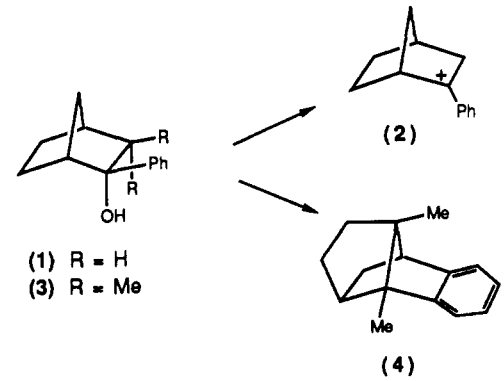
A series of 2-phenylethyl and 3-phenylpropyl carbinols have been reacted with HSO_3F at -78 °C, the solutions quenched, and the products isolated to give good yields of cyclization products. The 2-phenylethyl carbinols generally undergo rearrangement prior to cyclization, whereas the 3-phenylpropyl carbinols undergo direct cyclization of the initially formed carbocation, to give tetralins. The mechanisms and synthetic applications of these reactions are discussed.

Introduction

Carbocations are involved as reactive intermediates in numerous substitution, elimination, addition, and rearrangement reactions of synthetic, industrial, and biological importance.[1] Superacids,[2] such as fluorosulfuric acid, have been extensively employed for the generation and spectroscopic study of long-lived carbocations since the pioneering work in this area by Olah et al. Under these stable ion conditions carbocations can undergo complex rearrangements not accessible under less strongly acidic conditions. Such rearrangements are often highly sensitive to subtle changes in the structure of the precursors. For example we have long been interested in the study of aryl-norbornyl carbocations[3] whereas the parent 2-phenylnorbornanol 1 reacts with HSO_3F to produce the stable cation 2,[4] the 3,3-dimethyl analogue 3 undergoes rearrangement and cyclization to the tetracyclic product 4 (Scheme I).[5]

Scheme I



Such rearrangements can have useful applications in organic synthesis, and as a consequence superacids are being increasingly employed as reagents in organic synthesis.[6] In continuation of our studies[7] into the use of fluorosulfuric acid, we recently described[8] the reactions of

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