= NNN), 85116-19-4; 7^{2-} (XYZ = CCB), 85116-20-7; 7^{+} (XYZ = CBB), 85116-21-8; 7^{0} (XYZ = BBB), 85116-22-9; 7^{-} (XYZ = CBN), 85116-23-0; 7^{2-} XYZ = BBN, 85116-24-1; 7^{0} XYZ = BNN, 85116-25-2; **10b**, 85116-26-3; **12**, 85116-27-4; **13**, 85116-28-5; $C_9H_7^+$, 84598-40-3.

Supplementary Material Available: Tables listing MINDO/3 heat of formation, MO energies, charge densities, π-bond order, and ab initio optimized geometric parameters of [5.5.5]trefoilene, MO energies (4-31G, MINDO/3) of the bicyclic carbene **10**, and STO-3G optimized geometries and MO energies of the protonated trefoilene $C_9H_7^+$ (4 pages). Ordering information is given on any current masthead page.

Ester Aminolysis: New Reaction Series for the Quantitative Measurement of Steric Effects

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Abstract: Further development of theoretical methods for computing steric effects on chemical reactivity requires a large body of new reliable quantitative data for calibration and for testing. We report here on design criteria for reaction series suitable for obtaining these data and on a successful implementation that shows promise of providing access to a particularly broad range of steric hindrance and which additionally has shown a new form of steric hindrance. The series examined in the present study is ester aminolysis in the form $RCOOC_6H_4NO_2$-*p* + $R'NH_2$ in acetonitrile solution. A primary purpose of the examination has been to ascertain whether aminolysis may be a useful general series or whether known or unexpected complications might render it unsuitable. We have measured rate constants for a matrix of reactions using five different R groups and four different R′ groups, each reaction at a series of concentrations of amine. This is the first systematic study of the simultaneous action of steric hindrance effects in both the acylating agent and the entering nucleophile. The reactions showed both a second-order term k_2[ester][amine] and a relatively less important third-order term k_3[ester][amine]^2. The Taft equation was applied to subsets of the rate constants. For each amine there were data for a set of esters for which the R group was the variable. The slopes ρ_s for these sets were nearly unity. For each ester there were corresponding data for a series of amine reactions in which R′ was the variable. These sets also gave good correlations, but the slopes ρ_s' were considerably larger, about 2.3. This unusually large difference in response to structural effects in the acylating agent and in the nucleophile is unexpected and appears to arise from a new type of steric hindrance. An obvious explanation based on bond lengths proves to be quantitatively insufficient; that explanation postulates that there is greater hindrance for the amine because the C–N bond is short in comparison with the C–C bond. The difference may be due instead to a requirement for special orientation within the transition state, a matter currently under theoretical investigation. The k_2 and the k_3 sets gave similar correlations, an important finding in at least two respects. It means that steric effects are well-defined in this example of ester aminolysis, and it means also that the extra molecule of amine is far enough from the reaction center so that no additional steric hindrance results. The reactions observed in the present study cover a range of 5 powers of 10 in relative rate constants. Preliminary studies with other examples of aminolysis suggest that a range of relative rate constants covering well in excess of 12 powers of 10 should be observable.

Although steric effects can cause enormous variations in reactivity, quantitative studies have never achieved popularity. This neglect may be contrasted with the widespread interest in the investigation of polar effects. A major deterrent to the study of steric effects has been lack of general quantitative treatments. Linear free energy relationships (LFER) among sets of equilibria or of rates have generally been successful for gaining a quantitative correlation of polar effects. Although LFER treatments are also applicable to certain types of steric effects, the range of applicability is limited.

The most successful linear free energy treatments of steric effects are based on the Taft E_s constants or their derivatives.[1-4] A general form of the Taft expression, a linear free energy relationship, is shown in eq 1.[5,6] The σ_1 constants are the polar

$$\log k = a + \rho_1\sigma_1 + \rho_s E_s \qquad (1)$$

substituent constants applicable to saturated systems; $\sigma_1 = \sigma^*/6.22$ while ρ_1 and ρ_s are the LFER slopes. Equation 1 was originally derived for ester hydrolysis. It has proved generally applicable to esterification and ester hydrolysis and to a few other classes of reactions as well, certain forms of the Menschutkin reaction being an example.[3,7] Where applicable, the Taft equation provides a good starting point for the analysis of steric effects on reaction rates and equilibria.

Within the past few years our potential ability to predict steric effects has changed dramatically.[8-24] It appears now that it is

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feasible to make accurate quantitative estimates of steric effects directly from molecular structures for a wide variety of reactions. This is a highly significant development; theoretical predictions of relative rates based on molecular structure have only limited range of applicability for other effects such as polar effects.

The theoretical computations involve calculation of the differences in steric energies of models of transition states and of reactant states. In many cases the resultant ΔSE values are proportional to free energies of activation; in others appropriate estimates must be made of entropic effects.[17] Linear free energy relationships between log k values and the theoretically computed ΔSE values (or between ln $k - \Delta S/R$ and ΔSE when it is necessary to correct for entropic effects), eq 2, have been found for

$$\log k = a + b \cdot \Delta SE \tag{2}$$

all three types of steric effects. These are steric hindrance,[8,14-16,23,24] steric acceleration,[9-12,17,20-22] and steric orientation.[13,18,19] Agreement between observed and computed rate constants has generally ranged from good to excellent.

While the theoretical computations are in principle applicable to any desired reaction, quantitative experimental data suitable for testing this supposition are regrettably sparse. Most of the theoretical development has necessarily been based on esterification reactions and to a lesser extent on ester hydrolyses since these are the only reaction systems for which there is a broad base of quantitative rate data dependent primarily on steric influences.

Design Considerations. Esterification and ester hydrolysis merit extensive further study; of the hundreds of publications on esterification and on ester hydrolysis only a few relate to steric effects and most of these utilize a rather standard set of esters comprising only a modest range of rates.[25-34] There are only three studies that have investigated highly hinderded acids; all are based on rates of esterification in methanol.[35,36,4] A few studies have examined steric effects due to the alkoxyl group.[27,33,34]

For further development and for more rigorous evaluation of theoretical approaches, it is necessary to have additional reaction series that cover an extensive range of rate constants and that introduce new forms of steric effects. A factor of 10 in relative rates amounts to only 1.4 kcal in energy, and for developing and testing theoretical computations it is desirable to have a range of 15 kcal or more. It is also desirable to have data for reactions of different types such as S_N2, reduction, other types of acyl transfer, and so on.

In the present study we have selected ester aminolysis as a candidate reaction: RCOX + R′NH$_2$ or RCOX + R′NHR″. The potential advantages of aminolysis are several. Aminolysis, like esterification and ester hydrolysis, is a member of an important general class of reactions, acyl transfer. Ester aminolysis allows in principle for the study of a particularly extensive range of steric effects. With respect to the R group it should be possible to use most of the alkyl groups that have been previously studied in esterification of RCOOH in methanol. In addition, an even larger range of steric effects should be available in the nucleophile alone. As pointed out by Charton, the steric effect of OR can be approximated by equating it to the steric effect of CH_2R.[37] By extension, the steric effect of NR_2 should be similar to that of CHR_2. The available range of combined steric effects should therefore easily exceed 12 powers of 10 in relative rates. The X group can be varied as required to alter reactivity of the acylating agent as will surely be necessary in order to treat so broad a range of effects.

Quantitative theoretical analysis of steric effects in aminolysis may also provide new information about the mechanism, and in particular about its catalysis.

In selecting substrates it is, of course, necessary to choose examples for which steric effects are expected to be dominant and for which bonding, polar, and solvent effects are relatively constant.[5,17] Data based on acylating agents having different X groups will obviously have to be evaluated so as to allow for the bonding differences at the reaction site. Similar considerations hold in devising suitable comparisons of data for primary amines with data for secondary amines since the presence of the extra alkyl group also changes the bonding characteristics at the reaction site.

Certain mechanistic problems must be addressed. The most important concern the complexity of the mechanisms of aminolysis. There are two classes of complexity; one arises from acid–base catalysis,[38-60] while the other involves relationships between theoretical rate constants and observed constants or of the equivalent phenomenological constants derived from them by dividing by the concentration of some reactant.[6]

Acid–base catalysis is a general characteristic of acyl transfer reactions.[43-60] It is manifested in aminolysis as a catalysis by added bases, often including the reacting amine. The rate expression often contains a third-order term k_3[ester][amine]^2 as well as the expected second-order term in k_2. A point to be investigated was to find out whether this complication would interfere with the use of aminolysis as a probe of steric effects.

The problems involved in comparing observed rate constants or the derived phenomenological constants of acyl transfer reactions with theoretically computed rate constants have been analyzed in detail elsewhere.[6] In summary, for a reaction that involves a tetrahedral intermediate present in concentrations too low for direct measurement (eq 3), the theoretical rate expression

$$\mathrm{RCOOH} + \mathrm{R'OH} \underset{k_{21}}{\overset{k_{12}}{\rightleftharpoons}} \mathrm{RC(OH)_2OR'} \xrightarrow{k_{23}} \mathrm{RCOOR'} + \mathrm{H_2O} \tag{3}$$

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$$k_{obsd} = k_{12}f_p = k_{12}k_{23}/(k_{21} + k_{23}) \quad (4)$$

is that shown in eq 4. The phenomenological constant k_{obsd} is the product of a rate constant k_{12} and an unknown distribution fraction f_p. The constant to be compared with theoretical computations in the present instance is k_{12}. Unfortunately, there is usually no way to dissect out the required k_{12} value.[6] It is therefore necessary to evaluate each reaction system critically in order to judge whether the relative k_{obsd} values may be expected to be proportional to the theoretical k_{12} values.

In a previous analysis of this problem evidence was presented that for the alkaline hydrolysis of esters f_p is nearly unity.[6] This means that the mechanistic k_{12} values are equal to k_{obsd}. Since polar effects are small and nearly constant for alkyl groups, eq 1 with ρ_s equal to 0 may be applied and a set of E_s(base) may be derived. This approach provides reference values for comparison with other E_s scales. As noted earlier, f_p values for the acid-catalyzed reactions are not expected to be unity, and they may be expected to vary. If for a given esterification the equilibrium constant is about unity, then f_p might be the order of 0.5, while if the equilibrium constant is small, then f_p is also presumably small. For esters of the class RCOOEt with R = alkyl or cycloalkyl, the E_s(Taft) derived from rate data for acid-catalyzed hydrolysis and the E_s(base) for alkaline hydrolysis are nearly the same.[6] The E_s' values computed from rate constants for esterification of the acids in methanol[4] are also comparable. It follows, therefore, that for acid-catalyzed reactions of this particular class of esters the distribution fraction remains effectively constant and the observed rate constants are reasonably proportional to k_{12}. The small differences in the several E_s sets are within limits expected for LFER constants.

By a similar argument the fact that E_s correlations apply to aminolysis of esters suggests that f_p is also nearly constant for these reactions.[6] There is also direct evidence that for some aminolysis reactions the f_p value is nearly unity. For certain substrates it has been possible to generate the postulated tetrahedral intermediate by hydrolysis of imidate esters; the f_p values are computed from a measurement of relative yields of ester and amide.[49] At high pH the f_p values approach unity. Although these results do not necessarily apply to solvent systems other than water, nor to other reactant systems, it is plausible to postulate that for *p*-nitrophenyl esters and for more reactive acylating agents the observed k_2 values should be reliable relative measures of mechanistic k_{12} values.

A primary objective of the present study has been to find a specific form of the aminolysis reaction that might prove to have general applicability. It was our expectation that suitable aryl esters would provide the necessary range of reactivity for the aminolysis study, and we have chosen for initial work the well-studied *p*-nitrophenyl esters. We made the further choice of using very dilute solutions of the esters, 10^{-4}–10^{-5} M, to permit direct spectrophotometric monitoring of the solutions. Amine concentrations up to 1.5 M were used.

We selected acetonitrile as the solvent. Water is not suitable for our purposes for two reasons, limited solubility of reactants and complications due to hydrolysis. For highly hindered amines hydrolysis is expected (and has been observed) to become the dominant reaction. A dipolar solvent was chosen in order to reduce complications that are known to arise in using ethers or hydrocarbon-like solvents. For example, the third-order term in k_3 is reported to be the principal term in chlorobenzene solvent.[50]

Results and Discussion

The rate data are summarized in Table I for aminolysis reactions of four primary amines with each of five esters. The k_{obsd}'s are pseudo-first-order rate constants obtained at several concentrations of amine.

The reactions show both a second-order component and a third-order component, eq 5. The k_2 and the k_3 values that

$$k_{obsd} = k_2[RNH_2] + k_3[RNH_2]^2 \quad (5)$$

summarize the data in Table I were calculated in accordance with eq 5; the relative error in k_{obsd} was minimized.[61,62] The standard deviation for $\hat{k}_{calcd}$ was about 1%. The standard deviations for the several k_2 were about 3% and of the k_3 were about 7%.

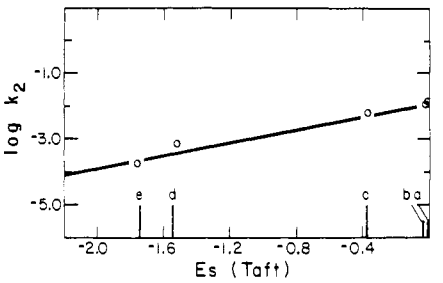

Figure 1. log k vs. the E_s value of the R group in the acyl moiety of esters for reaction with isopropylamine.

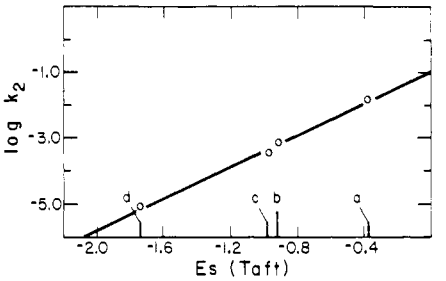

Figure 2. log k vs. the E_s value of the R'NH group of the nucleophile for reaction with *p*-nitrophenyl trimethylacetate.

Whatever the detailed explanation may prove to be for the k_3 term, which is usually thought to pertain to catalysis by a second molecule of amine, the catalysis is neither obligatory nor is it particularly large. At 0.2 M the k_3 term usually amounts to less than 20% of the total reaction. Presumably the k_2 values are the better measures of the structural effects on reactivity than are the k_3 values on the grounds that they represent relative rates at conditions of high dilution. It is indeed fortunate for interpretation of steric effects that a choice need not be made since the k_2 set and the k_3 set give nearly the same answers.

The k_2 values and the k_3 values have been treated by four linear free energy relationships, summarized in eq 6–9. For example,

$$\log k_{2ij} = a_{2j} + \rho_{s2i}E_{sj} \quad (6)$$

$$\log k_{2ij} = a_{2i} + \rho_{s2j}E_{si} \quad (7)$$

$$\log k_{3ij} = a_{3j} + \rho_{s3i}E_{sj} \quad (8)$$

$$\log k_{3ij} = a_{3i} + \rho_{s3j}E_{si} \quad (9)$$

eq 6 correlates the second-order rate constants k_{2ij} for a series of acylating agents R_jCOOAr in reaction with a given primary amine R_iNH_2, while eq 7 correlates the k_{2ij} for a series of amines R_iNH_2 with a single acylating agent. Values of log k_2 and log k_3, both observed (based on eq 5) and calculated from eq 6–9, are summarized in Table II and in Table III; the Taft E_s values we used are listed in Table IV.[3,5,6] The a_2 and a_3 values and the several ρ_s values are also reported in Tables II and III. Figures 1 and 2 illustrate the quality of the correlations. The ρ_s values for the acylating agents average 0.99 with a 10% scatter (standard deviation of the values) while the ρ_s' values for the nucleophiles average 2.3, also with a scatter of about 10%.

We find these results surprising in two respects, viz., the similarity in the steric effects as reflected in the closely similar ρ_s and ρ_s' values whether defined by k_2 or by k_3 and the significantly larger ρ_s' values. These indicate a much greater sensitivity to the steric effects of the nucleophile than to the steric effects of the acylating agent. Both have important implications about the mechanisms of aminolysis.

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Table I. Observed Pseudo-First-Order Rate Constants for the Aminolysis of *p*-Nitrophenyl Esters (10^{-5} M) by Primary Amines in Acetonitrile at 25.4 °C (s^{-1})

ester	*n*-butylamine, M	$k \times 10^3$	isopropylamine, M	$k \times 10^3$	*sec*-butylamine, M	$k \times 10^3$	*tert*-butylamine, M	$k \times 10^3$
acetate			0.106	2.24	0.105	2.065	0.225	0.0997
			0.345	8.22	0.210	4.27	0.997	0.650[a]
			0.8625	25.5[a]	0.530	11.75	1.610	1.262
					1.585	45.4		
propionate	0.080	18.4	0.106	1.37	0.210	1.74	0.0319	0.00744
	0.120	28.3	0.345	5.37[a]	1.06	18.55	0.200	0.0514[a]
	0.250	64.9	0.8625	18.3	1.585	33.65[a]	0.498	0.153
							1.610	0.765
valerate	0.080	9.89	0.106	0.757[a]	0.210	1.35[a]	0.289	0.0507
	0.120	15.03	0.345	3.36	0.530	4.50	0.723	0.165
	0.250	34.3[a]	0.8625	12.3	1.585	21.5	0.997	0.270[a]
trimethylacetate	0.269	4.26	0.100	0.0775	0.230	0.094	0.380	0.00383
	0.600	10.5[a]	0.345	0.303	0.315	0.138	0.650	0.00683[a]
	0.750	14.5	0.8625	0.925	0.530	0.270	0.997	0.0111
	1.00	21.0	1.725	2.60[a]	1.585	1.39	1.610	0.0183
tert-butylacetate	0.100	0.591	0.345	0.0995	0.210	0.053		
	0.250	1.66	0.862	0.862	0.530	0.1635		
	1.00	11.25	1.725	1.40	1.585	0.753		

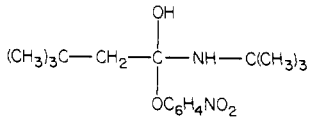
[a] k_{obsd} values for duplicate runs are reported as the average.

Table II. Linear Free Energy Correlations for Acyl Group[a]

amine and ester	$-\log k_2$ (eq 5) obsd	$-\log k_2$ (eq 6) calcd	$-\log k_3$ (eq 5) obsd	$-\log k_3$ (eq 8) calcd
n-butylamine				
propionate	0.67	0.65	0.76	0.74
valerate	0.93	0.94	1.08	1.03
trimethylacetate	1.86	1.98	2.15	2.09
tert-butylacetate	2.28	2.17	2.22	2.28
a		(−0.584 ± 0.13)[b]		(−0.671 ± 0.13)[c]
ρ_s		(0.910 ± 0.11)		(0.924 ± 0.11)
isopropylamine				
acetate	1.70	1.77	1.94	1.85
propionate	1.93	1.85	1.96	1.91
valerate	2.21	2.18	2.02	2.21
trimethylacetate	3.14	3.38	3.36	3.27
tert-butylacetate	3.79	3.59	3.41	3.45
a		(−1.774 ± 0.10)[b]		(−1.849 ± 0.10)[c]
ρ_s		(1.042 ± 0.10)		(0.921 ± 0.10)
sec-butylamine				
acetate	1.72	1.91	2.22	2.02
propionate	2.20	1.98	2.00	2.08
valerate	2.27	2.30	2.24	2.39
trimethylacetate	3.48	3.47	3.46	3.51
tert-butylacetate	3.66	3.67	3.78	3.70
a		(−1.908 ± 0.10)[b]		(−2.016 ± 0.10)[c]
ρ_s		(1.013 ± 0.10)		(0.968 ± 0.10)
tert-butylamine				
acetate	3.41	3.48	3.60	3.61
propionate	3.64	3.56	3.81	3.70
valerate	3.85	3.87	3.92	4.05
trimethylacetate	5.01	5.01	5.37	5.34
a		(−3.481 ± 0.11)[b]		(−3.614 ± 0.11)[c]
ρ_s		(0.992 ± 0.13)		(1.122 ± 0.13)

[a] See Table I for rate data. See Table IV for E_s values. [b] *a* and ρ_s for eq 6. Units of k_2 are M^{-1} s^{-1}. Standard deviations of *a* and of ρ_s are based on a global estimate of 0.16 for the standard deviation of log k_{calcd}. [c] *a* and ρ_s for eq 8. Units of k_3 are M^{-2} s^{-1}.

If the transition state for aminolysis has the conformational freedom expected for a tetrahedral intermediate such as **1**, then



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it would be expected as a first approximation that steric effects would be about the same for an R group and for an amine group R′NH having the same E_s values; in **1** the neopentyl group and the *tert*-butylamino group are presumed to have the same E_s value.

An obvious possibility is that since C–N bonds are shorter than C–C bonds, there should be a larger steric interaction with R′NH. This postulate is being evaluated by theoretical computations currently in progress; preliminary indications are that the postulated effect is too small. There is also some LFER evidence to indicate that the effect of bond lengths is relatively small. Estimates of steric effects for R in the acyl group of methyl and of ethyl esters and of the corresponding OR′ group of acetate esters have been reported in Tables III and IV of ref 5. The ρ_s value is 1.27 for R in alkaline hydrolysis of RCOOEt in 70% aqueous acetone (data of ref 26b) while ρ_s' for R′ of CH_3COOR' is 1.41, 12% larger (data of ref 27). Analysis of the data for the alkaline hydrolysis of $RCOOCH_3$ in 40% aqueous dioxane showed ρ_s = 0.93 while alkaline hydrolysis of CH_3COOR' under the same conditions showed ρ_s' = 1.27, 37% larger (data of ref 33). The bond length effect is apparent, but it is rather small. Since C–O bonds are shorter than C–N bonds, the bond length effect in ester hydrolysis should be larger than in amide formation, and the bond length effect in aminolysis should therefore amount to considerably less than 30%, not the 230% observed. We are currently exploring models of the transition state in an effort to find conformations that can quantitatively account for the extra steric hindrance.

The similarities of the ρ_s and of the ρ_s' values for k_2 and for k_3 require that the extra amine molecule must be oriented so as not to cause additional steric hindrance.

In the experimental section we report briefly on exploratory tests to evaluate the approximate size of salt effects and of the possible interference from hydrolysis. We also examined the possibility that nucleophilic aromatic substitution might be competitive; it is not. In a few runs with the 2,4-dinitrophenoxy leaving group we find that this reacts about 30 000 times as fast as does the *p*-nitrophenyl leaving group.

The data obtained in the present study show that ester aminolysis should prove a useful choice for further experimental investigations of steric effects. Even the limited sets of substrates used in the present study cover a range of relative rates of about 5 powers of 10. Preliminary work with secondary amines has shown that competing hydrolysis can be minimized by adopting adequate precautions and that the available rate range can be extended to more than 12 powers of 10.

Experimental Section

Materials. Reagent-grade acetonitrile was used as received. The *p*-nitrophenol was recrystallized from ethanol, mp 112–114 °C;[63] the

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Table III. Linear Free Energy Correlations for Nucleophiles[a]

ester and amine	$-\log k_2$ (eq 5) obsd	$-\log k_2$ (eq 7) calcd	$-\log k_3$ (eq 5) obsd	$-\log k_2$ (eq 9) calcd
PNP acetate				
isopropylamine	1.70	1.67	1.94	2.04
sec-butylamine	1.72	1.75	2.22	2.12
tert-butylamine	3.41	3.41	3.60	3.60
a		$(+0.331 \pm 0.24)^b$		$(-0.240 \pm 0.24)^c$
ρ_s		(2.149 ± 0.19)		(1.934 ± 0.19)
PNP propionate				
n-butylamine	0.67	0.76	0.69	0.69
isopropylamine	1.93	1.94	1.96	1.94
sec-butylamine	2.20	2.03	2.00	2.03
tert-butylamine	3.64	3.71	3.81	3.81
a		$(+0.090 \pm 0.14)^b$		$(+0.213 \pm 0.14)^c$
ρ_s		(2.184 ± 0.12)		(2.311 ± 0.12)
PNP valerate				
n-butylamine	0.93	0.99	1.08	1.00
isopropylamine	2.21	2.15	2.02	2.15
sec-butylamine	2.27	2.24	2.24	2.24
tert-butylamine	3.85	3.89	3.92	3.87
a		$(-0.149 \pm 0.14)^b$		(-0.177 ± 0.14)
ρ_s		(2.150 ± 0.12)		(2.123 ± 0.12)
PNP trimethylacetate				
n-butylamine	1.86	1.94	2.15	2.12
isopropylamine	3.14	3.19	3.36	3.40
sec-butylamine	3.48	3.29	3.46	3.50
tert-butylamine	5.01	5.07	5.37	5.32
a		$(-1.034 \pm 0.14)^b$		$(-1.198 \pm 0.14)^c$
ρ_s		(2.321 ± 0.12)		(2.370 ± 0.12)
PNP *tert*-butylacetate				
n-butylamine	2.28	2.29	2.22	2.21
isopropylamine	3.79	3.67	3.41	3.55
sec-butylamine	3.66	3.77	3.78	3.65
a		$(-1.291 \pm 0.21)^b$		$(-1.243 \pm 0.21)^c$
ρ_s		(2.558 ± 0.26)		(2.481 ± 0.26)

[a] See Table I for rate data. See Table IV for E_s values. [b] a and ρ_s for eq 7. Units of k_2 are M^{-1}. Standard deviations of a and of ρ_s are based on a global estimate of 0.12 for the standard deviation of $\log k_{calcd}$. [c] a and ρ_s for eq 9. Units of k_3 are $M^{-2}\ s^{-1}$.

Table IV. Taft $-E_s$ Values[a]

CH_3	0.00	$CH_3CH_2CH_2CH_2NH$	0.39
CH_3CH_2	0.07	$(CH_3)_2CHNH$	0.93
$CH_3CH_2CH_2CH_2$	0.39	$CH_3CH_2NH(CH_3)$	0.97[b]
$(CH_3)_3C$	1.54	$(CH_3)_3CNH$	1.74
$(CH_3)_3CCH_2$	1.74		

[a] Ref 3. [b] E_s' value from ref 4.

several acids were all commercial products. The boiling points of the commercial amines agreed with literature values: *n*-butylamine, 78–79 °C;[64] *sec*-butylamine, 64–65 °C;[65] isopropylamine, 34–35 °C;[66] *tert*-butylamine, 46–47 °C.[67] *p*-Nitrophenyl acetate, mp 78–79 °C,[68,69] and *p*-nitrophenyl trimethylacetate, mp 94–96 °C,[68,69] were commercial products from the Aldrich Chemical Co. These were recrystallized from ethanol.

***p*-Nitrophenyl Propionate, Valerate, and *tert*-Butylacetate.** These were prepared from the acid chloride by reaction with *p*-nitrophenol in pyridine. The melting points were as follows: *p*-nitrophenyl propionate, 62–64 °C;[68,69] *p*-nitrophenyl *tert*-butylacetate, 31–33 °C;[70] the valerate was a liquid at room temperature. The esters were assayed for *p*-nitrophenol content by hydrolysis with dilute sodium hydroxide followed by measurement of the absorbance at 420 nm. The propionate and the valerate showed a *p*-nitrophenol content of 96.5%; the others showed 99–100%. Infrared spectra and proton NMR spectra showed the expected peaks.

Kinetics Runs. A solution of the ester was made up in acetonitrile and serially diluted to about 10^{-5} M. The ester solutions were mixed with a stock solution of the appropriate amine. Reactions having a half-life of less than 60 s were run in the spectrometer cell, others were run in stoppered tubes in a water bath. All runs were made at 25.4 °C. To obtain reproducible results it was necessary to subject all glassware including the disposable pipets to a series of cleaning steps using detergent, dilute HCl, 5% $NaHCO_3$, distilled water rinse, and oven drying.

The reactions were monitored by increase in optical absorbance at 420 nm due to formation of the *p*-nitrophenoxide–amine cation ion pair, eq 10 and 11. The equilibrium constant for ion-pair formation ranged from

$$RCOOAr + R'NH_2 \rightarrow RCO\text{-}NHR' + ArOH \quad (10)$$

$$ArOH + R'NH_2 \rightleftharpoons ArO^-{}^+H_3NR' \quad (11)$$

70 to 100 with some indication of formation of a 2:1 amine–*p*-nitrophenol complex at amine concentrations in excess of 1 M. The apparent molar absorptivity index thus varied somewhat with the concentration of amine, but this did not cause complications within a kinetic run since the amine was present in large excess and its concentration remained effectively constant.

All computations in the present study were carried out by appropriate least-squares procedures.[61,62] For reasons stated elsewhere, we did not use full statistical designs, but we did take precautions to ensure that the observed rate differences are due to the reactions under study.[61] Computed infinity absorbances agreed with those observed and with those computed from the first-order equation $A = A_\infty + (A_0 - A_\infty)\exp(-kt)$.

Rate data were processed on a Hewlett-Packard HP-97 programmable calculator by using the program 1KIN3.[61] All units are molar and seconds.

Effects of added salts were as follows for reaction of *n*-butylamine with 10^{-5} M *p*-nitrophenyl trimethylacetate in the presence of added salts (concentrtion of amine, identity of salt, $k_{obsd} \times 10^3\ s^{-1}$): 0.10, none, 1.44; 0.125, none, 1.81; 0.135, none, 1.97; 0.10, 0.1 $n\text{-}C_4H_9NH_3Cl$, 0.84; 0.135, 0.08 $n\text{-}C_4H_9NH_3Cl$, 1.54; 0.125, 0.05 $(C_2H_5)_4Br$, 2.60.

The effects of added water were determined for reaction of 1 M $t\text{-}BuNH_2$ with $EtCOOC_6H_4\text{-}NO_2\text{-}p$. The rate was unchanged whether the regular solvent was used or whether 1% of water was added. Further, we find that competing hydrolysis shows up by rates that do not decrease with increasing hindrance, as with secondary amines unless special precautions are taken.

Reaction of 2,4-dinitrophenyl trimethylacetate and *tert*-butylamine showed no third-order term and k_2 was 0.27 $M^{-1}\ s^{-1}$, a rate constant some 27 000 times larger than that observed for the *p*-nitrophenyl ester.

We have examined the possible incursion of nucleophilic aromatic substitution by finding that the more reactive *p*-nitrochlorobenzene is

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unreactive under the conditions used for ester aminolysis. Also, in the reaction of di-*n*-propylamine and the 2,4-dinitrophenyl trimethylacetate there is no detectable di-*n*-propyl-2,4-dinitrophenylaniline produced.

Acknowledgment. This work was supported in part by a grant from the National Science Foundation.

Registry No. *p*-Nitrophenyl acetate, 830-03-5; *p*-nitrophenyl propionate, 1956-06-5; *p*-nitrophenyl valerate, 1956-07-6; *p*-nitrophenyl trimethylacetate, 4195-17-9; *p*-nitrophenyl *tert*-butylacetate, 22406-32-2; *n*-butylamine, 109-73-9; isopropylamine, 75-31-0; *sec*-butylamine, 13952-84-6; *tert*-butylamine, 75-64-9; propionoyl chloride, 79-03-8; valeroyl chloride, 638-29-9; *tert*-butylacetoyl chloride, 7065-46-5.

Optimization of Metallocene Substrates for β-Cyclodextrin Reactions

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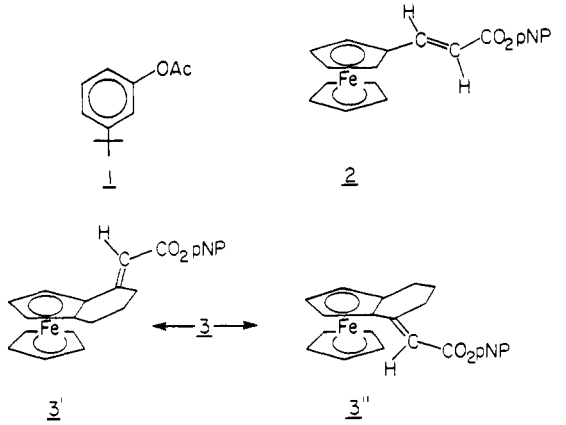
Abstract: The *p*-nitrophenyl ester of (*E*)-ruthenoceneacrylic acid reacts in a complex to acylate β-cyclodextrin, but with a poorer binding and rate constant than for the corresponding ferrocene derivative. The *p*-nitrophenyl ester of (*E*)-3-(carboxymethylene)-1,2-ferrocenocyclopentene is a mixture of two enantiomers. One enantiomer acylates β-cyclodextrin 5 900 000 times as fast in aqueous Me_2SO as it hydrolyzes under the same conditions (1.5×10^8 times as fast as hydrolysis in pure water at the same pH); the other enantiomer is 62-fold slower. These are the largest accelerations and enantiomeric selectivities known for such reactions. Ferrocene-1,3-diacrylate esters react with β-cyclodextrin in processes in which the first and second acylation reveal important geometric effects. β-Cyclodextrin 6-tosylate is used to block unproductive binding and clarify the structural effects.

In the imitation of enzymatic reactions by simpler components, there are two types of studies of interest. One group comprises intramolecular reactions, such as catalyses by neighboring groups. These help establish the magnitudes of rate effects one can expect when the functional groups of an enzyme and a substrate are held firmly in the correct geometry for reaction; intramolecular processes are also direct models for some reactions that involve covalent enzyme–substrate species, as in the hydrolysis of acyl-enzyme intermediates in peptidase and esterase reactions with intramolecular catalysis by the enzyme. The second class of enzyme model studies involves intermolecular catalysis, which imitate the reaction of independent enzyme and substrate molecules. As with enzymes themselves, such models are much more effective if the catalyst and substrate associate in some way so the intermolecular process can occur within a complex.

The cyclodextrins have excited much interest as the basis for enzyme models that can complex substrates.[3] α-Cyclodextrin (cyclohexaamylose) and β-cyclodextrin (cycloheptaamylose) are readily available, and in water or in polar organic solvents they bind hydrophobic organic segments of appropriate geometry with good affinities. Many catalysts have been constructed by attachment of appropriate functional groups to cyclodextrins, and the unmodified molecules themselves have also been studied as enzyme models. In one general approach, the cyclodextrin hydroxyls act as nucleophiles to react with bound substrates such as esters.[4,5] Such reactions produce acylated cyclodextrin, so they are not catalytic. However, acylation of a cyclodextrin hydroxyl within a complex is a partial model, but lacking the other catalytic groups, for the acylation steps of such serine proteases as chymotrypsin.

The results of such studies showed interesting geometric selectivities, but poor rate accelerations. By comparison of the deacylation of a substrate such as *m-tert*-butylphenyl acetate (**1**)



within a β-cyclodextrin complex with the rate of hydrolysis of the substrate under the same conditions in the absence of β-cyclodextrin, acyl transfer to a cyclodextrin hydroxyl was accelerated by a little more than 10^2 by the proximity effect within the complex.[5] Proximity effects in intramolecular processes[6] can lead to rate effects of 10^{10}; such large effects are generally invoked for enzyme–substrate complexes to explain enzymatic velocities. Thus it was important to see whether really large rate accelerations could be achieved in some intracomplex reactions, or whether unknown factors still separated the great effectiveness of enzymatic processes from the rates available in model systems. For this reason we have instituted a program of optimization for cyclodextrin acylation reactions.

Our first studies[7] showed that previously examined substrates had incorrect geometries for fast reaction. That is, the substrates fit the cyclodextrin cavities well, but molecular models suggested that much of the binding must be lost in the transition state for acyl transfer. When we modified the cyclodextrin by building in an intrusive floor, so the cavity was well defined and shallower, the *m-tert*-butylphenyl acetate reaction was improved by an order

(1) NIH Postdoctoral Fellow, 1979–1981.
(2) On leave from the Pharmaceutical Instutitue, Tohoku University, 1981–1982.
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