the magnitudes of the relevant torsion angles C(4)–C(5)–C(6)–C(7), C(5)–C(6)–C(7)–C(8), C(6)–C(7)–C(8)–C(9), and C(7)–C(8)–C(9)–C(10) are −73, 131, −48, and −53°, respectively.

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Hydrophobic Effect in Host–Guest Interactions. Hydrolysis of Nitrophenyl Carboxylates

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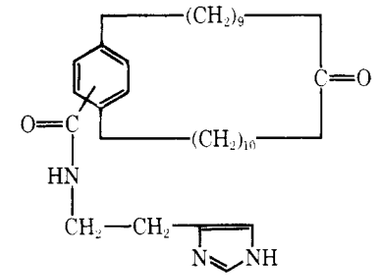
Widespread interest has developed in the catalytic effect of micelles on organic reactions.[1] The object of such studies has been to design simple model systems of enzymes, the parameters of which can be easily varied. Their study is expected to enhance our understanding of biochemical processes.

An elegant study along these lines, which goes a step below the micelle level, is that of Murakami et al.[2] who synthesized the [20]paracyclophane **1**. This molecule can be viewed as a "mini-enzyme" containing a hydrophobic pocket and the catalytically active imidazole moiety. This "enzyme" was used to hydrolyze esters of the type $RCOOC_6H_4$-*p*-NO_2 (Table I). In Table I, k_{rel} is the relative rate (pseudo-first-order) of hydrolysis in the presence of paracyclophane compared to hydrolysis in buffer alone. As Murakami et al. observed, it is apparent qualitatively that the more hydrophobic esters are hydrolyzed more rapidly in the presence of **1**.

We have been developing a quantitative scale of hydrophobicity of organic compounds and their substituents[3] in order to facilitate the study of structure–activity relationships of organic compounds interacting with macromolecules,[4] enzymes,[5] organelles,[6] bacteria,[6] and whole animals.[7] Our general model[3b] appears to be important in drug design.[8]

We have selected the logarithm of the octanol/water partition coefficient (P) as our model hydrophobicity scale for organic compounds. The hydrophobicity of a substituent (X) can be defined as $\pi_X = \log P_{R-X} - \log P_{RH}$. Making the extrathermodynamic assumption[9] that $\log k \propto \pi$, we have formulated eq 1 from the data in Table I. The figures in parentheses are the 95% confidence limits, n represents the number of data points used in deriving eq 1, r is the correlation coefficient, and s is the standard deviation. One data point (no. **3**) has not been used in formulating eq 1 and is seen to be poorly fit in Table I. Including this point gives essentially the same equation, but with $r = 0.950$ and $s = 0.324$. This poorer equation "explains" 90% of the variance in log P, while eq 1 "explains" 94%.



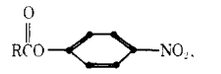
1

$$\log k = 0.45(\pm 0.09)\pi - 0.53(\pm 0.39) \quad (1)$$
$$n = 11;\ r = 0.968;\ s = 0.260$$

Equation 1 shows that hydrolysis is closely related to hydrophobicity as defined by the octanol/water system. With the exception of compounds **3**, **4**, and **7** of Table I, the relationship is sharp, showing that steric effects in general are of secondary importance. The rigid naphthyl or phenyl groups are as well fit as the more flexible alkyl groups.

The advantage of the numerical scale for hydrophobicity is that we can compare the results embodied in eq 1 with those from other systems, as the following examples illustrate. Gitler and Ochoa-Solano[10] studied the hydrolysis of esters like those in Table I in micelles of cetyltrimethylammonium bromide containing *N*-myristoyl-L-histidine. The lipophilic myristoyl group insures that the catalytic histidine moiety is held in the lipophilic micelle. An equation similar to eq 1 has been formulated[11] for the hydrolysis of five nitrophenyl carboxylates (eq 2). Log P rather than π was employed in eq 2 as the independent variable for relative hydrophobicity. This does not affect the slope of eq 2, which is close to that of eq 1, showing in quantitative terms that both processes depend almost entirely on the relative hydrophobicity of the substrates.

Table I. Hydrolysis and Hydrophobic Constants Used to Derive Equation 1

no.	 R =	Registry no.	log k_{rel} obsd[a]	log k_{rel} calcd[b]	π[c]
1	CH_3	830-03-5	0.00	−0.29	0.54
2	$(CH_2)_4CH_3$	956-75-2	0.79	0.70	2.70
3	$(CH_2)_8CH_3$	1956-09-8	2.38[d]	1.68	4.86
4	$(CH_2)_{10}CH_3$	1956-11-2	2.62	2.17	5.94
5	$(CH_2)_{14}CH_3$	1492-30-4	2.97	3.15	8.10
6	cyclohexyl	13551-17-2	0.74	0.85	3.05
7	CH_2-cyclohexyl	65426-79-1	0.66	1.10	3.59
8	$CH(CH_3)$-cyclohexyl	65426-80-4	1.30	1.23	3.87
9	CH_2-3,5-di-CH_3-cyclohexyl	65426-81-5	1.54	1.51	4.49
10	CH_2-cyclodecyl	65426-82-6	2.23	2.13	5.86
11	$CH_2C_6H_5$	1223-44-5	0.15	0.38	2.01
12	CH_2-1-naphthyl	51537-87-2	0.90	0.96	3.28

[a] k is the relative rate of hydrolysis in the presence of paracyclophane compared to hydrolysis without paracyclophane.[2] [b] Calculated using eq 1. [c] The value of 0.54 is used for each CH_2 increment. π values for **11** and **12** taken from C. Hansch et al., *J. Med. Chem.*, **16**, 1207 (1973). π values for **6–10** calculated using method of fragment constants: A. Leo et al., *J. Med. Chem.*, **18**, 865 (1975); for example, $\log P_{cyclohexane} - \log P_{H_2} = 3.51 - 0.46 = 3.05$. [d] This point was not used in deriving eq 1.

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$$\log K = 0.62(\pm 0.12) \log P - 0.28(\pm 0.34) \quad (2)$$
$$n = 5; r = 0.995; s = 0.060$$

Equations 1 and 2 for the simple model enzyme systems can be compared with the more complex interaction of ligands with proteins. Equation 3 correlates binding of miscellaneous organic compounds by bovine serum albumin. C in eq 3 is the molar concentration of ligand necessary to produce a 1:1 complex of albumin and ligand; hence, it can be regarded as a binding constant. The slope of eq 3 (as well as eq 2) is a little higher than that of eq 1. This is at least in part due to the fact that the system on which eq 1 is based is not pure water, but instead contains 11% ethanol and 1% dioxane. The solubilizing effect of these solvents would lower the effective partition coefficients of the esters in comparison to the π constants obtained in pure water and octanol. In fact, Murakami et al. noted that as one increased the ethanol content of the hydrolysis solution, the catalytic effect decreased; hence, one expects a slightly lower slope because of the alcohol.

$$\log 1/C = 0.75(\pm 0.07) \log P + 2.30(\pm 0.15) \quad (3)$$
$$n = 42; r = 0.960; s = 0.159$$

A more complex example is that of the formation of a complex between X-$C_6H_4CONH_2$ and the enzyme alcohol dehydrogenase.[12] In eq 4, π_4 and E_{s4} refer to the hydrophobic and steric effects of substituents in the 4 position of the benzamide inhibitors, while σ refers to the electronic effect of both the 3 and 4 substituents. Apparently, 3 substituents do not contact the enzyme but may promote their electronic effect through the framework of the benzene ring. The hydrophobic effects of 4 substituents binding to the enzyme are similar to those of eq 1 (i.e., similar coefficients indicate similar hydrophobic effects).

$$-\log K = 0.45(\pm 0.28)\pi_4 - 0.80(\pm 0.30)\sigma + 0.23(\pm 0.17)E_{s4} - 2.37 \quad (4)$$
$$n = 14; r = 0.953; s = 0.168$$

The results of eq 1 and 2 show that substituent constants and regression analysis can be used to study ligand interactions of various model enzyme systems and that the resulting correlation equations can be compared quantitatively with those which are now being generated with the natural macromolecules and enzymes. Much more complex comparisons can be made; for example, instead of using $RCOOC_6H_4$-p-NO_2 to develop eq 1, one could use $RCOOC_6H_4$-X. For such a set of congeners, the electronic effect of X, as well as its hydrophobicity, could be included in the correlation equation. By making a better selection of R for which E_s values are known, one could also assess the importance of steric effects around the reaction center. By making more sterically restricting cyclophanes, one could study steric effects such as those brought out by the E_s term of eq 4.

This is the first instance, to our knowledge, where π constants have been used to correlate the interaction of small organic compounds (not micelles) hydrophobically.

It must be noted that micelle formation with some of the very hydrophobic molecules used in this study is a serious problem. Murakami et al. were well aware of the possible complications which could result from micelle formation and took precautions to work below critical micelle concentrations. There is the possibility that some micelle formation may have occurred; however, if it did it would probably have little effect on the shape of eq 1. Equation 1 is very similar to eq 2, in which hydrolysis is occurring in micelles.

Through such comparative studies of model enzymes using correlation equations to disentangle the multiple effects of substituents, our understanding of the enzymic process will be greatly increased.

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Structure–Reactivity Relationships of *N*-Alkyl(trimethylsilyl)amides[1]

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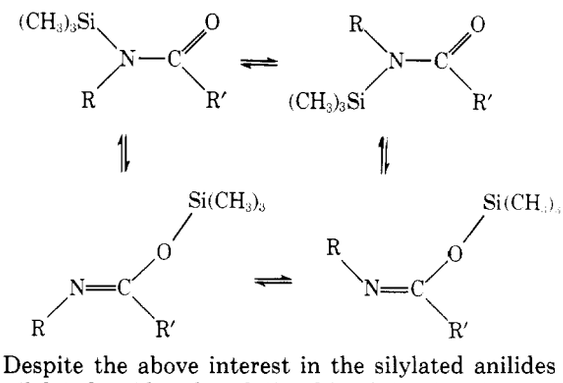
Silylating agents play an important role in both academic and industrial applications because of their ability to alter solubility, affect the course of some chemical reactions, increase volatility, etc. One important class of silylating agent, the silylamides, has sparked considerable interest because of their structural complexity and high chemical reactivity.[2,3]

Although bis(trimethylsilyl)amides[5] and (trimethylsilyl)-acetanilides[3,6,7] are thought to consist of a mixture of *N*-silylated amide and the *O*-silylated imidate tautomeric structures, the *N*-alkyl(trimethylsilyl)amides have been reported to be totally in the *N*-silylated amide form.[4] There is the possibility of additional structural complexity arising from restricted rotation or cis–trans isomerization for amide and imidate forms as illustrated below:



Despite the above interest in the silylated anilides and bissilylated amides, the relationship of structure to reactivity in the simple silylated *N*-alkylamides has been largely ignored.

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