reactant (2–5) was added to it. The solvolysis proceeded with continual stirring. The *p*-toluenesulfonic acid (or HBr) liberated during the solvolysis was automatically neutralized with 0.1 N NaOH solution. The titre was registered automatically on a graph, and the data was gathered in such a way that the Guggenheim method[25] could be employed for calculation of the rate constants.

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Registry No.—**2,** 57951-59-4; **3,** 57951-60-7; **4,** 57951-61-8; **5,** 39225-19-9; **6,** 27374-25-0; **7,** 13837-45-1; **8a,** 57951-62-9; **8b,** 57951-63-0; **8c,** 57951-64-1; **10** (R = C_6H_5), 57951-65-2; **10** (R = cyclopropyl), 57951-66-3; **11** (R = C_6H_5), 19307-74-5; **11** (R = cyclopropyl), 57951-67-4; **12** (R = CH_3), 57951-68-5; **12** (R = C_6H_5), 57951-69-6; **12** (R = cyclopropyl), 57951-70-9; **13** (R = C_6H_5), 57951-71-0; propynyl bromide, 2003-82-9; phenylacetylene bromide, 42560-90-7; cyclopropylacetylene, 6746-94-7; 1-cyclopropyl-1,1-dichloroethane, 40459-85-6; cyclopropylacetylene bromide, 57951-72-1; tosyl chloride, 98-59-9.

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Structure–Activity Relationships in Papain–Ligand Interactions

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Quantitative structure–activity relationships have been formulated for two sets of ligands (XC_6H_4O-$COCH_2NHSO_2Me$ and $XC_6H_4OCOCH_2NHCOC_6H_5$) binding to papain. The data of Williams and co-workers are analyzed to show that K_m is correlated with electron withdrawal by inductive-field effect by X and by the polarizability of X as measured by the molar refractivity of X. It is suggested that one part of the ligand interacts with a hydrophobic pocket via desolvation and that a second part binds in a polar area without desolvation.

We have been interested in developing quantitative structure–activity relationships (QSAR) for enzyme–ligand interactions. Our work,[1–4] taken with that of others,[5–9] provides convincing evidence that the use of a multiparameter approach, based on substituent constants and regression analysis, enormously extends one's ability to cast enzymic structure–activity relationships in numerical terms. Early QSAR studies with enzymes often attempted to rationalize substituent effects on enzyme–ligand interactions with the simple Hammett equation, generally by omitting those substituents which were not well fit. More recently, more comprehensive treatments have been based on electronic, steric, and hydrophobic[10] constants for substituents. However, there has been a long-standing interest in the use of polarizability of substituents to rationalize the affinity they impart to a parent molecule for interaction with a biomacromolecule. Pauling and Pressman[11] appear to be the first to have attempted the correlation of binding constants of haptens and antibodies with molar refractivity of substituents. They showed, with certain assumptions, that one could expect a linear relationship between log K and MR where K is an equilibrium binding constant and MR is defined by the Lorentz–Lorenz equation:

$$MR = \frac{n^2 - 1}{n^2 + 2}\frac{MW}{d} \quad (1)$$

In eq 1, n is the refractive index, MW the molecular weight, and d the density of a molecule. MR is an additive property of organic compounds and extensive tables of its values for substituents have been compiled.[12] While Pauling and Pressman did not obtain a high correlation between binding constants of haptens and antibodies (this was later shown to be controlled by steric effects of substituents),[13] their basic idea appears sound.

We have found two parameters (π and MR) in our studies of QSAR of enzymes for nonspecific interactions of substituents to be necessary to correlation work. A large amount of evidence has accumulated to establish the importance of hydrophobic regions in enzymes and log P or π (from octanol–water partition coefficients)[14] appear to correlate substituent interactions in these regions.[1–10]

One must also consider the "other space" which is not hydrophobic. This nonhydrophobic space must be polar in nature; hence, one would not expect desolvation of a substituent interacting with such space to play an important role in the interaction. Pauling and Pressman envisioned

Table IA. Data Used for Formulation of Equations 4–9 for $XC_6H_4OCOCH_2NHSO_2Me$

Registry no.	Substituent X	Log $1/K_m$ Obsd	Log $1/K_m$ Calcd[a]	σ	π	MR	$\mathcal{R}$-4	$\mathcal{F}$-3,4
39092-90-7	4-OH	2.05	1.888	−0.37	−0.67	0.28	−0.64	0.29
26322-96-3	4-OMe	2.13	2.194	−0.27	−0.02	0.79	−0.51	0.26
36092-92-9	4-Me	2.08	2.110	−0.17	0.56	0.56	−0.13	−0.04
36092-93-0	3-Me	2.23	2.147	−0.07	0.56	0.56	0.00	−0.04
36092-94-1	H	1.79	1.930	0.00	0.00	0.10	0.00	0.00
36092-95-2	4-F	1.95	1.946	0.06	0.14	0.09	−0.34	0.43
36092-96-3	3-OMe	2.29	2.339	0.12	−0.02	0.79	0.00	0.26
36092-97-4	4-CHO	2.33	2.397	0.42	−0.65	0.69	0.13	0.31
36124-81-9	4-Cl	2.38	2.279	0.23	0.71	0.60	−0.15	0.41
36124-82-0	3-F	1.98	2.050	0.34	0.14	0.09	0.00	0.43
36124-83-1	4-COMe	2.57	2.654	0.50	−0.55	1.12	0.20	0.32
36124-84-2	3-NO_2	2.53	2.531	0.71	−0.28	0.74	0.00	0.67
35960-92-0	4-NO_2	2.71	2.556	0.78	−0.28	0.74	0.16	0.67

[a] Calculated via eq 7.

Table IB. Data Used for Formulation of Equations 10–14 for $XC_6H_4OCOCH_2NHCOC_6H_5$

Registry no.	Substituent X	Log $1/K_m$ Obsd	Log $1/K_m$ Calcd[a]	σ	MR	π
30022-13-0	4-NH_2	3.58	3.559	−0.66	0.54	−1.23
29736-20-7	4-Me	4.02	3.931	−0.17	0.56	0.56
2979-54-6	H	3.77	3.700	0.00	0.10	0.00
2979-52-4	4-Cl	4.00	4.253	0.23	0.60	0.71
29736-22-9	4-F	3.69	3.736	0.06	0.09	0.14
2979-53-5	3-NO_2	4.74	4.710	0.71	0.74	−0.28
3101-11-9	4-NO_2	4.85	4.761	0.78	0.74	−0.28

[a] Calculated via eq 13.

dispersion forces playing the main role in the binding of substituents to antibodies and based their thinking on the London equation.

Franks[15] has recently summarized evidence for two types of "hydrophobic bonding". In addition to the traditional type in which desolvation of an aqueous shell is the driving force, there is considerable evidence to show that two solvated groups surrounded by their flickering clusters of water molecules may be held together in solution by mutual stabilization of their water "clathrates".

The view of Franks seems to us to be the best model to explain the efficacy of MR in correlating certain types of enzyme–ligand interactions. The thought is of course similar to that of Pauling and Pressman's except that a layer of water molecules separates ligand and enzyme. In searching for examples of data to support our hypothesis, one runs into the problem that collinearity between π and MR is often so high for a given data set that either vector will correlate the data. There are also inbetween cases where collinearity is high but one variable is significantly better so that one is led to suspect certain space as being predominantly hydrophobic or polar.[4,16–18] Of course, no region of significant size in or on an enzyme would be purely hydrophobic or purely polar; we are speaking of the predominant character.

While Franks speaks of a second kind of hydrophobic interaction, we prefer to regard a hydrophobic effect as being primarily determined by desolvation of substituent and enzyme and think of a second type of nonspecific interaction which does not involve significant desolvation. The nature of this type of interaction is not clear but appears to be well modeled by MR, not π.

An example of the characterization of nonhydrophobic space can be given using the work of Loontiens et al.[19] These authors measured the binding constants between Concanavalin A and 19 4-X-phenyl-β-D-glucosides. Their results have been correlated by the following two equations[20]

	n	r	s	
Log M_{50} = 0.097π + 2.37	19	0.664	0.095	(2)
Log M_{50} = 0.019MR + 2.23	19	0.950	0.038	(3)

in which n represents the number of data points, r the correlation coefficient, and s the standard deviation from the regression. Although there is considerable collinearity between π and MR (r^2 = 0.50), MR is obviously the much more important variable. Equation 3 is highly significant ($F_{1,17}$ = 172; $F_{1,17\ \alpha.001}$ = 15.7); MR has been scaled by 0.1 in this equation to make it more equiscalar with π.

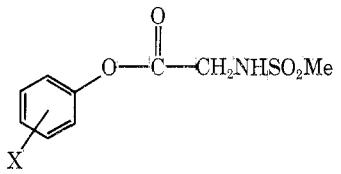
The studies of Williams[21,22] on the hydrolase papain have recently come to our attention. Williams and his coworkers have measured K_m and k_o of three sets of congeners reacting with papain. There is little variation in k_o so that hydrolysis of aryl esters by this enzyme depends mostly on K_m. An analysis of Williams' data shows that K_m correlates well with MR of the substituents and not with π.

Method

In formulating QSAR for the papain hydrolysis of the various esters, we have studied the following parameters: π, MR, σ, and σ^-. The values of these have been taken from our recent compilation.[12] As usual, we have scaled MR by 0.1. We have formulated eq 4–16 from the data in Tables I and II.

Results

The largest set of data for the papain hydrolysis studies is that for congeners of type 1. Williams[22] measured k_o/K_m for 14 derivatives and found that all but four points gave a good linear relationship with σ. The 4-$OCH_2C_6H_5$ deriva-



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tive was so insoluble that K_m values were not reported for this compound; hence we have derived eq 4–8 for 13 data points.

	n	r	s	
Log $1/K_m$ = 0.54(±0.34)σ + 2.14(±0.13)	13	0.730	0.192	(4)
Log $1/K_m$ = −0.16(±0.38)π + 2.23(±0.17)	13	0.271	0.271	(5)
Log $1/K_m$ = 0.69(±0.33)MR + 1.85(±0.21)	13	0.813	0.164	(6)
Log $1/K_m$ = 0.53(±0.23)MR + 0.37(±0.20)σ + 1.88(±0.13)	13	0.935	0.105	(7)
Log $1/K_m$ = −0.04(±0.30)π + 0.53(±0.37)σ + 2.14(±0.14)	13	0.732	0.201	(8)

Using all of the data, it is clear that MR is a more important variable than σ and that it is much more important than π. It is evident from Table IIB that π, σ, and MR are remarkably orthogonal. Therefore, we can say with some confidence that the space into which the substituents bind is not typically hydrophobic and that desolvation appears not to be involved in binding of enzyme and substrate. Equation 7 is a significant improvement over eq 6 ($F_{1,10}$ = 15; $F_{1,10\ \alpha.005}$ = 12.8). Hence, two properties of substituents are seen to promote binding: polarizability and electron-withdrawing power. The use of σ^- in place of σ in eq 7 results in a slightly poorer correlation (r = 0.922).

More insight into the nature of the electronic effect can be obtained by factoring σ into inductive and resonance components. Taft and his colleagues have discussed the importance of this operation for obtaining deeper insight into reaction mechanisms.[23] Swain and Lupton's $\mathcal{F}$ and $\mathcal{R}$ parameters[12] for inductive and resonance have been used since Taft's σ_I and σ_R set lacks values for OH and CHO groups. Because the contributions of $\mathcal{F}$ and $\mathcal{R}$ are position dependent, we first formulated an equation by the linear combination of the five terms: $\mathcal{F}$-3, $\mathcal{R}$-3, $\mathcal{F}$-4, $\mathcal{R}$-4, MR. This is of course too many terms for 13 data points; however, it was clear from this equation that $\mathcal{R}$-3 was unimportant and that the coefficients with $\mathcal{F}$-3 and $\mathcal{F}$-4 were close enough in value to be combined. This leads to eq 9

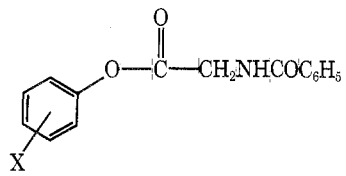
	n	r	s	
Log $1/K_m$ = 0.56(±0.22)MR + 0.51(±0.28)$\mathcal{F}$-3,4 + 0.23(±0.27)$\mathcal{R}$-4 + 1.79(±0.16)	13	0.949	0.098	(9)

which brings out the fact that the inductive-field effect and the polarizability of substituents determine K_m. While $\mathcal{R}$-4 is significant ($F_{1,9}$ = 3.5; $F_{1,9\ \alpha.1}$ = 3.4), it is of marginal importance (note confidence limits). The correlation using variables mentioned above has a standard deviation of 0.102 compared to 0.098 of eq 9.

Equations 10–14

	n	r	s	
Log $1/K_m$ = 0.90(±0.53)σ + 3.97(±0.25)	7	0.892	0.251	(10)
Log $1/K_m$ = 0.03(±0.90)π + 4.09(±0.54)	7	0.038	0.554	(11)
Log $1/K_m$ = 1.31(±1.5)MR + 3.46(±0.82)	7	0.708	0.392	(12)
Log $1/K_m$ = 0.77(±0.67)MR + 0.73(±0.37)σ + 3.62(±0.34)	7	0.971	0.148	(13)
Log $1/K_m$ = −0.17(±0.45)π + 0.96(±0.58)σ + 3.95(±0.28)	7	0.916	0.248	(14)

correlate K_m values for the hydrolysis of congeners of type 2 by papain. In this smaller set of congeners, σ appears to



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be slightly more important than MR; however, eq 13 is a significant improvement over eq 10 ($F_{1,4}$ = 9.1; $F_{1,4\alpha.05}$ = 7.7). π is of no importance. From the squared correlation matrix of Table IIB, π and MR are seen to be noncollinear. Equations 7 and 13 are in agreement with respect to π, MR, and σ. Taken alone, one cannot place much weight on eq 13 since only seven data points are correlated by two variables but, together with eq 7, a convincing case is made for a nonhydrophobic interaction of X.

A third set of congeners of the type $C_6H_5CONHCH_2COOR$ was also studied with papain.[21] However, suitable σ constants are not available for this mixed set and an analysis could not be made.

Williams correlated his data using k_o/K_m and, since k_o is essentially constant, this definition of activity produces a similar result. Equation 15 shows the relationship.

	n	r	s	
Log k_o/K_m = 0.60(±0.24)MR + 0.31(±0.20)σ + 2.95(±0.14)	13	0.930	0.110	(15)

It is again found that MR is a more important variable than σ (r for the linear relationship between log k_o/K_m and σ is 0.661, while for MR, r is 0.847). The dual-parameter equation gives an improved correlation ($F_{1,10}$ = 3.5); however, the improvement is not as great as with log $1/K_m$, indicating that electronic effects tend to cancel in the binding and hydrolysis steps.

Equations 7 and 13 can be combined by means of an indicator variable (I) which in eq 16

	n	r	s	
Log $1/K_m$ = 0.57(±0.26)MR + 0.56(±0.19)σ − 1.92(±0.15)I + 3.74(±0.17)	20	0.990	0.148	(16)

takes the value of 1 for congeners having the $NHCOC_6H_5$ moiety and zero for congeners with the $NHSO_2Me$ group; hence, the intercept of eq 16 should be the same as eq 13, which is the case within the confidence limits. One should not attach much importance to the very high correlation coefficient since this is partly the result of adding a large amount of variance by combining two data sets rather far apart in data space. The coefficients in eq 16 are close to those of eq 7 and of course within the confidence limits of those of eq 13. Equation 16 indicates the parallel QSAR for the two data sets and establishes the distance between the lines as 1.92 log $1/K_m$ units.

Table IIA. Squared Correlation Matrix for Variables Considered in Equations 4–7

	σ	π	MR	$\mathcal{F}$-3,4	$\mathcal{R}$-4
σ	1.00	0.08	0.13	0.52	0.58
π		1.00	0.06	0.14	0.00
MR			1.00	0.03	0.13
$\mathcal{F}$-3,4				1.00	0.01
$\mathcal{R}$-4					1.00

Table IIB. Squared Correlation Matrix for Variables Considered in Equations 10–14

	σ	π	MR
σ	1.00	0.07	0.17
π		1.00	0.02
MR			1.00

Discussion

Williams and his colleagues clearly showed that there is a correlation between K_m and σ in the hydrolysis of esters by papain. However, to do so it was necessary to omit a number of data points from consideration. We have advanced their efforts by showing that if the polarizability of the substituents is also considered, all data points can be correlated in a single equation. By factoring σ into resonance and inductive components it is possible to show that it is the inductive-field effect of substituents which is important in papain hydrolysis. Williams et al.[24] observed that a "lipophilic" force was also involved; by lipophilic they meant "a blanket term to cover donor–acceptor (or charge-transfer) hydrophobic and van der Waals–London dispersion forces". Our results clarify and quantify this nonspecific interaction and suggest that the classical hydrophobic interaction heavily dependent on desolvation is absent.

The role of the electronic effect of substituents is small and only the inductive-field effect is involved. It may be that electron withdrawal from the aromatic ring simply results in better van der Waals–London type interactions. Electron withdrawal could also facilitate binding of the thiol by the carbonyl group.

There is considerable knowledge of the structure of papain from both x-ray studies[25] and ligand–enzyme interactions.[26–28] Figure 1 suggests schematically how ligands of types **1** and **2** might bind to papain.

In formulating Figure 1, we have found the representation of papain by Dickerson based on the coordinates of Drenth to be most helpful.[29] The polar regions where the substituents are shown to be binding is a bank, open on one side to solvent, made up of the following nonhydrophobic amino acids: Lys 17, Asn 18, Glu 19, Gly 20, Ser 21, Gly 23, Gly 62, Asp 64, Gly 65. The pocket in which Y is depicted as interacting is made up largely of hydrophobic residues. There are two types of Y: $NHSO_2Me$ and $NHCOC_6H_5$.

Equation 16 shows that $NHCOC_6H_5$ produces 1.92 higher log $1/K_m$ than $NHSO_2Me$. Is this reasonable for the hydrophobic interaction suggested in Figure 1? The π values for these substituents are 0.49 and −1.18, respectively. The differences in hydrophobicity between the two groups is 1.67. What kind of coefficient with π would one expect for hydrophobic binding? In the case of substrates and ligands binding to the hydrophobic pocket in chymotrypsin, an average coefficient for π with eight sets of data was found to be 1.2. Assuming papain to be similar to chymotrypsin, we could expect an increase of 2.0 (i.e., 1.2 × 1.67) in log $1/K_m$. This agrees quite well with 1.92 found.

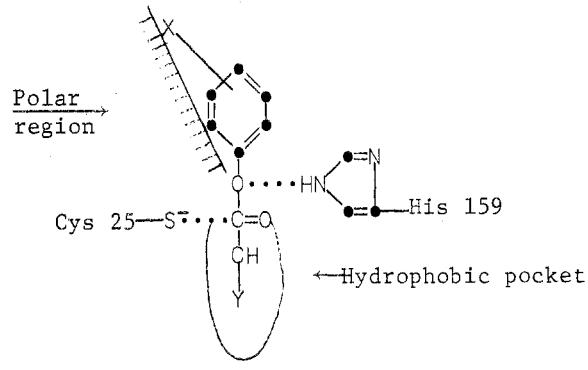

Figure 1.

We think that the model for substrate binding with papain accounts well for a variety of data now available and constitutes a basis for further study in the mapping of the papain active site.

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Registry No.—Papain, 9001-73-4.

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