Kinetic Steric Factors and Connectivity Indices

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Abstract □ In this study the relationships between previously reported connectivity indices described by Kier and Hall and steric contributions to the rate constants for several series of reactions are examined. Rate data were examined for four different series of reactions, which were chosen to represent a range of different reaction mechanisms and transition-state structures. For sterically controlled reactions, the relative rates of series of substrates can be correlated either with the connectivity indices of the substrates themselves or with the changes in the indices that accompany formation of transition states. As expected, the significant indices in the correlations are of the cluster and path-cluster types. The connectivity indices should be useful descriptors in helping relate equilibrium properties, chemical reactivities, and pharmacological data to one another.

Keyphrases □ Connectivity indices—relationship with steric contributions to rate constants □ Kinetic steric factors—relationship with connectivity indices to rate constants

The development of structure–activity relationships (SAR) in pharmacology (1, 2) has relied heavily on the use of physicochemical parameters which are based on chemical reactivity relationships, such as Hammett σ-ρ constants and Taft E_s values. Many of the more recent studies, including those in which pattern recognition methods are employed, also make use of other descriptors which reflect substructural information like molecular connectivity and branching characteristics (3). The connectivity indices described by Kier and Hall (4), which were introduced as a generalization of the Randic' branching index (5), have proved to be extremely useful in this regard.

Kier and co-workers and others have been quite successful in obtaining correlations (4, 6–8) of physical, thermodynamic, and pharmacological properties with the connectivity indices, but there has been only one report to date concerned with the relationship between connectivity indices and chemical reactivity (9). There obviously are very close relationships between physicochemical parameters, chemical reactivities, and pharmacological properties, and it is important that these relationships be understood. We have therefore undertaken the present study of correlations between molecular connectivity and chemical reactivity.

It is clear that the connectivity indices described by Kier and Hall carry information about the nature and number of atoms in the molecule, as well as the degree of branching and the amount of folding. The dependence of kinetic steric factors on molecular branching has been well established by the detailed studies of Charton (10), Dubois *et al.* (11), and Ruchardt and Beckhaus (12), among others; therefore, kinetic steric factors may be correlated with connectivity indices. In fact, the link between the two has already been made by Murray (9), who succeeded in finding correlations between the Taft E_s parameters (13) and effective connectivity indices for a series of substituted alkanes.

The connectivity indices are based on hyrogen-suppressed graphs and are defined by:

$$ {}^{m}\chi_t = \sum_{j=1}^{n_m} \left[\prod_{i=1}^{m+1} (\delta_i)^{-1/2} \right]_j \qquad \text{(Eq. 1)} $$

where m is the number of connected edges in the subgraph defined by the atoms whose valencies are denoted by δ_i. The summation is over the entire set of all n_m possible subgraphs of the given order and type. The different types which can occur for $m \geq 3$ are differentiated by t; the designation used is $t = P$ for path, C for cluster, PC for path-cluster, and CH for chain (cycle).

The approach taken by Murray was to correlate kinetic steric factors with χ values for a series of substrates in a particular reaction. This implies that steric factors simply reflect structural features of the ground-state substrate molecules. Although many kinetic data have been successfully correlated with ground-state properties of substrate molecules in the past, it seems that a better approach would be based on the transition-state theory. This would correlate kinetic data with parameters which measure the changes that take place during the activation process for a reaction. In particular, we suggest that a convenient set of parameters can be defined as:

$$ \Delta({}^{m}\chi_t) = {}^{m}\chi_t^{\ddagger} - {}^{m}\chi_t \qquad \text{(Eq. 2)} $$

where ${}^{m}\chi_t^{\ddagger}$ is the connectivity index for transition states and ${}^{m}\chi_t$ is the corresponding quantity for reactant molecules. The utility of $\Delta{}^{m}\chi_t$ to measure kinetic steric factors is suggested by the striking success that Kier and co-workers achieved in correlating molar heats of formation with ${}^{m}\chi_t$. If similar relations hold in the transition state, then it would be expected that the enthalpy of activation and the activation energy will be related to $\Delta{}^{m}\chi_t$.

Our goal was to determine whether correlations could be found between chemical reactivity and connectivity indices (either ${}^{m}\chi_t$ or $\Delta{}^{m}\chi_t$). We considered four different chemical reactions: quaternization of substituted pyridines, bromide exchange reaction of branched alkanes, acid-catalyzed hydrolysis of alkanoic esters, and a nucleophilic substitution process on chlorodinitrobenzene, all of which will be discussed below. In all cases, we have found that both sets of indices do generally correlate with the reactivity data.

Our calculations differed from those of Murray in two respects. First, we calculated ${}^{m}\chi_t$ for the actual full substrate molecules rather than replacing the reactive center with an effective atom that has some arbitrary valence. Second, we treated subgraphs of different types separately, since we expected the cluster or path-cluster terms to be most important. All of our indices were calculated with a FORTRAN program developed along the lines of the algorithm suggested by Kier and Hall (4). We simply employed the list of atomic valencies (δ_i) which they provided, including the empirical values they had found appropriate for halogen atoms[1].

[1] Values of δ used in this study were: $-CH_3$, 1; $-CH_2-$, 2; $-\overset{|}{C}H-$, 3; $-\overset{|}{\underset{|}{C}}-$, 4; $-NH_2$, 3; $\equiv N$, 5; $-N=$(pyridine), 5; $-\overset{|}{\underset{|}{N}}-$ (quaternary), 6; OH, 5; $-O-$, 6; $=O$, 6; $-Br$, 0.254.

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Table I—Standard Heats of Formation in the Gas Phase at 25°C

Compound	ΔH_f°, g/kcal·mol^{-1} Experimental[a]	Calculated (Eq. 2)[b]
Pyridine	34.55	33.96
2-Methylpyridine	23.70	24.79
3-Methylpyridine	25.42	25.01
4-Methylpyridine	24.41	25.01
2,3-Dimethylpyridine	16.32	15.70
2,4-Dimethylpyridine	15.27	15.83
2,5-Dimethylpyridine	15.88	15.83
2,6-Dimethylpyridine	14.03	15.62
3,4-Dimethylpyridine	16.74	15.92
3,5-Dimethylpyridine	17.40	16.05

[a] From Ref. 17. [b] See Table VII for values of $^m\chi_t$.

RESULTS AND DISCUSSION

Substituted Pyridines and Their Quaternization Rates—The alkylation of substituted pyridines is one of the most studied reactions from a structure–reactivity point of view (14–16). Because the steric and branching effects of pyridine alkylation are so well understood, this reaction seemed to be an ideal first candidate for a connectivity index study. Since some of the most striking correlations described by Kier and Hall are for molar heats of formation, we decided to first look at the available data of that type for the alkylpyridines. The only data available were those listed by Cox and Pilcher (17) for the 10 compounds listed in Table I. We found that these values could be described by the simple expression:

$$\Delta H_f^\circ(g)/(\text{kcal}\cdot\text{mol}^{-1}) = -21.80(^1\chi) + 74.27 \qquad \text{(Eq. 3)}$$

where $r = 0.9897$, $RSD = 0.98$, and $n = 10$. The correlation coefficient can be increased to 0.9922 by any of the following:

$$\Delta H_f^\circ(g)/(\text{kcal}\cdot\text{mol}^{-1}) = -32.97(^1\chi) + 10.05(^2\chi) + 84.49 \qquad \text{(Eq. 4)}$$

$$= -24.02(^1\chi) + 4.49(^4\chi_{PC}) + 78.47 \qquad \text{(Eq. 5)}$$

$$= -27.84(^1\chi) + 18.00(^3\chi_C) + 85.28 \qquad \text{(Eq. 6)}$$

Although these findings are not as impressive as the results of Kier and Hall for alkanes, they are significant. The size of the current data set is appreciably smaller than that of Kier and Hall, and the uncertainties in the experimental data are larger. In Fig. 1 are shown the types of subgraphs that contribute to the indices $^2\chi$, $^3\chi_C$, and $^4\chi_{PC}$. It is appropriate that these enter the correlations Eqs. 4–6 since they measure the degree of methylation of the pyridine nucleus; $^4\chi_{PC}$ also contains a measure of the degree of substitution at adjacent pyridine sites.

If one examines the series of rate constants previously reported (14–16) for the methylation of alkylpyridines, it appears that the relative rates are dominated by steric effects and have only subordinate electronic contributions. We have recently published (14, 16) some theoretical studies of this reaction based on the model transition state (TS) corresponding to the activation process shown in Scheme I. We used this model to calculate a set of ($^m\chi_t^\ddagger$) and $\Delta(^m\chi_t)$ for a series of 37 alkyl-substituted pyridines (Table II). The valency of nitrogen in the model transition states was taken to be 6, which is the value suggested by Kier and Hall for quaternized nitrogen (4). This corresponds to the assumption to a fully formed N—CH_3 bond in the TS; in subsequent studies, it may be desirable to use intermediate valencies which correspond to partially formed bonds. For the set of 37 alkylpyridines, in which the relative reaction rates cover four orders of magnitude, the best linear correlation we found was:

$$\ln(k_{rel}) = -10.7\,\Delta^5\chi_{PC} + 2.75 \qquad \text{(Eq. 7)}$$

where $r = 0.8786$, $RSD = 1.28$, $n = 37$, and k_{rel} is the second-order rate constant relative to that of pyridine.

Other powers of the parameters were investigated, and the best correlation obtained was:

$$\ln(k_{rel}) = -10.4(\Delta^5\chi_{PC})^2 - 7.24(\Delta^4\chi_{PC})^2 + 1.30 \qquad \text{(Eq. 8)}$$

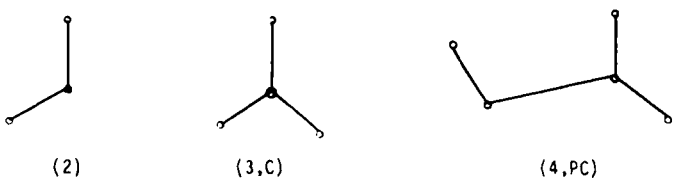
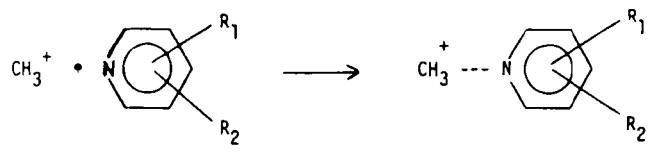


Figure 1—*Illustrative subgraphs of types* $^2\chi$, $^3\chi_C$, $^4\chi_{PC}$.



Scheme I

where $r = 0.9092$, $RSD = 1.13$, and $n = 37$. The results of Eq. 8 are compared with the observed values of [ln (k_{rel})] in Table II. In Figure 2 are shown some illustrative subgraphs that contribute to $\Delta^5\chi_{PC}$ and $\Delta^4\chi_{PC}$ for the model transition states. It is easy to see that these terms should constitute measures of steric hindrance in the reaction.

In the case of Eq. 8, as well as for all succeeding correlations involving multiple parameters, statistical tests were applied regarding the utility of the added parameters. Parameters were not added to the correlations unless they were significant at the 90% confidence interval, as indicated by the *F*-test.

Although Eqs. 7 and 8 are quite reasonable, better results might have been expected. Further consideration indicates that there may be a good reason for this discrepancy; although this reaction is dominated by steric factors, there are apparently sizeable electronic contributions in some cases. In fact, Berg *et al.* (18) have studied the iodomethylation of a series of 2-substituted pyridines, using heteroatom substituents as well as alkyl groups, and have arrived at a separation of electronic and steric contributions to the relative rates of reaction. They separated log (k_{rel}) into steric (S°) and electronic (E°) components:

$$\log(k_{rel}) = S^\circ + E^\circ \qquad \text{(Eq. 9)}$$

and, using a Brønsted relation to estimate E°, were able to determine S° and E° for the series of molecules. For the series of 2-alkylpyridines with alkyl groups being methyl, ethyl, isopropyl, and *tert*-butyl, they found values of E°/S° to be −0.59, −0.33, −0.24, and −0.061, respectively. Whether or not their values of S° and E° are precisely correct, it must be concluded that electronic effects are not insignificant in the above series of alkylpyridines and, furthermore, that their fractional contributions vary considerably through the series.

Table II—Relative Rates of Methylation of Substituted Pyridines

Compound	ln (k_{rel}) Observed[a]	Eq. 8[b]
Pyridine	0	0.925
2-Picoline	−0.844	−0.249
3-Picoline	0.531	0.490
4-Picoline	0.742	0.977
2,3-Lutidine	−0.844	−1.395
2,4-Lutidine	−0.083	−0.106
2,5-Lutidine	−0.198	−0.790
2,6-Lutidine	−3.219	−2.657
3,4-Lutidine	1.224	0.644
3,5-Lutidine	0.956	−0.247
2-Ethylpyridine	−1.514	−0.673
2-Isopropylpyridine	−2.590	−2.375
2-*tert*-Butylpyridine	−8.422	−5.570
2-Methyl-3-ethylpyridine	−0.734	−0.823
2-Methyl-3-isopropylpyridine	−0.673	−0.552
2-Methyl-3-*tert*-butylpyridine	−1.109	−0.364
2,6-Diethylpyridine	−5.599	−3.672
2,6-Diisopropylpyridine	−8.805	−9.238
2,4,6-Trimethylpyridine	−2.207	−2.307
2,3,5,6-Tetramethylpyridine	−4.343	−6.629
2,3,4,5,6-Pentamethylpyridine	−4.200	−5.694
3-Ethylpyridine	0.788	0.690
4-Ethylpyridine	0.833	0.971
3-Isopropylpyridine	0.875	0.774
4-Isopropylpyridine	0.788	0.969
3-*tert*-Butylpyridine	1.030	0.875
4-*tert*-Butylpyridine	0.788	0.924
2-Methyl-5-ethylpyridine	0.095	−0.531
2-Methyl-5-isopropylpyridine	0.182	−0.383
2-Methyl-5-*tert*-butylpyridine	0.262	−0.263
2,3-Cyclopentenopyridine	0.642	−0.935
2,3-Cyclohexenopyridine	−1.204	−0.935
2-Ethyl-3-methylpyridine	−1.427	−1.892
2-Ethyl-5-methylpyridine	−0.616	−1.509
2-Ethyl-6-methylpyridine	−5.655	−3.005
2-Isopropyl-3-methylpyridine	−5.776	−3.900
2-Isopropyl-5-methylpyridine	−1.772	−3.644

[a] From Refs. 14–16. [b] See Table VIII for values of $\Delta^m\chi_t$.

Table III—Relative Rates and Steric Factors for the Methylation of 2-Substituted Pyridines

2-Substituent	log (k_{rel})[a]	$S°$ (Experimental)[a]	$S°$ (Eq. 11)[a,b]	$S°$ (Eq. 12)[b]	$S°$ (Eq. 14)[b]
—CH_3	−0.30	−0.73	−0.82	−0.73	−0.80
—C_2H_5	−0.72	−1.08	−1.02	−1.02	−0.94
—Isopropyl	−1.10	−1.44	−1.65	−1.66	−2.07
—*tert*-Butyl	−3.70	−3.44	−4.02	−4.01	−3.78
—CH_2OH	−0.59	−0.67	−0.93	−0.88	−0.84
—CH_2CH_2OH	−0.68	−0.86	−1.20	−1.13	−0.99
—CH_2—Phenyl	−1.05	−1.16	−1.41	−1.29	−1.59
—$CO_2C_2H_5$	−2.14	−1.25	−1.24	−1.42	−1.17
—Phenyl	−2.00	−1.82	−1.62	−1.70	−1.73
—2-Pyridyl	−2.48	−2.35	−1.51	−1.63	−1.56
—NH_2	−0.30	−0.93	−0.89	−0.78	−0.73
—C≡N	−2.70	−0.89	−0.95	−1.00	−0.78
—Br	−2.36	−0.82	−0.67	−0.70	−0.95

[a] From Ref. 18. [b] See Table IX for values of ${}^m\chi_t$ and $\Delta^m\chi_t$.

For the whole set of molecules studied, Berg *et al.* (18) found that the ratio of $E°/S°$ varies from −0.68 to +2.03, so the data cover the range from predominant steric control to predominant electronic control. The values of $S°$ which they obtained for the 2-substituents —CHO and —$COCH_3$ seemed out of line with the rest of their data, so we dropped those compounds from further consideration, leaving a total of 13 compounds to be considered (Table III). No significant correlations could be found for log (k_{rel}); this is consistent with the conclusion that both electronic and steric factors are important in this series (18). The situation was dramatically different when the values of $S°$ were examined. The best single-parameter linear correlation was:

$$S° = -4.43\Delta^6\chi_{PC} + 0.26 \qquad \text{(Eq. 10)}$$

where $r = 0.8739$, $RSD = 0.46$, and $n = 13$. The situation improved dramatically when multiple parameters were permitted. The best linear relation obtained was:

$$S° = -4.11(\Delta^6\chi_{PC}) - 70.1(\Delta^3\chi_C) + 3.00(\Delta^4\chi_P) + 7.27 \qquad \text{(Eq. 11)}$$

where $r = 0.9430$, $RSD = 0.35$, and $n = 13$. When other powers of the parameters were examined, slightly better agreement was found by:

$$S° = -0.584(\Delta^4\chi_{PC})^{-1} - 0.117(\Delta^4\chi_P)^{-1} + 0.338(\Delta^6\chi_{PC})^{-1} + 0.460 \qquad \text{(Eq. 12)}$$

where $r = 0.9585$, $RSD = 0.30$, and $n = 13$. The values of $S°$ calculated from Eqs. 11 and 12 are compared with the experimentally derived values of Berg *et al.* (18) in Table III. These investigators did a credible job of identifying steric contributions to these relative rates. Furthermore, as we expected, Eqs. 10–12 are dominated by path-cluster- and cluster-type terms.

If we correlate $S°$ with the indices of the substrate molecules themselves, the best single-parameter equation is somewhat better than Eq. 10:

$$S° = -3.41({}^5\chi_{PC}) - 0.35 \qquad \text{(Eq. 13)}$$

where $r = 0.9127$, $RSD = 0.47$, and $n = 13$. However, the best multiple-parameter equation is not quite as good as Eqs. 11 or 12:

$$S° = -13.69({}^5\chi_C) - 0.93({}^4\chi_P) - 0.38 \qquad \text{(Eq. 14)}$$

where $r = 0.9270$, $RSD = 0.44$, and $n = 13$. If the calculated values of $S°$ in Table III are examined it is hard to decide whether Eq. 11, 12, or 14 is preferable to the others. The single-parameter correlations behave as expected in that the index occurring in Eq. 10 (${}^6\chi_{PC}$) is of a higher order than that in Eq. 13 (${}^5\chi_{PC}$).

The success of Eqs. 10 and 13 indicates that there should exist a linear relationship between the activation indices ($\Delta^6\chi_{PC}$) and the substrate indices (${}^5\chi_{PC}$). The relation was found to be:

$$\Delta^6\chi_{PC} = 0.712({}^5\chi_{PC}) + 0.154 \qquad \text{(Eq. 15)}$$

where $r = 0.9660$, $RSD = 0.0483$, and $n = 13$. The existence of this relationship is consistent with results of a previous study on the Menschutkin reaction, which has established that relative reactivities of substituted pyridines can be interpreted either in terms of TS calculations or in terms of substrate equilibrium structures with essentially equal success (14–16).

Bromide Exchange Reaction—Another reaction which is generally accepted as being largely sterically controlled is the bromide exchange reaction of alkyl groups:

$$Br^- + RBr \rightarrow BrR + Br^- \qquad \text{(Eq. 16)}$$

which was studied experimentally by de la Mare *et al.* (19). For these reactions, Abraham and co-workers have estimated the nonbonded interactions in a model transition state (Fig. 3) and concluded that steric effects are highly dominant (20). More recently, deTar *et al.* (21) have applied molecular mechanics to the same transition state; they concluded that although steric effects apparently predominate, polar effects must be invoked to interpret the rate constants for the α series of alkyl groups (methyl, ethyl, isopropyl, *tert*-butyl).

We examined the rate constants at 25°C (Table IV) which were listed by deTar *et al.* (21). As before, transition-state valencies were assigned on the basis of fully formed bonds. This included use of the empirical value of 0.254 for bromine.

The best single-parameter correlation was rather poor:

$$\ln(k) = -2.73(\Delta^5\chi_C) - 7.50 \qquad \text{(Eq. 17)}$$

where $r = 0.7269$, $RSD = 3.70$, $n = 7$, and k is in $s^{-1}\ M^{-1}$. With two parameters the results were much better:

$$\ln(k) = -3.70(\Delta^5\chi_C) - 1.30(\Delta^3\chi_C) - 3.44 \qquad \text{(Eq. 18)}$$

where $r = 0.9763$, $RSD = 1.30$, $n = 7$, and k is in $s^{-1}\cdot M^{-1}$.

In this case, the substrate connectivity indices do a slightly better job than do the $\Delta\chi$. In comparison with Eq. 17, we have:

$$\ln(k) = -2.87({}^2\chi) - 2.87 \qquad \text{(Eq. 19)}$$

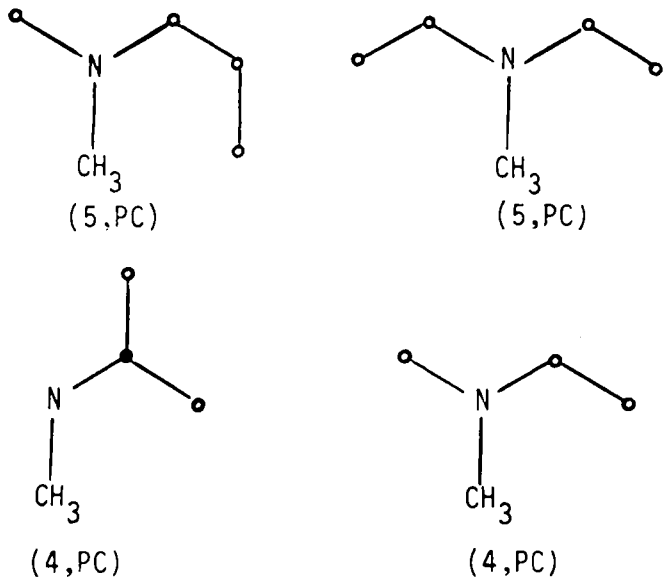


Figure 2—*Illustrative subgraphs contribution to terms in Eq. 8.*

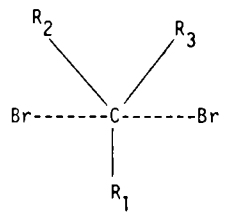


Figure 3—*Transition state for Eq. 16.*

Table IV—Second-Order Rate Constants and Steric Contributions to Activation Energies for Br^- Exchange Reactions [a]

R	ln (k)			$\Delta E^{\ddagger}_{ST}$		
	Observed [b]	Eq. 18 [c]	Eq. 20 [c]	Calc [d]	Eq. 22 [c]	Eq. 23 [c]
Methyl	−2.00	−3.44	−2.81	7.41	7.20	7.50
Ethyl	−6.41	−6.39	−6.08	13.61	12.55	12.95
n-Propyl	−6.81	−5.52	−6.29	13.65	14.40	13.30
Isopropyl	−10.96	−9.63	−9.50	17.77	18.44	18.65
Isobutyl	−9.74	−9.90	−10.42	15.48	16.79	16.07
tert-Butyl	−12.17	−13.27	−13.24	25.38	25.04	24.90
Neopentyl	−17.35	−17.28	−17.08	20.64	19.52	20.57

[a] Rate constants are in seconds^{-1}·Molar^{-1}, activation energies are in kilocalories·moles^{-1}, and the exchange reaction is depicted in Eq. 16. [b] From Ref. 19. [c] See Table X for values of $^{m}\chi_t$ and $\Delta^{m}\chi_t$. [d] From Ref. 21.

where $r = 0.8606$, $RSD = 2.73$, $n = 7$, and k is in $s^{-1}\cdot M^{-1}$. The counterpart of Eq. 18 is:

$$\ln(k) = -2.33(^{2}\chi) - 3.06(^{4}\chi_{PC}) - 2.87 \qquad \text{(Eq. 20)}$$

where $r = 0.9829$, $RSD = 1.10$, $n = 7$, and k is in $s^{-1}\cdot M^{-1}$. Note that Eqs. 19 and 20 contain lower-order indices than do Eqs. 17 and 18. The values of ln (k), as calculated from Eqs. 18 and 20 are compared with the experimental values in Table IV.

We also examined the steric contributions to the activation energies, $\Delta E^{\ddagger}_{st}$, which deTar *et al.* calculated *via* molecular mechanics (21). Correlation of these numbers with the $\Delta\chi$ values yielded the best single- and multiple-parameter correlations:

$$\Delta E^{\ddagger}_{st} = 1.64(\Delta^{3}\chi_C) + 11.96 \qquad \text{(Eq. 21)}$$

where $r = 0.7575$, $RSD = 4.11$, $n = 7$, and $\Delta E^{\ddagger}_{st}$ is in kcal·mol^{-1}, and:

$$\Delta E^{\ddagger}_{st} = 2.35(\Delta^{3}\chi_C) + 2.13(\Delta^{4}\chi_C) + 7.20 \qquad \text{(Eq. 22)}$$

where $r = 0.9865$, $RSD = 1.15$, $n = 7$, and $\Delta E^{\ddagger}_{st}$ is in kcal·mol^{-1}. These are slightly better than Eqs. 17 and 18 involving the rate constants.

When the substrate indices were used, we obtained:

$$\Delta E^{\ddagger}_{st} = 3.89(^{2}\chi) + 7.50 \qquad \text{(Eq. 23)}$$

where $r = 0.9951$, $RSD = 0.62$, $n = 7$, and $\Delta E^{\ddagger}_{st}$ is in kcal·mol^{-1}. In this case no statistically significant second parameter could be added to the correlation. However, Eq. 23 is already superior to Eq. 22. Equations 22 and 23 are compared with the molecular mechanics values of deTar *et al.* in Table IV.

Linear regression of the best single activation index ($\Delta^{3}\chi_C$) against the best single substrate index ($^{2}\chi$), yielded a correlation coefficient of only 0.752. This low value is to be expected in view of the small r associated with Eq. 21.

Whether the substrate connectivity indices ($^{m}\chi_t$) or the changes that occur in them during activation ($\Delta^{m}\chi_t$) are employed, we had slightly better correlations with the steric portion of the activation energy than we did with the rate constants. This tends to support the conclusion of deTar *et al.* (21) that polar effects are not negligible in these reactions.

E_s Values of Taft—The E_s values described by Taft (13) for alkyl groups were derived as steric contributions to the relative rates of hydrolysis reactions:

$$RCOOC_2H_5 + H_3O^+ \rightarrow RCOOH + C_2H_5OH + H^+ \qquad \text{(Eq. 24)}$$

Murray (9) correlated the E_s values with effective connectivity indices obtained for RX molecules, and assigned X an effective valency of 2. We examined these reactions using the model transition state shown in Fig. 4.

By using the $\Delta\chi$ values, the best one-parameter equation obtained was:

$$E_s = -2.48(\Delta^{6}\chi_{PC}) - 0.31 \qquad \text{(Eq. 25)}$$

where $r = 0.9181$, $RSD = 0.58$, and $n = 19$. The use of multiple parameters improved this to:

$$E_s = -2.25(\Delta^{6}\chi_{PC}) - 1.58(\Delta^{4}\chi_{PC}) + 0.08 \qquad \text{(Eq. 26)}$$

where $r = 0.9372$, $RSD = 0.53$, and $n = 19$. When the substrate indices were used for the ethyl esters, we obtained:

$$E_s = -1.57(^{3}\chi_P) + 0.69 \qquad \text{(Eq. 27)}$$

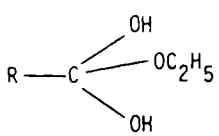
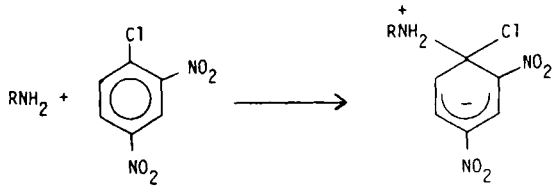


Figure 4—*Transition state for Eq. 24.*



Scheme II

Table V—E_s Values [a]

R	E_s		
	Observed [b]	Eq. 26 [c]	Eq. 27 [c]
CH_3—	0.0	−0.14	0.15
C_2H_5—	−0.07	−0.47	−0.24
$CH_3CH_2CH_2$—	−0.36	−0.48	−0.50
$CH_3CH_2CH_2CH_2$—	−0.39	−0.60	−0.94
$CH_3CH_2CH_2CH_2CH_2$—	−0.40	−0.56	−1.33
$(CH_3)_2CHCH_2CH_2$—	−0.38	−0.85	−1.24
$(CH_3)_2CH$—	−0.47	−1.00	−0.50
$(CH_3)_3C$—	−1.54	−1.67	−0.70
$(CH_3CH_2)_2CH$—	−1.98	−1.28	−1.82
$(CH_3)_3CCH_2$—	−1.74	−1.21	−0.84
$(CH_3CH_2CH_2)_2CH$—	−2.11	−1.55	−2.27
$(CH_3)_3CCH_2C(CH_3)_2$—	−2.57	−2.84	−2.13
$((CH_3)_3C)_2CH$—	−3.18	−3.55	−2.84
$(CH_3)_3CC(CH_3)_2$—	−3.90	−3.83	−3.48
$(CH_3CH_2)_3C$—	−3.80	−2.67	−3.60
$((CH_3)_2CHCH_2)_2CH$—	−2.47	−2.03	−2.65
$((CH_3)_3CCH_2)((CH_3)_3C)(CH_3)C$—	−4.00	−4.62	−4.43

[a] E_s values described by Taft (13). [b] From Ref. 13. [c] See Table XI for values of $^{m}\chi_t$ and $\Delta^{m}\chi_t$.

where $r = 0.9317$, $RSD = 0.53$, and $n = 19$.

In Table V is shown a comparison between Eqs. 26 and 27 with the E_s values given by Taft (13). Equations 25 and 27 are better than the single-parameter correlations described by Murray (9), and Eq. 26 is better than his two-parameter relation.

Here, again, there is a significant correlation between the indices used in Eqs. 25 and 27, *viz.*:

$$\Delta^{6}\chi_{PC} = 0.567(^{3}\chi_P) - 0.303 \qquad \text{(Eq. 28)}$$

where $r = 0.9106$, $RSD = 0.225$, and $n = 19$.

Nucleophilic Substitution of 1-Chloro-2,4-Dinitrobenzene by Alkylamines—As a final example, we chose the nucleophilic substitution of 1-chloro-2,4-dinitrobenzene by an aliphatic amine by the activation process shown in Scheme II. The relative rate constant data were obtained from the experiments of Brady and Cropper (22) (Table VI).

Table VI—Relative Rate Constants for Eq. 28

R	ln (k_{rel}) [a]	Eq. 29 [b]	Eq. 30 [b]
Ethyl	2.219	2.163	2.106
Propyl	2.262	2.269	2.106
Isopropyl	0	0.076	0.796
Butyl	2.303	2.264	2.106
sec-Butyl	−0.094	0.137	1.180
tert-Butyl	−3.270	−3.376	−3.261
Isobutyl	1.917	1.800	0.502
Octyl	2.303	2.307	2.106

[a] From Ref. 22. [b] See Table XII for values of $^{m}\chi_t$ and $\Delta^{m}\chi_t$.

Table VII— $^{m}\chi_t$ Values for Substituted Pyridines [a]

Compound	$^{1}\chi$	$^{2}\chi$	$^{3}\chi_C$	$^{4}\chi_{PC}$
Pyridine	1.850	1.025	0.0	0.0
2-Methylpyridine	2.270	1.471	0.1291	0.1491
3-Methylpyridine	2.260	1.530	0.1667	0.1708
4-Methylpyridine	2.260	1.525	0.1667	0.1925
2,3-Dimethylpyridine	2.687	1.906	0.2561	0.5331
2,4-Dimethylpyridine	2.681	1.975	0.2958	0.3186
2,5-Dimethylpyridine	2.681	1.977	0.2958	0.3198
2,6-Dimethylpyridine	2.691	1.920	0.2582	0.2782
3,4-Dimethylpyridine	2.677	1.960	0.2887	0.6032
3,5-Dimethylpyridine	2.671	2.040	0.3333	0.3157

[a] Equations 3-6.

Table VIII— $\Delta\,^{m}\chi_t$ Values for Substituted Pyridines [a]

Compound	$\Delta^{4}\chi_{PC}$	$\Delta^{5}\chi_{PC}$
Pyridine	0.1571	0.1361
2-Picoline	0.3588	0.2427
3-Picoline	0.1401	0.2525
4-Picoline	0.1571	0.1164
2,3-Lutidine	0.3203	0.4324
2,4-Lutidine	0.3596	0.2114
2,5-Lutidine	0.3432	0.3440
2,6-Lutidine	0.5334	0.4262
3,4-Lutidine	0.1410	0.2209
3,5-Lutidine	0.1231	0.3708
2-Ethylpyridine	0.2856	0.3636
2-Isopropylpyridine	0.2404	0.5585
2-*tert*-Butylpyridine	0.2103	0.7939
2-Methyl-3-ethylpyridine	0.3248	0.3606
2-Methyl-3-isopropylpyridine	0.3268	0.3212
2-Methyl-3-*tert*-butylpyridine	0.3280	0.2908
2,6-Diethylpyridine	0.3958	0.6064
2,6-Diisopropylpyridine	0.3093	0.9714
2,4,6-Trimethylpyridine	0.5352	0.3831
2,3,5,6-Tetramethylpyridine	0.4586	0.7836
2,3,4,5,6-Pentamethylpyridine	0.4616	0.7228
3-Ethylpyridine	0.1420	0.2103
4-Ethylpyridine	0.1571	0.1186
3-Isopropylpyridine	0.1529	0.1842
4-Isopropylpyridine	0.1571	0.1196
3-*tert*-Butylpyridine	0.1434	0.1616
4-*tert*-Butylpyridine	0.1751	0.1202
2-Methyl-5-ethylpyridine	0.3451	0.3043
2-Methyl-5-isopropylpyridine	0.3459	0.2793
2-Methyl--5-*tert*-butylpyridine	0.3464	0.2574
2,3-Cyclopentenopyridine	0.2608	0.4084
2,3-Cyclohexenopyridine	0.2608	0.4084
2-Ethyl-3-methylpyridine	0.2551	0.5104
2-Ethyl-5-methylpyridine	0.2700	0.4673
2-Ethyl-6-methylpyridine	0.4646	0.5125
2-Isopropyl-3-methylpyridine	0.2137	0.6831
2-Isopropyl-5-methylpyridine	0.2208	0.6632

[a] Equations 7 and 8.

An excellent correlation of ln (k_{rel}) was obtained with activation indices:

$$\ln(k_{rel}) = -4.506(\Delta^{5}\chi_{PC}) - 1.087(\Delta^{5}\chi_{P}) + 10.800 \quad \text{(Eq. 29)}$$

where $r = 0.9984$, $RSD = 0.134$, and $n = 8$. The only relation found between ln (k_{rel}) and the substrate alkylamine indices was not nearly as good:

$$\ln(k_{rel}) = -3.929(^{3}\chi_C) + 2.106 \quad \text{(Eq. 30)}$$

where $r = 0.9177$, $RSD = 0.848$, and $n = 8$. The results of Eqs. 29 and 30 were compared with the experimental data (Table VI).

In addition, there is a reasonable linear relation between the indices of Eqs. 29 and 30:

$$^{3}\chi_C = 0.959(\Delta^{5}\chi_{PC}) - 1.559 \quad \text{(Eq. 31)}$$

where $r = 0.9248$, $RSD = 0.191$, and $n = 8$.

CONCLUSIONS

The correlations presented here indicate that the connectivity indices can serve as useful steric parameters in reactivity studies. It appears that they are capable of distinguishing between cases of steric control and electronic control. Either the connectivity indices in the substrate molecules or the changes that occur in formation of the transition state can apparently be used. This ambiguity is consistent with the fact that it is often possible to interpret relative reaction rates for a series of molecules either in terms of transition-state calculations or in terms of substrate-molecule equilibrium properties. For any particular reaction, the activation indices which appear in the correlations are always of higher order than the corresponding substrate indices, and the two sets are generally correlated with one another. We strongly feel that any empirically derived steric parameters must correlate with these indices if they

Table X— $^{m}\chi_t$ Values for Compounds Involved in Bromide Exchange Reactions [a]

R	$^{2}\chi$	$\Delta^{3}\chi_C$	$\Delta^{4}\chi_C$	$^{4}\chi_{PC}$	$\Delta^{5}\chi_C$
Methyl	0.0	0.0	0.0	0.0	0.0
Ethyl	1.403	2.273	0.0	0.0	0.0
n-Propyl	1.492	1.607	0.0	0.0	0.0
Isopropyl	2.868	4.776	1.969	0.0	0.0
Isobutyl	2.204	1.237	0.0	0.8100	1.312
tert-Butyl	4.476	7.577	6.065	0.0	0.0
Neopentyl	3.362	0.9419	−0.0649	2.105	3.410

[a] Equations 17-23.

Table XI— $^{m}\chi_t$ Values for Ethyl Esters Involved in Hydrolysis Reactions [a]

R	$^{3}\chi_P$	$\Delta^{4}\chi_{PC}$	$\Delta^{6}\chi_{PC}$
CH_3—	0.3476	0.0990	0.0289
C_2H_5—	0.5940	0.2194	0.0905
$CH_3CH_2CH_2$	0.7595	0.1781	0.1254
$CH_3CH_2CH_2CH_2$—	1.040	0.1781	0.1796
$CH_3CH_2CH_2CH_2CH_2$—	1.290	0.1781	0.1590
$(CH_3)_2CHCH_2CH_2$—	1.231	0.1781	0.2872
$(CH_3)_2CH$—	0.7580	0.4398	0.1716
$(CH_3)_3C$—	0.8878	0.7275	0.2683
$(CH_3CH_2)_2CH$—	1.606	0.3022	0.3936
$(CH_3)_3CCH_2$—	0.9800	0.1489	0.4704
$(CH_3CH_2CH_2)_2CH$—	1.894	0.3022	0.5126
$(CH_3)_3CCH_2C(CH_3)_2$—	1.800	0.6271	0.8586
$((CH_3)_3C)_2CH$—	2.254	0.2195	0.1461
$(CH_3)_3CC(CH_3)_2$—	2.661	0.5561	0.1348
$(CH_3CH_2)_3C$—	2.739	0.4576	0.8999
$((CH_3)_2CHCH_2)_2CH$—	2.132	0.3022	0.7244
$((CH_3)_3CCH_2)((CH_3)_3C)(CH_3)C$—	3.265	0.4735	0.1754

[a] Equations 25-27.

Table IX— $^{m}\chi_t$ Values for 2-Substituted Pyridines [a]

2-Substituent	$\Delta^{3}\chi_C$	$^{4}\chi_P$	$\Delta^{4}\chi_P$	$\Delta^{4}\chi_{PC}$	$^{5}\chi_C$	$^{5}\chi_{PC}$	$\Delta^{6}\chi_{PC}$
—CH_3	0.1066	0.4481	0.1208	0.3588	0	0.1291	0.2392
—C_2H_5	0.1099	0.6073	0.2591	0.2856	0	0.1967	0.3321
—Isopropyl	0.1114	0.7175	0.3463	0.2404	0.0745	0.4174	0.5240
—*tert*-Butyl	0.1122	0.8064	0.0600	0.2013	0.1937	0.9880	0.8750
—CH_2OH	0.1099	0.4917	0.1837	0.2900	0	0.1384	0.2567
—CH_2CH_2OH	0.1099	0.6606	0.2148	0.2879	0	0.1947	0.3420
—CH_2-phenyl	0.1099	1.308	0.1829	0.2896	0	0.4430	0.3709
—$CO_2C_2H_5$	0.1122	0.6685	0.2000	0.2412	0.0108	0.2283	0.3018
—Phenyl	0.1122	1.142	0.2289	0.2377	0.0215	0.4249	0.4163
—2-Pyridyl	0.1122	1.029	0.2171	0.2392	0.0167	0.3582	0.3802
—NH_2	0.1114	0.3760	0.1235	0.2647	0	0.0745	0.1764
—C≡N	0.1122	0.4289	0.1672	0.2449	0	0.0979	0.2081
—Br	0.0955	0.6162	0.1144	0.5780	0	0.2562	0.3853

[a] Equations 10-14.

Table XII—$\Delta^m\chi_t$ Values for Compounds Undergoing Nucleophilic Substitution [a]

R	$^3\chi_C$	$\Delta^5\chi_P$	$\Delta^5\chi_{PC}$
Ethyl	0.0	0.8533	1.711
Propyl	0.0	1.096	1.629
Isopropyl	0.3333	0.9303	2.156
Butyl	0.0	1.100	1.629
sec-Butyl	0.2357	1.128	2.094
tert-Butyl	0.1366	0.9923	2.907
Isobutyl	0.4082	1.257	1.695
Octyl	0.0	1.061	1.629

[a] Equations 29 and 30.

are at all reasonable. Charton (10) has recently concluded that no one set of steric parameters is suitable for all reactions. Since they take into account the TS structure, the $\Delta^m\chi_t$ values may have sufficient flexibility to be generally useful. This is illustrated by the fact that different indices are important for different reactions.

Within the last year Edward has published two studies in which the molecular basis for the relationship of a number of physical properties and connectivity indices is beginning to be unraveled (7). The inclusion of connectivity indices in recent pattern recognition investigations of pharmacological activities suggests that this type of descriptor variable encodes structural features which influence *in vivo* tests. Our present findings bring together connectivity indices as a descriptor for structural effects in both chemical reactivity and pharmacological activities.

APPENDIX

Tables VII–XII contain the values of $^m\chi_t$ and $\Delta^m\chi_t$ that were employed in all correlations. There is one table for each table in the text. Table VII gives the values employed in Table I, *etc.*

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