A Huckel Molecular Orbital Study of Electronic Coupling in Bifunctional Catalysis[1]

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Abstract: In order to facilitate a study of the role of electronic coupling in bifunctional catalysis, a coupling index is defined as a linear combination of mutual perturbations between the functional groups. Comparison with the limited data available in the literature shows the index to be well correlated with the log of reactivity of various bifunctional catalysts. The relation to models of enzyme catalysis is briefly discussed.

Efforts to explain the rather large catalytic activity of enzymes have often involved the hypothesis of the simultaneous and concerted involvement of two or more catalytic groups. Such a possibility has received support from the well-known studies of Swain and Brown[2,3] on the mutarotation of tetramethylglucose in benzene. They found that 0.001 *M* 2-hydroxypyridine had roughly 7000 times the catalytic activity of a mixture of pyridine and phenol. Moreover the 2-hydroxypyridine reaction was shown to be bimolecular, whereas the mixed catalyst gave termolecular kinetics. They also studied a number of other catalysts which gave bimolecular kinetics. More recently Menger[4] has found that the amidinolysis of *p*-nitrophenyl acetate is several orders of magnitude more rapid than the aminolysis, and again a change from termolecular to bimolecular kinetics was found.

It is noteworthy that in all cases the two functional groups in question are part of a single π-electronic system. One is led therefore to ask about the effect of mutual perturbations between the groups involved. This is more especially the case since it appears unlikely that the change in entropy of activation in going from a termolecular to a bimolecular mechanism would account for all of the observed rate increase. A relevant statistical model set forth by Koshland[5] would, in fact, suggest a factor of between 5 and 55, depending upon the orientational requirements of initiating the reaction.

Convenient expressions for the desired perturbation effects within the Hückel molecular orbital approximation are the polarizabilities of Coulson and Longuet-Higgins.[7,8] The present communication is an examination of the relationship between mutual polarizabilities of various bifunctional catalysts and their observed catalytic activity.

The computer program for the calculations was built around the eigenvalue program of Clyde, Cramer, and Sherin.[9] Electron densities, bond orders, and polarizabilities were calculated in the usual way.[10] Hückel parameters were those of Pullman and Pullman.[10a]

The Coupling Index

In all of the catalysts considered by Swain and Brown[2,3] and both of those considered by Menger[4] the reaction proceeds with the making and breaking of π bonds in the catalysts. Suppose for example we have a catalyst of the following general structure

$$\mathrm{X{=}L\overset{\text{intervening system}}{\text{----------}}Q{-}Y{-}H}$$

During the course of the reaction the X=L linkage is converted to a single bond, while Y is converted from a singly to a doubly bonded atom. Its coulomb and bond integrals (denoted by α and β, respectively) may undergo marked changes.

In the Hückel approximation, the calculated energy of a system is a function of all the α_i and β_{ij}. As the system moves along the reaction coordinate, the change in energy can be expressed in terms of the changing values of these parameters, and the difference in energy between the transition complex and the initial reactants may, accordingly, be expanded in a Taylor series. Those second-order terms of the series, which involve parameters of both X and Y, may be taken as an approximation to the energy contribution due to the fact that the atoms are part of a single π system. Neglecting the integrals for incipient bonds between catalyst and substrate, these terms are

$$\delta E^{\ddagger}_{\text{coupling}} = \frac{\partial^2 E}{\partial\alpha_x\partial\alpha_y}(\delta\alpha_x)(\delta\alpha_y) + \frac{\partial^2 E}{\partial\alpha_x\partial\beta_{y-Q}}(\delta\alpha_x)(\delta\beta_{y-Q}) + \frac{\partial^2 E}{\partial\alpha_y\partial\beta_{x-L}}(\delta\alpha_y)(\delta\beta_{x-L}) + \frac{\partial^2 E}{\partial\beta_{x-L}\partial\beta_{y-Q}}(\delta\beta_{x-L})(\delta\beta_{y-Q}) = \pi_{x,y}(\delta\alpha_x)(\delta\alpha_y) + \pi_{y-Q,x}(\delta\alpha_x)(\delta\beta_{y-Q}) + \pi_{x-L,y}(\delta\alpha_y)(\delta\beta_{x-L}) + \pi_{x-L,y-Q}(\delta\beta_{x-L})(\delta\beta_{y-Q}) \quad (1)$$

(1) Work supported by NIGMS Training Grant No. GM 678-07.
(2) C. G. Swain and J. F. Brown, Jr., *J. Am. Chem. Soc.*, 74, 2538 (1952).
(3) J. F. Brown, Jr., Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, Mass., 1950.
(4) F. M. Menger, *J. Am. Chem. Soc.*, 88, 3081 (1966).
(5) D. E. Koshland, Jr., *J. Theoret. Biol.*, 2, 75 (1962). See also T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, Inc., New York, N. Y., 1966, pp 119–125. In applying this model, the mechanism discussed as being most likely, in footnote 10 of Swain and Brown,[6] was assumed.
(6) C. G. Swain and J. F. Brown, Jr., *J. Am. Chem. Soc.*, 74, 2534 (1952).
(7) C. A. Coulson and H. C. Longuet-Higgins, *Proc. Roy. Soc.* (London), **A191**, 39 (1947).
(8) C. A. Coulson and H. C. Longuet-Higgins, *ibid.*, **A193**, 456 (1948).
(9) D. J. Clyde, E. M. Cramer, and R. J. Sherin, "Multivariate Statistical Programs," Biometrics Laboratory, University of Miami, Miami, Fla., 1966.
(10) See, for example (a) B. Pullman and A. Pullman, "Quantum Biochemistry," Interscience Publishers, Inc., New York, N. Y., 1963; (b) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, New York, N. Y., 1961.

where $\pi_{x,y}$, $\pi_{y-Q,x}$ and $\pi_{x-L,y-Q}$ are, respectively, atom–atom, bond–atom, and bond–bond polarizabilities, and the symbol δ indicates the change in the appropriate parameter in going to the transition complex. It is now assumed that at the transition state, the Hückel parameters have all changed by approximately the same proportion of their total changes for the complete reaction. This assumption allows us to define a coupling index

$$\xi_{x,y} = \pi_{x,y}(\Delta\alpha_x)(\Delta\alpha_y) + \pi_{y-Q,x}(\Delta\alpha_x)(\Delta\beta_{y-Q}) + \pi_{x-L,y}(\Delta\alpha_y)(\Delta\beta_{x-L}) + \pi_{x-L,y-Q}(\Delta\beta_{x-L})(\Delta\beta_{y-Q}) \quad (2)$$

where Δ indicates the total change. If one of the atoms is connected *via* two separate σ bonds to the π system, such as the nitrogen in 2-hydroxypyridine, each bond must be considered separately. $\xi_{x,y}$ has dimensions of energy in units of $\beta_{C=C}$. Since $\beta_{C=C}$ is negative, a positive value of $\xi_{x,y}$ indicates facilitation of the reaction, while a negative value indicates inhibition.

Mutarotation of Tetramethylglucose. Table I shows the coupling index for the bifunctional catalysts studied by Swain and Brown.[2] Trichloroacetic acid, which is not amenable to the Hückel treatment, is not included. Comparison is made with the rate constant given by Swain and Brown, $k = k_1(T)/(C:R)$, where k_1 is the measured first-order rate constant, (T) is the total sugar concentration, and (C:R) is the concentration of a hydrogen-bonded 1:1 complex between sugar and catalyst. The final column of Table I shows the first-order rate constants for the mutarotation of 0.09 *M* tetramethylglucose with 0.01 *M* catalyst (corrected for a blank of 1.3×10^{-6}) taken from Brown.[3,11]

Table I. Coupling Index and Reactivity for Catalysts of Swain and Brown[2,3]

	ξ_{xy}	k, sec^{-1}	$k_1 \times 10^6$, sec^{-1}
2-Hydroxypryidine			
Tautomer A	0.0542		
Tautomer B	0.0806	0.0163	873
2-Hydroxy-4-methylquinoline			
Tautomer A	0.0711		
Tautomer B	0.0789	0.00638	289
2-Aminopyridine			
Tautomer A	0.0230	0.002	197
Tautomer B	0.0482		
Picric acid	~0	0.00076	25.7
Benzoic acid	0.2059	0.0636	3669
Coefficient of correlation: ξ *vs.* log rate		0.938	0.916
Level of significance		0.01	0.025

One would expect the coupling index to be related to the log of the rate. The last two rows of Table I show, respectively, the coefficient of linear correlation between the index and the log of the expressions for catalytic activity, and the level at which each correlation is statistically significant.

In the case of the pyridine and quinoline derivatives, one has the problem of deciding whether to base the calculations on the form with the singly bonded (tautomer A) or doubly bonded (tautomer B) substituent. In this connection we note, as Swain and Brown have pointed out, that at least in aqueous solution the B form of 2-hydroxypyridine predominates. The π-bond energy ($E_\pi - \sum_{i=1}^{n}\alpha_i$) calculations indicate greater stability for the B forms of all of these catalysts, except 2-aminopyridine (Table II). The lowest energy form was used in each case for the correlation calculations.[12]

Table II. π-Bond Energy of Tautomers of Pyridine and Quinoline Derivatives

Compound	π-Bond energy (units of β) A[a]	B[b]
2-Hydroxypyridine	10.302	10.957
2-Hydroxy-4-methylquinoline	20.163	20.934
2-Aminopyridine	9.419	9.202
8-Hydroxyquinoline	15.975	16.455

[a] Singly bonded substituent. [b] Doubly bonded substituent.

Amidinolysis of *p*-Nitrophenyl Acetate. Menger studied two amidines: benzamidine and a nonaromatic amidine. The coupling indices and reactivities relative to n-butylamine are shown in Table III.

Table III. Coupling Index and Reactivity for Catalysts of Menger[4]

	ξ_{xy}	Reactivity[a]
Benzamidine	0.0612	1.5×10^4
Amidine, nonaromatic	0.0637	3×10^5

[a] Relative to *n*-butylamine.

Discussion

Two assumptions are inherent in the definition and use of the proposed coupling index. (a) The Hückel parameters vary continuously during the reaction and the amounts of the changes at the transition state are in the same proportion as the total changes. (b) The transition state occurs at a similar point along the reaction coordinate in all cases being compared.

These assumptions, of course, limit valid comparison to closely related reactions and certainly invalidate any direct comparison between the mutarotation and the amidinolysis. The data of Tables I and III would seem to indicate a strong relationship between electronic coupling and bifunctional catalytic activity.

An interesting comparison in the case of the mutarotation reaction may be made between the coupling index and the observed first-order rate constants. The regression equation in this case is

$$\log(k_1 \times 10^6) = 1.822 + 9.172\xi_{x,y}$$

The intercept corresponds to a rate constant of 66.3 $\times 10^{-6}$ and may be taken as an estimate of the rate constant to be expected with 0.01 *M* of a bifunctional catalyst in which there is no coupling between the groups involved. A first-order rate constant for a solution containing 0.01 *M* pyridine and 0.01 *M* phenol of 2.1

(11) The correction is necessary in this case, since we wish to extrapolate to small values.

(12) An additional problem arises in determining values of $\delta\alpha$ and $\delta\beta$ for the nitro-group oxygen of picric acid. Consideration of the arguments on p 125 of ref 10b, and references cited there, suggested that these could be neglected, giving an approximate value of zero for the coupling index. Omission of the point for picric acid does not materially affect the results.

$\times 10^{-6}$ is obtained from eq 1 of Swain and Brown.[2] A factor of 31.6 is thus estimated as being due simply to the position effect, well within the expected range.

It is perhaps worth mentioning that if one plots $\xi_{x,y}$ *vs.* the log of reactivity for the catalysts of Menger, appending a point corresponding to $\xi_{x,y} = 0$ and reactivity of 31.6 times that of *n*-butylamine, the correlation coefficient is 0.964 and is, despite only a single degree of freedom, significant at the 0.1 level.

Swain and Brown[2] made a single measurement using 8-hydroxyquinoline as catalyst and found a k_1 of only 20×10^{-6} for a concentration of 0.25 *M*. The exceedingly low activity of this compound is associated with a coupling index of −0.0126.

In evaluating the results reported here, one must bear in mind the approximate nature of the method used and the fact that certain effects, such as the involvement of the π system of the substrate, are beyond the scope of the Hückel approximation. Further work, both experimental and theoretical, is clearly called for. It seems safe to conclude, however, that electronic coupling is a factor in bifunctional catalysis. If the reactions of Swain and Brown and of Menger are to be taken as a basis for models of enzyme catalysis, it would seem that such models should include provision for the possibility of coupling through the protein molecule. Further work, using more complete molecular orbital methods, is in progress.

Electrical Effects of Cycloalkyl Groups[1]

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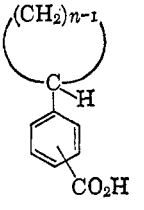
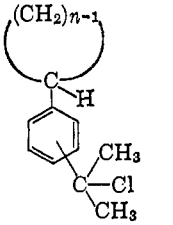
Abstract: A study has been made of (1) the syntheses and ionization constants of *m*- and *p*-cyclopropyl-, -cyclobutyl, -cyclopentyl-, -cyclohexyl-, -(1-cyclopentenyl)-, and -(1-cyclohexenyl)benzoic acids and (2) the syntheses and unimolecular hydrolysis rates of *m*- and *p*-cyclopropyl-, -cyclopentyl-, -cyclohexyl-, and *p*-cyclobutylphenyldimethylcarbinyl chlorides in 90% aqueous acetone. The effects of ring size on the ionization constants of the *m*-(1-cycloalkenyl) and *m*-cycloalkylbenzoic acids and on the rates of hydrolysis of *m*-cycloalkylphenyldimethylcarbinyl chlorides are small and are interpreted primarily on the basis of electron release of substituents in the order: cyclohexenyl > cyclopentyl > cyclobutyl > cyclopropyl > 1-cyclohexenyl > 1-cyclopentenyl. *p*-Cycloalkylphenyldimethylcarbinyl chlorides solvolyze more rapidly than do their *meta* isomers; hydrolysis of *p*-cyclopropylphenyldimethylcarbinyl chloride is much faster than that of its *p*-cycloalkyl homologs. The marked reactivity of *p*-cyclopropylphenyldimethylcarbinyl chloride is attributed to stabilization of the reaction transition state through the large π character of the cyclopropyl carbon–carbon bonds. The fact that *p*-cyclopropylbenzoic acid is weaker than its homologous *p*-cycloalkylbenzoic acids provides additional evidence for the electron-donor abilities of a cyclopropyl group.

The reactivities of cycloalkyl derivatives are markedly affected by ring size. In order to divorce electrical effects from classical steric factors and to avoid complications arising from carbon skeleton rearrangement of alicyclic substituents, a study has been made of the ionization constants of homologous *m*- and *p*-cycloalkylbenzoic acids **1**, **2**, **3**, and **4**, and the rates of solvolysis of *m*- and *p*-cycloalkyl-*t*-cumyl chlorides **34**, **35**, **36**, and **37**.[2,3] The objectives are to determine the electrical effects of cycloalkyl groups in the systems of interest. Synthetic routes to the compounds studied are summarized in Charts I, II, and III. The present paper also includes comments on the unusual isomer distribution in nitration of cyclopropylbenzene.



1, $n=3$
2, $n=4$
3, $n=5$
4, $n=6$
p, para; m, meta



34, $n=3$
35, $n=4$
36, $n=5$
37, $n=6$
p, para; m, meta

Syntheses

Cyclopropylbenzoic Acids. Cyclopropylphenyldimethylcarbinols. Synthesis of the desired cyclopropylbenzene derivatives involved (a) ring closure of substituted benzenoid intermediates and (b) preparation, nucleophilic substitution, and subsequent transformations of cyclopropylbenzene. While the former method allowed nuclear-substituted phenylcyclopropanes (*p*-bromocyclopropylbenzene was obtained from 1-bromo-

(1) (a) Abstracted in part from the Ph.D. dissertation of R. C. Hahn, The Ohio State University, Columbus, Ohio, 1960; *Dissertation Abstr.*, **21**, 2891 (1961); University Microfilms, Inc., Ann Arbor, Mich., Library of Congress Card No. Mic 61-911; *Chem. Abstr.*, **55**, 18632 (1961). (b) Presented at the 139th National Meeting of the American Chemical Society, St. Louis, Mo., March 21, 1961, Abstracts of Papers, 35-O.

(2) L. B. Jones and V. K. Jones, *Tetrahedron Letters*, 1493 (1966), have reported a large rate acceleration in solvolysis of *p*-cyclopropylphenyldimethylcarbinyl chloride in 90 vol % acetone as compared to *p*-alkylphenyldimethylcarbinyl chlorides. These authors were not aware of our studies[1] of these systems upon initial submittal of their communication (footnote d).

(3) H. C. Brown and J. D. Cleveland, *J. Am. Chem. Soc.*, **88**, 2051 (1966), have used the present research as an initial basis for their elegant study of steric inhibition of interaction of a cyclopropyl substituent with the electron-deficient center in solvolysis of *t*-cumyl derivatives.