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Some Electronic Factors in Drug–Receptor Interactions

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Many of the physicochemical approaches to the study of drug action are shown to be interrelated. The principle of hard and soft acids and bases, in its quantitative form, is indicated as applying to drug action.

Physicochemical approaches are being applied increasingly to the study of drug action. The intent of the application of these approaches is either to supplement the information at hand with regard to a given type of drug activity or to provide a rational guide to the synthesis of new compounds of greater activity. A number of attempts have been made to apply molecular orbital methods in these endeavors, but progress has been slow due to the lack of a reasonable theoretical framework within which to work. We wish to report a portion of our perspective on this problem.

Current theories of drug action liken the interaction of a drug with its receptor to the combination of a substrate with an enzyme. By this analogy, the elicitation of a pharmacologic response may be generalized in the Michaelis–Menten formalism as

$$S + R \underset{}{\overset{a}{\rightleftharpoons}} SR^* \xrightarrow{b} \text{response}$$

where S is a drug, R its receptor, and SR* the drug–receptor complex leading to a given biological response. Once this formalism is accepted, the distinction between the current theories of drug action may be considered as corresponding to the choice of response (rate)-determining step. Thus, in the kinetic theory of Paton,[2a] the association–dissociation of a drug and receptor (step a) is the response-determining step, while Ariëns' theory[2b] places the response-determining step "after" the formation of the drug–receptor complex (step b).

Extending this kinetic analogy further, it may be stated that, in the absence of supplemental studies, the number of steps preceding and following the response-determining step is largely unknown. In principle, there are an infinite number of steps that can lead to and follow the response-determining step. As in chemical systems, the actual steps that are taken, which if known would constitute the molecular mechanism of action for a drug, may be considered specific for a given type of drug and receptor. Hence, the theories which invoke a change in the structure[3] or function[4] of the receptor substance seem to provide mechanistic detail to the Paton and Ariëns theories and represent probable mechanisms of action, at the molecular level, for a given drug–receptor system. According to our rationale, the latter theories may be associated with a category into which a given type of drug action may be placed; they do not appear to be general theories of drug action.

Since the "activated" drug–receptor complex implicit in the Paton theory or the relatively more stable drug–receptor complex considered in Ariëns' theory is presumed to be the response-determining factor, we will equate drug activity A to the free-energy of formation of a drug–receptor complex, ΔG_{RS}. Electronic and steric interactions between the drug and its receptor, as well as conformational changes of the receptor substance, are some of the factors that can affect ΔG_{RS}. Following the procedure of Leffler and Grunwald,[5] and considering only first-order interactions, ΔG_{RS} is approximately given by

$$\begin{aligned} A = \Delta G_{RS} = {} & \Delta G^e + \Delta G^d + \Delta G^s + \Delta G^p + \\ & \Delta G^e(\Delta G^d + \Delta G^s + \Delta G^p) + \\ & \Delta G^d(\Delta G^e + \Delta G^s + \Delta G^p) + \\ & \Delta G^s(\Delta G^e + \Delta G^d + \Delta G^p) + \\ & \Delta G^p(\Delta G^e + \Delta G^d + \Delta G^s) \end{aligned} \quad (1)$$

where ΔG^e, ΔG^s, and ΔG^p are independent contributions to the free-energy due to electronic and steric interactions between drug and receptor and to conformational changes in the receptor, respectively. The quantity ΔG^d is introduced to represent the free-energy change due to desolvation which would accompany the union of drug and receptor. In this report, we will consider the case where the interaction terms in eq 1 are constant or negligible. Thus, eq 1 is reduced to the relatively simple expression

$$A_n = \Delta G_{RS} = \Delta G^e{}_n + \Delta G^d{}_n + \Delta G^s{}_n + \Delta G^p{}_n + k \quad (2)$$

The subscript n designates that for a series of N compounds tested against a common receptor there will be n of these equations, *i.e.*, $N = 1, 2, \ldots, n$.

If compounds in a congeneric or a homologous series of compounds differ only by a substituent, it is not un-

(1) Temple University, School of Pharmacy, Philadelphia, Pa. 19140.

(2) (a) W. D. M. Paton, *Proc. Roy. Soc.* (London), **B154**, 21 (1961); (b) E. J. Ariëns, A. M. Simonis, and J. M. van Rossum, *Mol. Pharmacol.*, **1**, 136 (1964).

(3) B. Belleau *J. Med. Chem.*, **7**, 776 (1964).

(4) B. M. Bloom and I. M. Goldman, *Advan. Drug Res.*, **3**, 121 (1966).

(5) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963.

reasonable to assume that the difference in their biological activities is due solely to differing properties of the substituents. The activity change resulting from the change in substituent is from eq 2.

$$\delta A_n = \delta(\Delta G^e)_n + \delta(\Delta G^d)_n + \delta(\Delta G^s)_n + \delta(\Delta G^p)_n \quad (3)$$

When the conformational change of receptor substance makes a constant contribution to the total free energy, eq 3 can have its terms directly related to one of the linear free-energy equations discussed by Hansch[6]

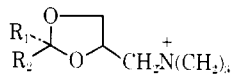
$$\delta A_n = a\sigma + b\pi + cE_s + k' \quad (4)$$

where σ, π, and E_s are the Hammett,[7] Hansch,[8] and Taft[9] constants identified with electronic, lipophilic, and steric properties of a substituent, respectively. It is appropriate to point out that desolvation in eq 4 is specifically identified with hydrophobic interactions.[10]

Belleau appears to have used a special case of eq 3 in arriving at his perturbation theory of drug action.[3,11] When the contribution of one substituent relative to the other is negligible, the difference in activity between two structurally related compounds is due solely to the properties of a single substituent. Thus, assuming the allosteric term constant, Belleau accounted for the difference in AChE activities between I and II (Table I) on the basis of a sum of the electronic and hydrophobic properties associated with a methyl group. On the other hand, the sum of the activity difference between I and II and I and III is greater than the observed activity of IV (Table I). Hence, it was concluded[11] that a conformational change of the receptor substance (AChE) had occurred.

TABLE I

INHIBITION OF AChE BY 1,3-DIOXOLANE DERIVATIVES[11]



Compd	R_1	R_2	Rel potency
I	H	H	0.1
II[a]	CH_3	H	100
III[a]	H	CH_3	20
IV	CH_3	CH_3	0.5

[a] DL forms.

In further extending eq 2, it shall be assumed that the contribution due to conformational changes in the receptor substance is constant. Within the present approximation, estimates of drug activity, based on calculated or otherwise determined atomic or substituent properties, which greatly exceed the observed drug activity will be tentatively attributed to conformational changes of the receptor substance.

Since there is usually no *a priori* or *a posteriori* knowledge of the particular atoms primarily responsible for the activity of a drug, we will *formally* require each atom of a drug, s, to interact with each atom, r, of the drug receptor site. Each pair of interacting atoms may then be considered as making an independent contribution to the electronic, desolvation, and steric free-energy terms in eq 2.

$$A_n = \sum_r \sum_s (E_{rs} + L_{rs} + V_{rs})_n + k \quad (5)$$

Based on a recent theory of chemical reactivity,[12,13] which is discussed later in some detail, the electronic and desolvation components, E_{rs} and L_{rs}, respectively, can be considered additive. In the case of steric interactions, V_{rs}, the assumption of constant receptor conformation enables us to think of this component as constituting a geometrically dependent volume requirement analogous to the Madelung constant used in crystallography.[14]

In a series of structurally related drugs, if E_{rs}, L_{rs}, and V_{rs} are constant for atoms common to each drug, the terms corresponding to these atoms in eq 5 may be included with the constant k. Noting that the contribution of a group is the sum of its atomic contributions, eq 5 can also be written

$$A_n = \sum_g a_{n,g} + \mu \quad (6)$$

where an atom or group contribution is defined as

$$a_g = \sum_{r'} \sum_{s'} (E_{r's'} + L_{r's'} + V_{r's'}) \quad (7)$$

in which the primes designate interactions identified with a given atom or group. Equation 6 can be recognized as the mathematical model used by Free and Wilson[15] in correlating certain types of drug activity.

While it may be suitable to consider E_{rs} and L_{rs} constant for aliphatic or saturated compounds, it is evident that conjugation of atoms essential to drug activity with a varied substituent can lead to changes in E_{rs}. This should be particularly true for aromatic substances, in which case the Free and Wilson method affords averaged values of a_g. These considerations suggest that the Free and Wilson approach should be least accurate when applied to aromatic compounds. This seems true from the data at hand (compare Tables II and III).

Molecular orbital (MO) methods have been highly successful in predicting the electronic properties of aromatic compounds[16,17] and a theory has been developed[12,13] which places these methods within the present scheme.

Neglecting desolvation for the present, the Klopman and Hudson[12,13] treatment of chemical reactivity is based on the limits of eq 8 for small electronic perturbations, *i.e.*, small β.

$$E_{rs} = -\frac{q_r q_s e^2}{\epsilon_{rs} D_{rs}} + \sum_{m}^{occ} \sum_{n}^{unocc} \frac{2c_{mr}^2 c_{ns}^2 \beta^2}{E_m^* - E_n^*} \quad (8)$$

Only the first approximation to the first term of eq 8 is given here, since in this form it is readily recognized as

(6) C. Hansch and E. W. Deutsch, *Biochim. Biophys. Acta*, **126**, 117 (1966).

(7) J. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940; for a compilation of values see H. H. Jaffe, *Chem. Rev.*, **53**, 191, (1953).

(8) T. Fujita, J. Iwasa, and C. Hansch, *J. Am. Chem. Soc.*, **86**, 5175 (1964).

(9) R. W. Taft, "Steric Effects in Organic Chemistry," M. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956.

(10) C. Hansch, "Annual Review of Medicinal Chemistry," C. K. Cain, Ed., Academic Press, New York, N. Y., 1967.

(11) B. Belleau and G. Lacasse, *J. Med. Chem.*, **7**, 768 (1964).

(12) G. Klopman and R. F. Hudson, *Theoret. Chim. Acta*, **8**, 165 (1967).

(13) G. Klopman, *J. Am. Chem. Soc.*, **90**, 223 (1968).

(14) G. M. Barrow, "Physical Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1966.

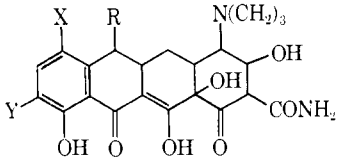
(15) S. M. Free and J. W. Wilson, *J. Med. Chem.*, **7**, 395 (1964).

(16) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 1961.

(17) B. Pullman and A. Pullman, "Quantum Biochemistry," Academic Press, New York, N. Y., 1963.

TABLE II

FREE AND WILSON APPROACH APPLIED TO SOME TETRACYCLINES (TC)

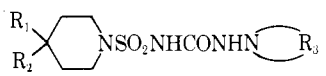


R	X	Y	*In vitro* act. against *S. aureus* rel to TC Obsd[a]	Calcd[b]
H	Cl	NH_2	525	443
H	Br	NH_2	320	343
H	NO_2	NH_2	275	333
CH_3	NO_2	NH_2	160	146
CH_3	Br	NH_2	140	156
CH_3	Br	CH_3CONH	75	51
H	NO_2	NO_2	60	−8
H	Cl	NO_2	21	102
H	Br	NO_2	15	2
CH_3	NO_2	CH_3CONH	15	41

[a] J. L. Spencer, J. J. Hlavka, J. Petisi, H. M. Krazinski, and J. H. Boothe, *J. Med. Chem.*, **6**, 405 (1963). [b] As given in ref 15, Table II.

TABLE III

FREE AND WILSON APPROACH APPLIED TO A SERIES OF HYPOGLYCEMICS



R_1	R_2	R_3	Max % fall in blood glucose in rats at constant dose Obsd[c]	Calcd[d]
CH_3	C_2H_5	$(CH_2)_6$	42.0	37.8
CH_3	CH_3	$(CH_2)_5$	39.1	39.9
$(CH_2)_2$[a]	$(CH_2)_2$[a]	$(CH_2)_5$	35.6	33.5
CH_3	CH_3	$(CH_2)_6$	34.9	39.2
C_2H_5	C_2H_5	$(CH_2)_6$	34.4	36.5
H	CH_3	$(CH_2)_6$	33.9	26.7
$(CH_2)_2$[a]	$(CH_2)_2$[a]	$(CH_2)_6$	30.8	32.8
H	CH_3	$(CH_2)_5$	26.1	27.4
$(CH_2)_{2.5}$[b]	$(CH_2)_{2.5}$[b]	$(CH_2)_6$	25.0	25.0
H	H	$(CH_2)_5$	14.8	14.8
H	H	$(CH_2)_6$	11.1	14.1

[a] A 4,4-tetramethylene group. [b] A 4,4-pentamethylene group. [c] J. M. McManus and C. F. Gerber, *J. Med. Chem.*, **9**, 256 (1966). [d] W. R. Smithfield and W. P. Purcell, *J. Pharm. Sci.*, **56**, 577 (1967).

Coulombs law for the interaction of two net charges, q_r and q_s, separated by a distance, D_{rs}, and a medium whose effective dielectric constant is ϵ_{rs}. The second term essentially contains the difference in energy $E_m^* - E_n^*$ between the highest occupied MO of the receptor, Ψ_m, and the lowest empty MO of the drug, Ψ_n. The coefficients c_{mr} and c_{ns} are the atomic orbital coefficients associated with each MO. A similar expression applies if the highest bonding MO of the drug is filled and the lowest antibonding MO of the receptor is empty.

When the difference between E_m^* and E_n^* is large, the interaction between the atoms r and s is primarily determined by the total charges on the two reagents. Klopman and Hudson have termed such an interaction a *charge-controlled reaction*. For this type of interaction eq 8 becomes eq 9 where $\gamma = \beta^2/(E_m^* - E_n^*)$average.

$$E_{rs} = -\frac{q_r q_s e^2}{\epsilon_{rs} D_{rs}} + 2\left(\sum_m c_{mr}^2\right)\left(\sum_n c_{ns}^2\right)\gamma \qquad (9)$$

On the other hand, when the two frontier orbitals are nearly degenerate, *i.e.*, $E_m^* \approx E_n^*$, then the interaction between these orbitals becomes predominant and a *frontier-controlled reaction* is said to occur. Equation 8 can then be written

$$E_{rs} = 2c_{mr}c_{ns}\beta \qquad (10)$$

The reactivity in this case is essentially determined by the frontier electron density, f_{ns}.[12,13] Because of the simplicity of this equation, its application to biological systems will be discussed first.

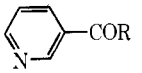
When a series of drugs can be said to function at the same biological receptor site, the coefficient c_{mr} is constant with respect to the coefficient c_{ns} of each drug. By selecting a series of congeneric drugs (*e.g.*, benzoic acid derivatives, nicotinic acid derivatives), a simple proportionality should exist between E_{rs} and c_{ns}. Substitution of eq 10 into eq 5 leads, therefore, to an expression which could be evaluated by the usual multiple regression techniques.

$$A_n = \sum_s b_{ns}c_s + C \qquad (11)$$

While no multiple regression analyses appear to have been reported involving either c_{ns} or f_{ns}, relationships between drug activity and frontier orbital charge density are often observed.[18] For example, the inhibition potency of some nicotinic acid derivatives seems to be related to the frontier orbital charge density (highest occupied MO) of the carbonyl carbon[18] (Table IV).

TABLE IV

RELATION BETWEEN THE INHIBITION POTENCY OF SOME NICOTINIC ACID DERIVATIVES AND THE FRONTIER ORBITAL CHARGE DENSITY (HOMO) AT THE CARBONYL CARBON[18]



R	pI_{50}	Frontier orbital density, *f*
OH	0.3	0.262
NH_2	1.2	0.616
CH_3	2.3	0.657
OC_2H_5	3.1	0.699

Charge-controlled interactions (eq 9) can be similarly treated. In this case, considering only directly interacting atoms leads to the possible regression equation

$$A_n = \sum_s b_{ns}'q_s + C' \qquad (12)$$

in which the coefficients b_{ns}' are given by

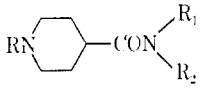
$$b_{ns}' = \left(\frac{2e^2q_r}{\epsilon_{rs}D_{rs}} - \gamma\right)$$

Again, multiple regression analyses of equations similar to eq 12 do not seem to have been reported, but a simple example of the influence of total electronic charge on biological action can be given (Table V).

(18) A. Inouye, Y. Shinagawa, and Y. Takaishi, *Arch. Intern. Pharmacodyn.*, **144**, 319 (1963).

TABLE V

RELATION BETWEEN CHOLINESTERASE INHIBITORY PROPERTIES OF 1-DECYL-3-[(N-ALKYL OR N,N-DIALKYL)CARBAMOYL]PIPERIDINES AND THE TOTAL ELECTRONIC CHARGE ON THE AMINO NITROGEN[a]



R = $CH_3(CH_2)_9$

R_1	R_2	pI_{50}	q_N
H	H	4.206	+0.137
H	CH_3	4.459	+0.212
H	C_2H_5	4.864	+0.209
CH_3	CH_3	4.666	+0.276
C_2H_5	C_2H_5	5.27	+0.273
C_3H_7	C_3H_7	5.979	+0.270

[a] W. P. Purcell, *J. Med. Chem.*, **9**, 294 (1966).

As a very special case of eq 8, the energies E_m^* identified with orbitals of the receptor could be assumed a constant. This would correspond to a situation in which the energy levels of the receptor are very close together and the value E_m^* used in eq 8 is an average value. The second term in eq 8 can then be approximated using superdelocalizability.[19]

$$E_{rs} = -\frac{q_r q_s e^2}{\epsilon_{rs} D_{rs}} + {}^1/_2\, q_r S_s^E \beta \qquad (13)$$

This leads to the possible regression equation

$$A_n = \sum_s (\xi_{ns} q_s + \zeta_{ns} S_s^E) + C \qquad (14)$$

when direct interactions between the atoms of drug and receptor are considered. A limited number of 3-hydroxyphenyltrimethylammonium derivatives (a total of six methyl, methoxy, and unsubstituted compounds) can have their inhibitory potency against AChE related to properties of the 3-hydroxy oxygen by the equation[20]

$$pK_1 = \underset{(-5.27)}{-2571 q_O^T} - \underset{(-6.58)}{283 S_O^{(E)}} - 645$$

$$(F = 44.44,\ r = 0.98)$$

where q_O^T is the total of the σ and π net charges on oxygen and $S_O^{(E)}$ is the π-electrophilic superdelocalizability of oxygen. The value in parentheses below each term is the t test on the significance of the coefficients.[20a]

Desolvation may be introduced into eq 11, 12, and 14 by including the limits to the expression tentatively given by Klopman[21]

$$I_{rs} = \frac{(q_s - 2b^2 c_{ns}{}^2 x)^2 - q_s{}^2}{2R_s}\left(1 - \frac{1}{\epsilon}\right) + \frac{(q_r - 2b^2 c_{mr}{}^2 x)^2 - q_r{}^2}{2R_r}\left(1 - \frac{1}{\epsilon}\right) \qquad (15)$$

where R is the effective radius of an atom, b is the variational parameter giving the contribution of Ψ_n to the perturbed MO Ψ_{mn}, and, empirically, $x = q - q(q-1)\cdot\sqrt{\kappa}$ for $q > 0$, κ being a universal constant. From this equation it can be noted that each interacting atom seems to contribute independently to the desolvation energy. Thus, each atom of a receptor should make an independent and constant contribution to the desolvation accompanying the interaction of a drug with a given receptor.

When there is no charge transfer between two interacting centers, as in an ideal ionic interaction, $b^2 = 0$ and eq 15 becomes

$$I_{rs} = 0 \qquad (16)$$

Desolvation effects therefore seem to be relatively unimportant in charge-controlled interactions, and correlations of drug action by eq 12 and 14 may therefore be associated with charge-controlled drug–receptor interactions (*cf.* Table V).

At the other extreme, when there is complete charge transfer between drug and receptor, as in the formation of an ideal covalent bond, $b^2 = {}^1/_2$ and eq 15 reduces to[17]

$$I_{rs} = \frac{(q \pm 1)^2}{2R}\left(1 - \frac{1}{\epsilon}\right) \qquad (17)$$

For this frontier-controlled interaction, eq 11 can be written

$$A_n = \sum_s (b_{ns} c_s + \lambda_{ns} q_s \pm \lambda_{ns}' q_s{}^2) + C'' \qquad (18)$$

and correlations of drug action by this equation should be indicative of a frontier-controlled interaction between drug and receptor. One series of sulfanilamides given in Table VI may fit this category, their *in vitro* activities against *Escherichia coli* (minimum inhibitory concentration, C_r) being correlated by the following equations. The necessary calculations were done for

Benzoyl derivatives

$$\log(1/C_r) = \underset{(1.02)}{2.04 c_N} + \underset{(1.91)}{146.69 q_N} - \underset{(-5.09)}{1549.99 q_N{}^2} + 17.63$$

$$(F = 29.68,\ r = 0.97)$$

Phenyl derivatives

$$\log(1/C_r) = \underset{(1.29)}{2.26 c_N} + \underset{(2.21)}{122.36 q_N} - \underset{(-1.36)}{456.63 q_N{}^2} - 3.19$$

$$(F = 42.99,\ r = 0.99)$$

the anilines and the benzamides from which the corresponding sulfanilamides were derived using the Hückel MO parameters suggested by Streitwieser.[16] It is interesting to note that linear relations between the activities of these compounds and the Hammett σ constant (or pK_a) are of opposite slope,[22] which may reflect the importance of desolvation of the sulfonamide nitrogen in the benzoyl series as opposed to its relative lack of importance in the phenyl series.

The effect of halide ions on the rate of hydrolysis of ACh by AChE also appears to depend on desolvation effects. The effect of these ions on ACh hydrolysis parallels reasonably well the ratio of the index $E^\pm$ to the desolvation energy of these ions (Table VII), where $E^\pm$ is defined as the electronic component, E_{rs}, associated with a free center.[13] The ratio used may be considered as the atomic analogy of the more familiar thermodynamic ratio $\Delta H/\Delta S$.

Within the approximations used in arriving at eq 12 and 17, MO methods appear capable of adequately accounting for the desolvation requirements associated

(19) *Cf.* K. Fukui, T. Yonezawa, and C. Nagata, *J. Chem. Phys.*, **27**, 1247 (1957).

(20) A. Cammarata and R. L. Stein, *J. Med. Chem.*, **11**, 829 (1968).

(20a) NOTE ADDED IN PROOF.—Dr. Federico Peradejordi and Dr. Alfred N. Martin have obtained correlations based on eq 14 in which more than one atom of a drug seems to be involved in leading to the observed response (bacterial inhibition).

(21) G. Klopman, *Chem. Phys. Letters*, **1**, 5 (1967).

(22) A. Cammarata and R. C. Allen, unpublished results.

TABLE VI

ELECTRONIC CHARACTER OF THE NITROGEN OF ANILINES AND BENZAMIDES RELATIVE TO THE *in Vitro* ACTIVITIES OF THE CORRESPONDING SULFONAMIDES

Substituent	Log $(1/C_r)^{a,b}$	σ_N	q_N	q_N^2
		Anilines		
4-NH_2	4.35	0.383	0.077	0.006
4-CH_3O	4.47	0.453	0.081	0.007
4-CH_3	4.57	0.453	0.081	0.007
H	4.80	0.477	0.083	0.007
4-Cl	4.80	0.459	0.082	0.007
4-NO_2	5.85	0.484	0.106	0.011
		Benzamides		
3-CH_3, 4-CH_3O	5.25	0.041	0.148	0.022
4-CH_3O	5.40[c]	0.035	0.148	0.022
3,4-CH_3	5.40	0.042	0.148	0.022
4-CH_3	5.40	0.036	0.148	0.022
3-CH_3	5.40	0.018	0.149	0.022
H	5.25	0.000	0.149	0.022
4-Cl	5.10[c]	0.027	0.148	0.022
4-CN	4.05[c]	0.000	0.151	0.023
4-NO_2	4.50[c]	0.000	0.153	0.023

[a] Minimum inhibitory concentration, C_r, against *E. coli*. [b] Data of J. K. Seydel, *Mol. Pharmacol.*, **2**, 259 (1966); J. K. Seydel and E. Wempe, *Arzneimittel-Forsch.*, **14**, 705 (1964). [c] We are extremely grateful to Dr. Seydel for testing these compounds for us.

TABLE VII

EFFECT OF HALIDE IONS ON AChE HYDROLYSIS OF ACh

Ion[a]	r, A[b]	$E^{\ddagger}$, ev[b]	Δ ev[b]	$E^{\ddagger}/\Delta$	μmoles of ACh split/hr per ml of enzyme[c]
F^-	1.36	−12.18	5.22	−2.33	9.1
I^-	2.16	−8.31	3.29	−2.52	35.6
Br^-	1.95	−9.22	3.64	−2.53	36.3
Cl^-	1.18	−9.94	3.92	−2.53	38.2

[a] Sodium salt in equivalent concentrations. [b] Data of ref 13. [c] B. N. Smallman and L. S. Wolfe, *Enzymologia*, **17**, 133 (1954).

with drug–receptor interactions and therefore show promise of greater utility in the study of drug action. The obvious extension of these equations to a form consistent with the Fujita–Hansch expression (eq 4) will be discussed in a forthcoming paper. It is readily shown that the Hansch parameter π may be considered a measure of drug–receptor interactions that fit the category of frontier-controlled reactions, but because of the demonstrated[10] importance of this quantity further development warrants separate consideration.

An interesting feature of the current approach results from the parallelism between the implications provided by eq 9 and 10[8,9] with regard to the principle of hard and soft acids and bases.[23,24] If future work bears out the presently promising indications, it may well turn out that a hard–hard, soft–soft complimentarity between the atoms of drug and receptor is a requisite for certain types of drug action.

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The Stereoisomers of α-(1-Aminoethyl)-*m*-hydroxybenzyl Alcohol

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A synthesis of the racemic and optically active isomers of *threo*-α-(1-aminoethyl)-*m*-hydroxybenzyl alcohol is reported. A discussion of the absolute configuration of these compounds and α-methyl-*m*-tyramine is presented. Norepinephrine displacement from adrenergic neurons by the *threo* isomers is discussed.

The sympathomimetic amine, metaraminol (**4**), (−)-*erythro*, has received extensive use as a pharmacological tool in studies on the mechanism of amine binding in adrenergic nerve endings.[1] Metaraminol is rapidly taken up by sympathetic tissue where it stoichiometrically displaces the normal neurotransmitter, norepinephrine.[2] Our interest in the relationship between amine stereochemistry and affinity for norepinephrine binding sites has led us to prepare the racemic and optically active forms of the *threo* isomer of **4**.

The method of Van Dijk and Moed[3] was used to prepare previously unreported racemic *threo*-**4** from *m*-benzyloxy-α-bromopropiophenone (**1**). Reduction of the amino ketone **2** with $LiAlH_4$ gave the *threo* alcohol **3** (Scheme I). Debenzylation of **3** to **4** was accomplished in two stages. Catalytic hydrogenation over a Pd–C catalyst in ethanolic HCl at room temperature removed two of the benzyl groups; the third was removed with a Pd–Al_2O_3 catalyst at higher temperature.

The optically active *threo* enantiomers **4** were prepared by reaction of the optically active *erythro* amides **6** with $SOCl_2$ followed by hydrolysis of the intermediate oxazolines with dilute HCl. This method has been used frequently in the past to convert *erythro* amido alcohols to *threo* amino alcohols in the ephedrine and norephedrine series.[4] Nmr spin-coupling constants for the hydrogens situated on C-1 and C-2[5] were 8.4 ± 0.2 Hz for the optically active and racemic products,

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(4) H. K. Müller, *Ann.*, **599**, 61 (1956); H. Pfanz and H. Müller, *Arch. Pharm.*, **288**, 65 (1955).
(5) See formula **4** for numbering.