Superdelocalizability and Charge Density. A Correlation with Partition Coefficients

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Since maximum biological response (drug activity, plant growth, insect toxicity, etc.) for a series of related aromatic chemicals has been defined in terms of molecular partitioning across nonpolar–polar phases (membrane permeability) and chemical reactivity,[1,2] it seemed desirable to see whether the partition coefficient, a measure of lipophilicity for a molecule, could be represented by indices obtained from molecular orbital theory. Attempts to correlate experimentally determined partition coefficients by linear multiple-regression analyses with molecular orbital indices (energy of highest occupied molecular orbital, HOMO; energy of lowest empty molecular orbital, LEMO; total π energy; HOMO or LEMO frontier electron densities; atom charge density; atom electrophilic or nucleophilic superdelocalizabilities) suggested that only two parameters, charge density and electrophilic superdelocalizability, may be related to the partitioning process. Data pertinent to our following discussion are presented in Table I.

TABLE I

TOTAL ABSOLUTE CHARGE DENSITIES ($\Sigma|Q_r|$), TOTAL ELECTROPHILIC SUPERDELOCALIZABILITIES (ΣS_r), AND LOGARITHMS OF PARTITION COEFFICIENTS ($\ln \bar{P}$) FOR AROMATIC MOLECULES

Compd	ΣS_r	$\Sigma\|Q_r\|$	$\ln \bar{P}$	$\ln \bar{P}^*$	$\ln \bar{P}^*/\ln \bar{P}$
Carbazole	12.177	0.448	7.576	7.462	0.985
Diphenylamine	12.302	0.496	7.427	7.423	0.999
Biphenyl	10.292	0.000	7.272	7.342	1.010
Thianaphthene	14.698	1.340	7.113	6.878	0.967
Naphthalene	8.874	0.000	6.932	6.397	0.922
5-Bromoindole	11.451	0.552	6.906	6.714	0.972
1,2-Dimethylindole	12.051	0.744	6.498	6.626	1.020
5-Methylindole	10.427	0.614	6.180	5.873	0.950
N,N-Dimethylaniline	10.226	0.315	6.026	6.498	1.078
3-Methylindole	10.691	0.529	5.984	6.265	1.047
Indole	9.114	0.518	5.182	5.241	1.011
Toluene	6.253	0.170	4.852	4.217	0.869
Quinoline	8.333	0.484	4.754	4.807	1.011
Anisole	7.672	0.235	4.700	4.998	1.063
Benzothiazole	12.000	1.426	4.673	4.860	1.040
Indazole	8.991	0.708	4.190	4.677	1.116
Benzoxazole	8.114	0.884	3.664	3.645	0.995
Benzene	4.998	0.000	3.584	3.811	1.063
Oxindole	8.843	1.558	2.639	2.419	0.917

[a] Ratio expresses closeness of calculated data to experimental data.

Herein, equations (1–3) are described with the molecular orbital variables, obtained for the π-electron framework of the aryl compound, that seem to correlate with the degree of partitioning for aromatic molecules across the interface barrier of a 1-octanol–aqueous sodium phosphate buffer (pH of 7.4) mixture where $\bar{P}$ is

$$\ln \bar{P} = 0.4314\sum S_r + 1.3297 \quad (t = 3.872) \qquad r = 0.685 \quad F = 14.99 \quad (1)$$

$$\ln \bar{P} = 6.1320 - 0.0304\sum |Q_r| \quad (t = -1.264) \qquad 0.293 \quad 1.60 \quad (2)$$

$$\ln \bar{P} = 0.6670\sum S_r - 2.5395\sum |Q_r| + 0.4777 \quad (t = 17.97;\ t = -13.46) \qquad 0.978 \quad 177.48 \quad (3)$$

the partition coefficient, S_r is the atom electrophilic superdelocalizability, and Q_r is the atom charge density. ΣS_r refers to the summation of S_r for all aryl atoms; likewise, $\Sigma|Q_r|$ refers to the summation of the absolute value of Q_r for all aryl atoms. Comparison of the statistical values (F, significance of the equation; r, the multiple correlation coefficient, for the fit of experimental points to the equation; t, contribution of each variable to the correlation) for eq 1–3 indicates that the best formulation of the experimental results is obtained with eq 3. Calculated values for $\ln \bar{P}^*$ from eq 3 are compared with the experimental $\ln \bar{P}$ values in Table I. Although atom charge density contributions from the aryl σ-electron framework[3] may be neglected here for correlation with this series of compounds, they probably should be included for satisfactory results with other series.

Partitioning of aromatic molecules between nonpolar and polar phases may be represented by molecular orbital indices, charge density, and electrophilic superdelocalizability. $\Sigma|Q_r|$, reflecting hydrophilicity, contributes negatively in eq 3. ΣS_r, reflecting lipophilicity, contributes positively in eq 3, and $\ln \bar{P}$ represents the relative magnitudes of the two quantities, ΣS_r and $\Sigma|Q_r|$, for the aryl compound. Q_r, a result of π-electron delocalization, might reflect aqueous solubilization of the aromatic compound through a classical charge–dipole interaction mechanism. The other term, S_r, has a more complex relationship to the partitioning process since it was developed from perturbation theory[4] as an index for a favorable charge-transfer transition state for a reaction whereby a weak π bond is formed between attacking reagent (perhaps in this case, 1-octanol) and a specific atom of the substrate. S_r has also been considered to reflect electronic polarizability[3] and as such might also indicate aryl solubilization in 1-octanol by van der Waal forces.

Although exact theoretical solutions for charge density and electrophilic superdelocalizability as related to partitioning are unknown at this time, empirical correlation of ΣS_r and $\Sigma|Q_r|$ with $\ln \bar{P}$ has provided a new example for the applicability of molecular orbital theory to a physical system, pertinent in studies of biological activity and chemical structure interrelationships.

Partition Coefficient Assay.—Partition coefficients of aromatic compounds were determined for the 1-octanol–50 mM sodium phosphate buffer (pH of 7.4) mixture

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using a procedure previously described.[5] The partition coefficient was calculated from the concentration of aryl compound in each phase (ratio of octanol solubility to aqueous phase solubility).

Molecular Orbital Theory Calculations.—The matrix equations for Hückel molecular orbital treatment of the aryl π-electron framework were solved with the use of an IBM 1130 computer. Coulomb and bond integrals were obtained from Streitwieser.[6] Methyl substituents were treated as heteroatoms. Charge density (Q_r) and electrophilic superdelocalizability (S_r) values for aryl atoms were calculated from the appropriate equations also given by Streitwieser.[6]

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Iodinated Derivatives of Histamine and N-Acetylhistamine

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Although it has been reported that histamine loses its biological activity by reaction with iodine, probably by iodination,[2] and kinetic studies have indicated iodine substitution in its imidazole ring,[3] iodinated derivatives of histamine have not yet been described. With the purpose of obtaining authentic iodinated derivatives for the chromatographic estimation of reaction products in studies of the kinetics of iodination of histamine and N-acetylhistamine, the following compounds were prepared: 5-iodohistamine dihydrochloride, 2,5-diiodohistamine, N-acetyl-5-iodohistamine, and N-acetyl-2,5-diiodohistamine. The position of the iodine atom in the imidazole ring of these compounds was determined from their nmr spectra. The limited iodination of histamine resulted in only one of the two possible isomers of monoiodohistamine, in which the iodine atom is in the 5 position, in analogy with what has been reported for monoiodoimidazole[4a] and monoiodohistidine.[4b]

None of the four compounds described here showed any spasmogenic activity upon the isolated guinea pig ileum in doses up to 10^4 times higher than an effective concentration of histamine on the same preparation. Slight antihistaminic activity was present only in N-acetyl-2,5-diiodohistamine and in 2,5-diiodohistamine. The latter was the more active of the two; at a concentration of 2×10^{-8} *M* it caused 50% reversible inhibition of the contraction produced by 5.5×10^{-9} *M* histamine on the isolated guinea pig ileum.

Experimental Section

Microanalyses for C, H, N, I, and Cl were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.[5] Melting points were determined on the Kofler micro melting point apparatus and are reported uncorrected. Nmr spectra were obtained at 60 Mc on a Varian T-60 or a Perkin-Elmer R-10 spectrometer, using D_2O as the solvent and Me_2CO-d_6 as an internal standard. Tlc was performed on silica gel G (E. Merck, A.G., Darmstadt) plates and the solvent system most adequate for separation of the iodinated compounds was *n*-BuOH saturated with 9 *N* NH_4OH, in which histamine had an R_f value of 0.08. Biological activity was tested by four-point assays on the isolated guinea pig ileum using histamine as standard. Antihistaminic activity was tested by the inhibition of response to histamine using acetylcholine as a control for specificity.

5-Iodohistamine Dihydrochloride.—A solution of 2.0 g of histamine dihydrochloride in 200 ml of 0.5 *N* NaOH and 100 ml of *n*-C_6H_{14} was cooled in an ice bath, and 2.76 g of I_2 dissolved in 300 ml of *n*-C_6H_{14} was added dropwise (90 min) with vigorous stirring. The stirring was continued for 10 min after the addition of I_2, and then 0.56 g of KIO_3, dissolved in 20 ml of H_2O and 10 ml of concentrated HCl, was added, followed by the extraction of I_2 with *n*-C_6H_{14}. The solution was concentrated to dryness *in vacuo* at 35°. The residue was suspended in 200 ml of absolute EtOH and 10 ml of concentrated HCl and refluxed for 30 min. The addition of a large volume of Me_2CO produced a white voluminous precipitate which was collected and, after charcoal decolorizing, crystallized from Me_2CO–H_2O as the dihydrochloride, yielding 1.5 g (45%) of a white solid that melted at 211–213° dec and was very soluble in H_2O, sparingly soluble in EtOH, and insoluble in Me_2CO. This product gave only one spot on tlc with R_f 0.33. *Anal.* ($C_5H_8IN_3 \cdot 2HCl$) C, H, N, Cl, I.

2,5-Diiodohistamine.—To 1.0 g of histamine dihydrochloride, dissolved in 200 ml of 0.25 *N* NaOH and 100 ml of *n*-C_6H_{14}, was added 3.04 g of I_2 dissolved in 240 ml of *n*-C_6H_{14}, as described in the preceding section. After addition of 0.50 g of KIO_3, dissolved in 20 ml of H_2O and 5 ml of concentrated HCl, I_2 was removed by extraction with *n*-C_6H_{14} and the solution was concentrated *in vacuo*, at 35°, to 35 ml. When the pH was brought to 9 by addition of concentrated NH_4OH a yellowish precipitate was formed. This was purified by repeated dissolution in concentrated HCl, treatment with charcoal, and precipitation by adding concentrated NH_4OH to bring the pH to 9, yielding 0.85 g (43%) of a white powder that melted at 163–164° dec, and gave one spot on tlc with R_f 0.52. *Anal.* ($C_5H_7I_2N_3$) C, H, N; I: calcd, 69.93; found, 69.44.

N-Acetylhistamine was prepared according to van der Merwe,[6a] but the mixture of histamine and Ac_2O was not refluxed, which prevented darkening of the product and afforded better yields. The light yellow oily residue, obtained after evaporation of the solvent, was dissolved in absolute EtOH and passed through a column of neutral alumina. On concentration of the eluate white crystals were obtained in a yield of 73%. The product melted at 145–147° (lit.[6b] mp 147–148°) and gave one spot on tlc with R_f 0.47.

N-Acetyl-5-iodohistamine.—The reaction of 1.0 g of N-acetylhistamine with 1.66 g of I_2 was performed as described above. After addition of KIO_3, extraction of I_2, and concentration *in vacuo*, at 40°, to 10 ml, alkalinization to pH 8 produced a white precipitate that was repeatedly dissolved in H_2O and reprecipitated by adjusting to pH 8. The final product, obtained in a yield of 0.78 g (44%), melted at 188–190°, and gave one spot on tlc with R_f 0.66. *Anal.* ($C_7H_{10}IN_3O$) C, H, I, N.

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