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QUANTUM CHEMICAL STUDIES ON DRUG ACTIONS

IV. Correlation of Substituent Structures and Anti-Serotonin Activity in Lysergamide Series

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ABSTRACT: Several hypotheses have been put forward relating the structures of LSD-25 and its congeners to the indolyl structure of tryptamines, and especially serotonin. However, most of these hypotheses do not pay attention to the substituent and side chain structures of the lysergates. Our present work points out the importance of the latter structures. The anti-serotonin activity of several lysergate derivatives seems to be dependent on the total orbital energy, but not on the HOMO energy of the molecule. The logarithm of hallucinogenic activity is apparently related to the logarithm of anti-serotonin activity. Our investigations suggest a high degree of electron delocalization over the entire ring structure, indicating possible resonance leading to effectual partial pi bonding between all four rings. Interestingly, the HOMO energies of N-methyl lysergic acid butanolamide, d-lysergic acid propylamide and d-iodoLSD-25 are sharply different from the other seventeen lysergates studied. The alkoxyl side chain may be partly responsible for this effect. The univer-

sal importance claimed for HOMO energy cannot be considered valid in the light of these studies.

INTRODUCTION: Most of the emphasis in studies on the structure-activity relationships in the lysergate series of compounds has been on the ring structure and comparison with indole structures and amphetamines. However, the biological activities of derivatives obtained by substitutions in the side chain of the molecule vary tremendously. There is no apparent correlation between the structures of these compounds and their biological activities (Doepfner, 1962).

In continuation of our quantum studies on indole and catechol derivatives (Kumbar and Sankar, 1973), we investigated the quantum parameters of the lysergates. This paper reports on the correlation of these parameters with the anti-serotonin activity of derivatives of LSD-25. Previously, we (Kumbar and Sankar, 1973) have correlated the hallucinogenic activity of LSD derivatives with the total orbital energy and postulated a high degree of electron delocalization over t entire ring portion of the LSD molecule.

The twenty compounds presented here are limited to those whose anti-serotonin and hallucinogenic activity in humans have been determined (Doepfner, 1958; Gyermek, 1961; Nistico, 1968; and Abramson, 1959).

METHOD: In computing the quantum mechanical parameters, the semiempirical Hückel method with omega-technique has been used. This technique with a single parameter introduces electronic repulsion within the framework of simple LCAO

(Linear Combination of Atomic Orbitals) methods. The hyperconjugation model has been selected for the present investigation. The various parameters needed in the calculations are taken from Pullman and Pullman (1963). The detailed technique and methodology have been described previously (Kumbar and Sankar, 1973). The relative trend of any property may remain the same regardless of the method used, even though the magnitude might not necessarily be the same. Due to this reason, the method should not make a significant difference, as we are interested in relative information rather than absolute information. The latter is difficult to obtain without detailed conformational analyses with sophisticated programs and is planned for future studies. The HOMO and LEMO energy values respectively indicate the electron donor and acceptor ability of a given molecule. The HOMO energy value can be further interpreted as the first ionization potential. The total orbital energy is calculated by taking twice the sum of all the occupied atomic orbital energies. Total orbital energy may be thought of as a first approximation to the total energy or the binding energy of a molecule only in case of neutral and non-polar molecules. However, the seriousness of this statement depends upon the magnitude of the exchange integral (Dewar, 1969). The energy indices for serotonin have also been included in the table for the sake of comparison. The computation is carried out on neutral, planar molecules.

Further calculations on the relation between the anti-serotonin activity and ΔE, the energy change involved in the interaction between the drug and the receptor molecule have been carried out as suggested by Cammarata (1970). The biological activities have been obtained from the studies of Cerletti and Doepfner (1958), Gyermek (1961), Nistico (1968) and Abramson (1959).

RESULTS: The results are presented in Table I and Figures 2 and 3. The HOMO and the LEMO energy values of the lysergates are compared with those of serotonin. The anti-serotonin activity and the hallucinogenic activity of the lysergates are also presented in this Table. It is clear that the lysergate congeners are both better donors and acceptors.

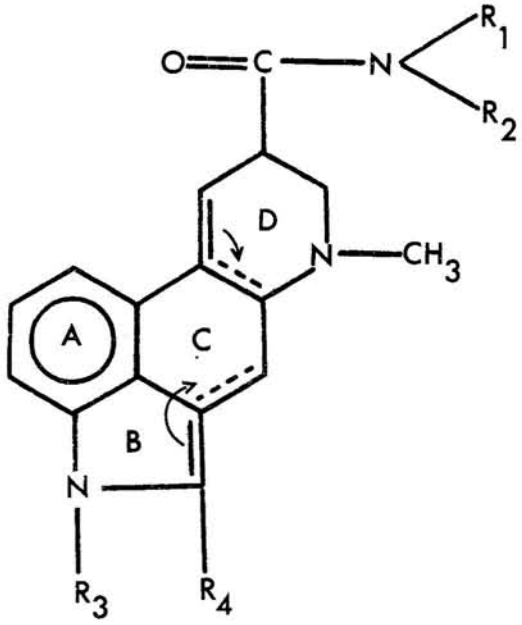

Figure 1. Structural representation of lysergamides showing possible delocalization of pi electrons over the rings A, B, C, and D.

Most of the LSD analogs themselves have identical HOMO and LEMO energy values, except 1-methyl-d-lysergic acid butanolamide, 2-iodo-lysergic acid diethylamide, and d-lysergic acid isopropylamide, which have negative values, indicating that these molecules are powerful electron donors. In spite of the conformational differences that exist in the molecules studied here, the calculated HOMO and LEMO energy values predict that all the compounds have very similar electron donor or acceptor capacity except the compounds numbered 3, 5, 10, 11 and 13.

The HOMO or LEMO energy values do not correlate with anti-serotonin activity. However, the total orbital energies seem to correlate with the anti-serotonin activity (see Figure 2). Previously, the non-correlation of HOMO or LEMO with many biological activities has been observed by many workers (Green and Kang, 1970; Neely, 1970; Purcell and Clayton, 1970; Snyder, 1970). Therefore, one should get away from the idea that these are the only two parameters which need to be correlated with biological activity, and of course, there is nothing universal about these two parameters. In addition to HOMO, LEMO, charge density, etc., the total orbital energy should also be treated as relevant parameters. Among the 20 compounds studied, the orbital energies of 5 compounds numbered 1, 15, 17, 19 and 20 do not correlate with the activity. The least square correlation equation excluding these five compounds, is given by:

$$\text{Log (anti-5HT)} = -2.7092 + 0.07955\ (\text{total orbital energy}) \pm 0.2715 \qquad \text{(Eq. I)}$$

or

$$\text{Log (anti-5HT)} = -16.2811 + 10.2838 \log\ (\text{total orbital energy}) \pm 0.2709 \qquad \text{(Eq. II)}$$

where the last quantity is the standard deviation. A correlation coefficient of 0.889 has been obtained.

Out of the five compounds that do not fall on the correlation line, four are cyclic alkyl derivatives of LSD. This discrepancy may be due to either questionable values for biological activity or in turn may throw some doubts on the validity of our method and/or inferences, especially in the case of the cyclic substitutions. There is no apparent direct correlation between the (illucino-genic) hallucinogenic activity and anti-serotonin activity of these compounds. The former activity may be mediated through the central nervous system and the latter through in situ action on smooth muscle (Sankar, et al., 1964). However, when the logarithm of the ratio of hallucinogenic activity to the anti-serotonin activity is plotted against the logarithm of the anti-serotonin activity, the following least square equation has been obtained relating the ratio of the hallucinogenic activity to the anti-serotonin activity to anti-serotonin activity alone.

$$\text{Log (H/S)} = 1.1614 - 1.1093 \log S \pm 0.6499 \qquad \text{(Eq. III)}$$

TABLE I

QUANTUM CHEMICAL DATA ON LYSERGAMIDE DERIVATIVES

COMPOUND NUMBER	R_1	R_2	R_3	R_4	NAME OF COMPOUND	anti-5HT activity	Halluci-nogenic	HOMO $X\beta^{-1}$	LEMO $X\beta^{-1}$	TOTAL ORBITAL ENERGY β^{-1}
1	C_2H_5	H	CH_3	H	1-methyl d-lysergic acid ethylamide	835	4.0	0.148	-0.568	54.228
2	C_2H_5	C_2H_5	CH_3	Br	1-methyl-2-bromo-LSD	533	<1	0.144	-0.569	65.352
3	C_4H_8OH	H	CH_3	H	1-methyl-d-lysergic acid butanolamide	400	0.6	-0.394	-0.585	63.294
4	C_2H_5	C_2H_5	CH_3	H	1-methyl-LSD	368	36,33	0.148	-0.567	62.294
5	C_2H_5	C_2H_5	$COCH_3$	3	1-acetyl-LSD	210	91,100	0.153	-0.564	67.824
6	C_2H_5	C_2H_5	H	Br	2-bromo-LSD	150,103	7.2,<2	0.145	-0.569	61.294
7	C_2H_4——	C_2H_4	CH_3	H	1-methyl-d-lysergic acid pyrrolidide	130	<5	0.148	-0.567	62.502
8	C_2H_5	C_2H_5	H	H	d-LSD	100	100	0.148	-0.567	58.250
9	C_2H_5	C_2H_5	OCH_3	H	1-methoxy-LSD	58.9	66	0.136	-0.569	63.718
10	C_2H_5	C_2H_5	H	I	2-iodo-LSD	57.4	--	-0.009	-0.599	59.516
11	C_2H_5	H	$COCH_3$	H	1-acetyl-d-lysergic acid ethylamide	39	7	.153	-0.565	59.756
12	CH_3	CH_3	H	H	d-lysergic acid dimethylamide	23.2	10	0.149	-0.567	50.262
13	$CH(CH_3)CH_3$	H	H	H	d-lysergic acid isopropylamide	22.2	--	-0.384	-0.585	51.024
14	C_2H_5	H	H	H	d-lysergic acid ethylamide	11.9	3.4,5	0.148	-0.568	50.180
15	C_2H_4-CH_2-C_2H_4		H	H	d-lysergic acid piperidide	8.5	--	0.148	-0.567	62.442
16	CH_3	H	H	H	d-lysergic acid methylamide	6.3	--	0.148	-0.568	46.188
17	C_2H_4——C_2H_4		H	H	d-lysergic acid pyrrolidide	4.7	5.3,10	0.148	-0.567	58.440
18	H	H	H	H	d-lysergic acid amide	4.3	0	0.148	-0.569	42.292
19	CH_2-CH=	CH-CH_2	H	H	d-lysergic acid pyrrolinide	4.1	10	0.148	-0.568	52.968
20	C_2H_4-O-	C_2H_4	H	H	d-lysergic acid morpholide	8.0	11.0	0.148	-0.567	62.728
	Serotonin							0.425	-0.926	28.792

where H and S respectively are the hallucinogenic and anti-serotonin activities. The last quantity refers to the standard deviation. A correlation coefficient 0.814 has been calculated (Figure 3). The notable exceptions to this relation are the N-1 derivatives (compounds 2,3,4,5,8 and 9). This may denote an as yet undefined stereochemical peculiarity resulting from substitution on the N-1 position.

DISCUSSION: d-LSD-25 possesses several biological activities, including hallucinogenic, anti-serotonin, anti-histamine activities, hyperthermic effects, excitatory effects, and effects on blood pressure, EEG patterns, oxygen uptake, etc. (Sankar, 1974). However, both l-LSD and d-isoLSD are devoid of activity. 2,3-dihydroLSD is 1/5 to 1/8 as potent as LSD-25 in man and is slower acting (Gorodetzky and Isbell, 1964). Substitution (except an acetyl group on N_1) on N_1 and C_2 positions decreases hallucinogenic activity, but not necessarily anti-serotonin activity on smooth muscle. These observations point out that the main locus of hallucinogenic activity may depend on: i) the unsubstituted indole ring, ii) the optically preferred isomer and iii) a stringent steric specificity of the whole molecule, and especially, the side chain (Baker, et al., 1973). The anti-serotonin activity may depend less on the rigidity of the total structure; lipid solubility by N-1 alkyl substitution being facilitatory. Our observation that these activities are dependent on the total orbital energy suggests the

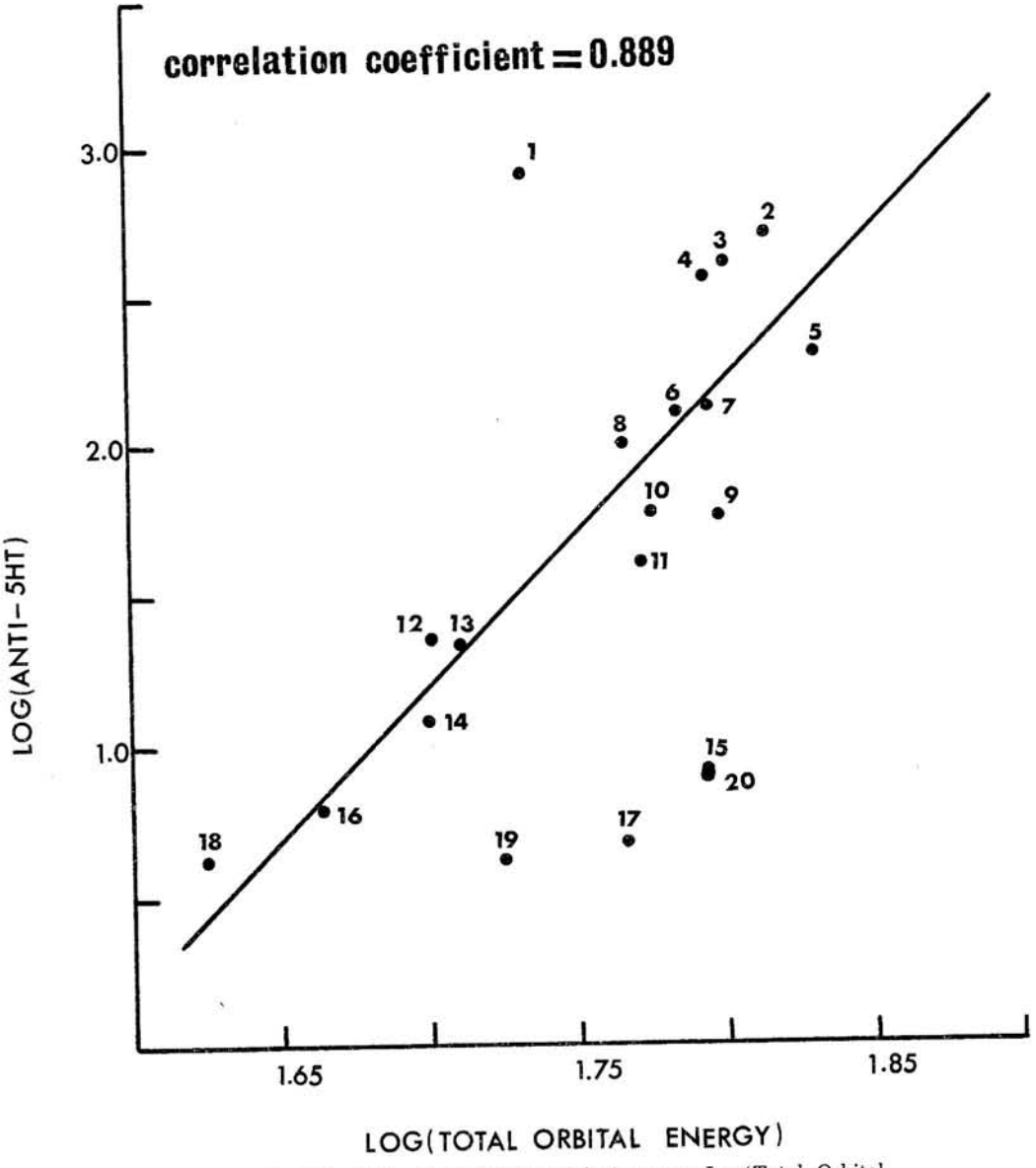

Figure 2. Plot of Log(Anti-5HT Activity) versus Log(Total Orbital Energy) for lysergamide derivatives. The numbers on the graph correspond to the numbers of the compounds given in Table I. The line represents the locus obtained from least square analysis.

validation for a specific structural requirement. This requirement is apparently quite stringent for hallucinogenic activity and more flexible for anti-serotonin activity. Further, the relation between the two activities (Figure 3) shows that the logarithm of hallucinogenic activity is possibly a function of the logarithm of the anti-serotonin activity.

The previously proposed (Baker, et al., 1973; Kang and Green, 1970; and Snyder and Richelson, 1968) models for the biological activities of compounds like LSD-25, amphetamines, etc., put greater emphasis on the ring structures of LSD-25. These models are not yet adequate to explain the large variations in the activities of the derivatives obtained by substitutions in the lysergates. The molecular orbital calculations and crystallographic studies (Baker, et al., 1973; Kang and Green, 1970) have shown that 5-hydroxytryptamine (5HT, serotonin) exist in a single preferred conformation; namely, the extended one. This extended conformation which matches the portion of the LSD ring is responsible for the blockage of 5HT. Contrary to that, Ison, et al.,(1972) indicated that both extended and non-extended conformation of serotonin are probable.

It is logical to assume that 5HT in solution might assume various conformations. LSD-25 and its derivatives might be capable of duplicating all or few of the existing conformations of 5HT (depending upon the substituents). This

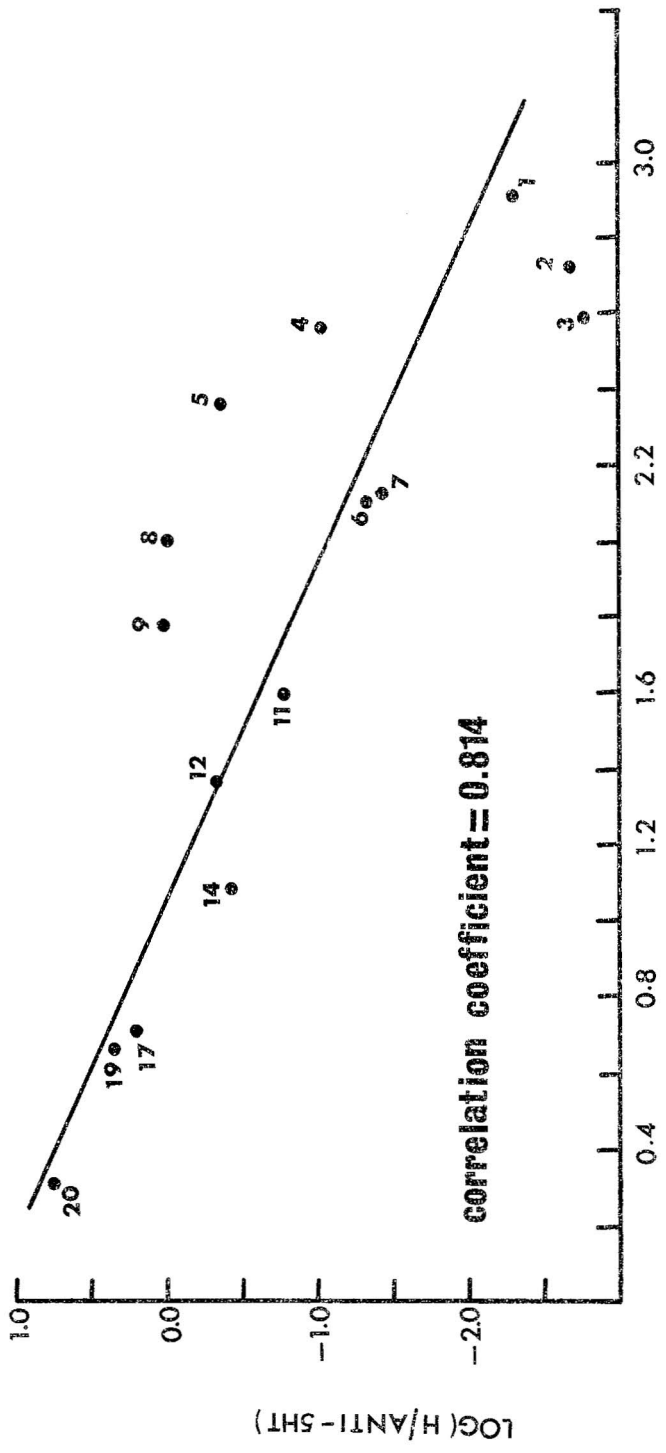

Figure 3. Plot of Log(Hallucinogenic Activity/Anti-5HT Activity) for the lysergamide derivatives. The numbers on the graph correspond to the numbers of the compounds in Table I. The line represents the locus obtained from least square analysis.

might be achieved by a slight twisting and/or bending of the ring portion of the LSD-25 molecule. The bending or twisting motion might be controlled by the substituents present on the ring and the side chain. Therefore, if such a situation truly exists, then LSD molecule might possess some flexibility, which one might consider as a manifestation of the alteration in electronic and steric factors. According to this, then l-methyl-d-lysergic acid ethylamide which has the anti-5HT of 835 might be more flexible and more capable of duplicating a large number of the existing conformations of 5HT. As the activity decreases, the flexibility decreases, and hence the duplicating power of the molecule. d-Lysergic acid morpholide might be considerably stiffer than l-methyl-d-lysergic acid ethylamide, and probably is unable to duplicate as many of the conformations of 5HT. The x-ray work (Baker, et al., 1973) of LSD iodobenzene describes that N_6 is above the plane of the indole ring at brain pH. This observation supports the idea that the ring portion may be associated with some flexibility, especially for anti-serotonin activity.

From the quantum parameters and the dependence on the total orbital energy (not on HOMO energy), we would like to postulate a high degree of electron delocalization (not exclusive of stringent structural requirements) over the entire molecule of LSD-25. To facilitate this, there may be resonance between rings A, B and C, or (less likely) between rings C and D (see Figure 1), with resonating electron migration

resulting in effectual partial pi bonds from the sigma bonds. The interatomic interactions might (comparable to the hydrogen bonding in DNA) involve N_1, N_6, amide N and other atoms in producing the conformational end products (Baker, et al., 1973); Stoll, et al., 1954).

The relation between the anti-serotonin activity (A) and the energy change involved in the binding of the drug to the macromolecular receptor could be considered along the lines suggested by Cammarata (1970). The following equation may be postulated:

$$\text{Log } A = - \frac{1}{(2.303)RT} \Delta E + d \qquad \text{(Eq. IV)}$$

Where ΔE is the change of energy in the drug-receptor interaction, d is a constant, R is the gas constant, and T is the absolute temperature. The ΔE is the sum of the contributions, which, in a general form can be represented by

$$\Delta E = a_1 \Delta E^e + a_2 \Delta E^d + a_3 \Delta E^s + a_4 \Delta E^p \qquad \text{(Eq. V)}$$

Where ΔE^e, ΔE^d, ΔE^s, and ΔE^p are the electronic, solvation, steric and conformational energy changes respectively. The a_1, a_2, a_3, and a_4 are the coefficients associated with respective energy terms. In writing equation V, we have assumed that ΔE is not a simple summation of various energy terms. If it is a simple summation, then $a_1 = a_2 = a_3 = a_4 = 1$. Since we have correlated the log (anti-5HT) activity with the total orbital energy (TOE), we assume that the electronic energy change arises due to the change in TOE. On this basis, the final activity equation takes the following form:

$$\text{Log } A = - \frac{a_1\beta}{(2.303)RT} \text{ (TOE)} + (a'_2\Delta E^d + a'_3\Delta E^s + a'_4\Delta E^p + d) \quad \text{(Eq. VI)}$$

where β is the resonance integral. The $- \frac{1}{(2.303)RT}$ term has been absorbed in a'_2, a'_3, and a'_4. Comparing equation VI with the equation I, we evaluate

$$- a_1\beta = (0.07955) \times (2.303RT) \quad \text{(Eq. VII)}$$

$$\text{and } a'_2\ \Delta E^d + a'_3\ \Delta E^s + a'_4\ \Delta E^p + d = 2.7902 \quad \text{(Eq. VIII)}$$

the electronic coefficient a_1 in equation VII can be evaluated by substituting the value of R and T. At a physiological temperature of 37°C, equation VII becomes

$$- a_1\beta = 113.5862 \text{ cal mole}^{-1} \quad \text{(Eq. IX)}$$

If we assume the value of β as -18 kcal mole^{-1}, which has been established for hydrocarbons (Pullman and Pullman, 1963), then the value of a_1 becomes

$$a_1 = 6.310 \times 10^{-3} \quad \text{(Eq. X)}$$

However, the assumption of 18 kcal mole^{-1} for β is questionable. From these derivations, it is clear that ΔE is not a simple summation as $a_1 \neq 1.0$. Since we do not know other energy changes, the coefficients a'_2, a'_3 and a'_4 cannot be evaluated.

The above discussion is of relevance in an effort to determine the ΔE involved. However, its use is rather limited because the contributions of the individual energy changes cannot be assessed adequately. It also illustrates the inadequacy of simplified equations. While this dis-

cussion is not yet fruitful in the present study, considerations of this nature along with lipophilicity and other physical chemical properties are important in molecular pharmacological studies.

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