Proc. Indian Acad. Sci., Vol. 88 A, Part I, Number 3, June 1979, pp. 171–177,

A quantitative aspect of charge-transfer phenomenon in the biological activity of hallucinogens, local anesthetics and nicotinic agents

S P GUPTA and P SINGH
Department of Chemistry, Birla Institute of Technology and Science, Pilani 333 031

MS received 16 November 1978; revised 5 February 1979

Abstract. The qualitative electronic structure-activity relationships, that had led some workers to suggest that hallucinogens, local anesthetics, and nicotinic agents exert their biological effect through the formation of charge-transfer complexes with the receptors, are tested statistically. The statistical test is found to support the suggestion along with the observation that in addition to the charge-transfer mechanism, a secondary binding is also involved in the activity of nicotinic agents.

Keywords. Structure-activity relationship; electronic parameters; drug-receptor interaction; hallucinogens; local anesthetics; nictotinic agents.

1. Introduction

A qualitative theoretical study has suggested that hallucinogens (Snyder and Merril 1965; Karreman *et al* 1959), local anesthetics (Yoneda and Nitta 1965), and nicotinic agents (Fukui *et al* 1960; Crow *et al* 1969) exert their biological effect through the formation of charge-transfer complexes with the receptors. In case of these drugs, the biological activity was shown to be related with some molecular orbital (MO) parameters which involve the concept of charge-transfer. Tables 1–3 list these series of drugs with their activity and the related MO parameter(s).

However any conclusion, drawn on the basis of only qualitative structure-activity relationship studies, should not be completely relied upon. As a matter of fact, the exact information, to the extent the theory or method applied for structure-activity relationship studies is able to provide, must be extracted only when the relationships are tested statistically. The aim of the present communication is, therefore, to perform the regression analysis on the electronic structure-activity relationships studied by earlier workers in case of hallucinogens, local anesthetics and nicotinic agents and judge the suggestion to the involvement of charge-transfer phenomenon in their activity from a quantitative aspect.

2. The regression analysis and discussions

The hallucinogenic activity of some tryptamines and phenylethylamines as listed in table 1 was shown by Snyder and Merril (1965) to be related with the energy of the highest occupied molecular orbital, E_{HOMO}, of the compound. A regression analysis reveals this relationship to be statistically very significant (eq. 1).

$$\log C = -10{\cdot}259\ E_{HOMO} + 5{\cdot}956$$
$$n = 6,\ r = 0{\cdot}972,\ s = 0{\cdot}327,\ F_{1,4} = 68{\cdot}81 \qquad (1)$$

In eq. (1), C represents the ratio of effective dose of mescaline to that of drug, n is the number of data points, s the standard deviation, r the correlation coefficient and F the F ratio between the variances of calculated and experimental values. In this equation F is significant at 99% level [$F_{1,4}$ (0·01) = 21·20].

In case of some local anesthetics (table 2), the activity was shown to be related with the stabilisation energy of the complex, δE, (Yoneda and Nitta 1965). The regression analysis, however, does not reveal any significant correlation between the activity and δE.

$$\text{Anesthetic activity} = -9{\cdot}171\ \delta E + 5{\cdot}641$$
$$n = 9,\ r = 0{\cdot}718,\ s = 0{\cdot}580,\ F_{1,7} = 7{\cdot}44. \qquad (2)$$

The activity of nicotinic agents, such as phenylcholine ethers (table 3), was shown first by Fukui *et al* (1960) to be related with the frontier electron density at ether oxygen, f_0^E, and with nucleophilic superdelocalisibility at the ring ortho position, S^N_{ortho}, (table 3A). Later Crow *et al* (1969) showed the nicotinic activity of meta-substituted phenylcholine ethers (table 3B) to be related to E_{HOMO} and electrophilic superdelocalisibility at ring positions 2 and 6, S_2^E and S_6^E. By the regression analysis, however, the most significant correlations that surfaced with the use of data of table 3A are given by eqs (3) and (4), and those with the use of data of table 3B by eqs (5) and (6).

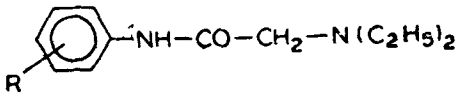
Table 1. Some hallucinogens with the values of their activity and related MO parameter(s).*

Compound	E_{HOMO} (β)	log C^a	
		Obsd.	Cald. eq. (1)
LSD	0·2180	3·5682	3·7198
4-Hydroxy-N, N-dimethyl tryptamine (psilocin)	0·4603	1·4914	1·2339
6-Hydroxydiethyltryptamine	0·4700	1·3979	1·1344
2,4,5-Trimethoxyamphetamine	0·4810	1·2304	1·0215
3,4,5-Trimethoxyamphetamine	0·5357	0·3424	0·4603
3,4,5-Trimethoxyphenylethylamine (mescaline)	0·5357	0·0000	0·4603

* Snyder and Merril (1965).

[a] The ratio of effective dose of mascaline to that of drug.

Table 2. Some local anesthetics with the values of their activity and related MO parameter(s).*



R	$\frac{(-\beta')^2}{\delta E\ \beta}$	Anesthetic activity[a]	
		Obsd.	Cald. eq. (2)
2-Cl, 6-CH_3	0·4350	0·80	1·65
2, 6-diCH_3	0·5397	1·05	0·69
2-CH_3	0·4000	1·40	1·97
H	0·3706	1·80	2·24
2-Cl	0·3689	2·00	2·26
3, 4-diCH_3	0·4117	2·10	1·87
2-Cl, 4-CH_3	0·4254	2·30	1·74
2-CH_3, 3-Cl	0·3531	2·70	2·40
2-CH_3, 5-Cl	0·3341	3·25	2·58

* Yoneda and Nitta (1965).

[a] Conc. with 1 hr anesthetic duration (%).

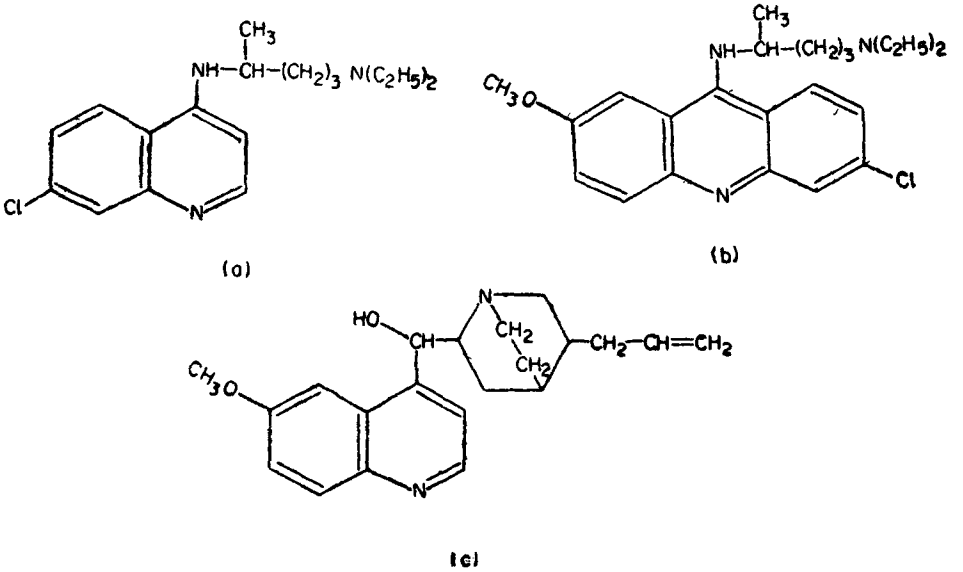


Figure 1. Antimalarial drugs (a) chloroquine, (b) quinacrine, (c) quinine.

$$\log (\text{RNAc-1}) = 27{\cdot}836\ f_0^E - 19{\cdot}005$$

$$n = 8,\ r = 0{\cdot}977,\ s = 0{\cdot}240,\ F_{1,6} = 128{\cdot}28 \qquad (3)$$

$$\log (\text{RNAc-2}) = 26{\cdot}365 f_0^E - 17{\cdot}952$$

$$n = 8,\ r = 0{\cdot}983,\ s = 0{\cdot}198,\ F_{1,6} = 169{\cdot}30 \qquad (4)$$

Table 3A. MO indices and relative nicotinic activity of phenylcholine ethers.*

$R - OCH_2CH_2N^+(CH_3)_3$

R	f_0^E	Q_0	S^N_{ortho}	log (RNAc)[a]			
				log (RNAc-1)[b]		log (RNAc-2)[c]	
				Obsd.	Calcd. eq. (3)	Obsd.	Calcd. eq. (4)
3, 5-Dibromo-phenyl	0·764	0·179	0·952	2·5276	2·2623	2·4281	2·1906
m-Bromophenyl	0·766	0·179	0·938	2·5682	2·3179	2·4116	2·2434
m-Chlorophenyl	0·764	0·180	0·931	2·3424	2·2623	2·2833	2·1906
Phenyl	0·768	0·180	0·911	2·0000	2·3736	2·0000	2·2961
m-Tolyl	0·730	0·179	0·847	1·1173	1·3158	1·1303	1·2942
p-Chlorophenyl	0·723	0·186	0·911	1·0170	1·1210	1·0043	1·1097
3, 5-Xylyl	0·710	0·179	0·811	0·7160	0·7591	0·7160	0·7669
p-Tolyl	0·664	0·165	0·915	−0·3979	−0·5214	−0·3279	−0·4459

* Fukui *et al* (1960).

[a] Relative nicotinic activity on blood pressure of cats after atropine; [b]Suprarenals intact; [c] Suprarenals ligated.

$$\log (RNAc) = -26{\cdot}825\ S_2^E + 26{\cdot}234\ S_6^E - 1{\cdot}821\ E_{HOMO} + 2{\cdot}104$$
$$n = 7,\ r = 0{\cdot}888,\ s = 0{\cdot}261,\ F_{3,3} = 3{\cdot}72 \qquad (5)$$

$$\log (RNAc) = -2{\cdot}904\ E_{HOMO} + 2{\cdot}247$$
$$n = 9,\ r = 0{\cdot}821,\ s = 0{\cdot}306,\ F_{1,7} = 14{\cdot}50. \qquad (6)$$

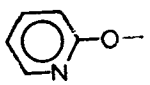
In eqs. (3)–(6), RNAc's stand for relative nicotinic activities as defined in the respective tables.

Now in case of hallucinogens, the highly significant correlation between activity and E_{HOMO} (eq. 1) very well accounts for the involvement of charge-transfer phenomenon in their action. Equation (1) shows that as the value of E_{HOMO} decreases, the value of C increases which means that the greater is the electron-donor capability of the drug, the greater would be its activity. In effect, this is found very true. The LSD which has the lowest E_{HOMO} value (table 1) is found to possess the greatest activity.

However in case of local anesthetics, a comparatively poor correlation (eq. 2) suggests that the charge-transfer phenomenon may not be the only factor responsible for the anesthetic activity of these drugs, although it does play a major role in the drug-receptor interaction. This theoretical observation does not fully support the already existing experimental fact. It was observed by Eckert (1962) with absorption spectroscopy that local anesthetics exert their effect by forming a charge-transfer complex with thiamine, a base that has been recognised to parti-

Table 3B. MO indices and relative nicotinic activity of phenylcholine ethers.*

$R — CH_2CH_2N^+(CH_3)_3$

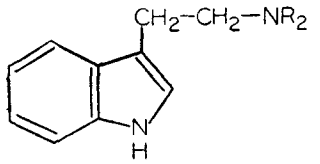
R	S_2^E	S_6^E	$E_{HOMO}(\beta)$	log (RNAc)[a]	
				Obsd.	Cald. eq. (5)
m-I-C_6H_4-O-	0·9947	0·9928	0·4812	0·7993	0·7893
m-NH_2-C_6H_4-O-	1·2800	1·2781	0·5322	0·5682	0·5849
m-Br-C_6H_4-O-	0·9869	0·9837	0·7671	0·5051	0·2373
m-Cl-C_6H_4-O-	0·9779	0·9742	0·7671	0·3802	0·2276
m-F-C_6H_4-O-	0·9746	0·9706	0·7685	0·1761	0·2184
C_6H_5-O-	0·9751	0·9751	0·7692	0·0000	0·3227
m-NO_2-C_6H_4-O-	0·9483	0·9228	0·7738	−0·3979	−0·3493
	..	..	0·8040	−0·3010	−0·0875[b]
	..	..	0·9467	−0·6990	−0·5018[b]

* Crow *et al* (1969).

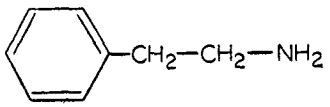
[a]Relative nicotinic activity, molar basis-cat superior cervical ganglion (nictitating membrane).

[b]Calculated from Eq. (6).

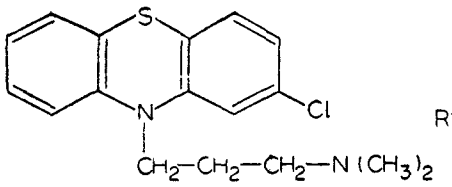
cipate in some manner in nerve conduction (von Muralt 1958). This lack on the part of theory may be attributed to the crudeness of Hückel theory with the help of which δE and other MO parameters discussed in this paper were calculated.



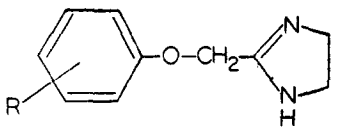
(I)



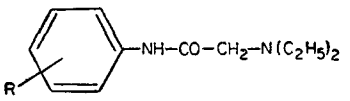
(II)



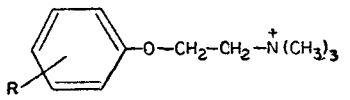
(III)



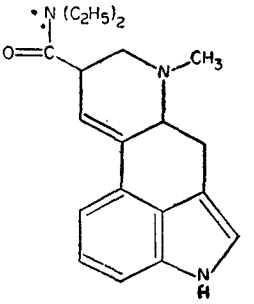
(IV)



(V)



(VI)



(VII)

In case of nicotinic agents, the activity of compounds listed in table 3A is found to be well correlated with f_0^E. Thus highly significant correlations of RNAc–1 and RNAc–2 with f_0^E, exhibited by eqs (3) and (4) respectively, suggest that in addition to charge-transfer phenomenon some secondary binding is also responsible for the nicotinic action of these compounds, as the parameter f^E not only involves the concept of charge-transfer but also is a measure of ability of an atom to attract an electrophile. Now for the secondary binding, the ability of ether oxygen to attract an electrophile would be solely responsible. The participation of ether oxygen in nicotinic action was also indicated by Hey (1952); but he had assumed that it was the positive charge (a measure of ability to attract a nucleophile) at oxygen atom, which contributed to the activity. But this positive charge on ether oxygen was found by us to be poorly correlated wih the activity.

In case of only *m*-substituted phenylcholine ethers (table 3B), the activity of the first seven compounds was found to be significantly correlated with S_2^E, S_6^E and E_{HOMO}; but individually none of these parameters was found to bear any significant correlation with the activity. Out of them E_{HOMO} was, however, found to be significantly correlated with activity when the last two compounds of series were also included in the regression analysis. Thus eqs (5) and (6), here too, support the idea of involvement of charge-transfer phenomenon in nicotinic activity, but eq (5) also establishes the role of the two ortho positions of the ring and suggests that the activity would partly depend upon the ability of these two ortho positions to attract an electrophile, and donate an electron to a receptor, as S^E is a measure of this. This latter observation is in agreement with the suggestion of Ormerod (1956) and of Sekul and Holland (1961a, b) that a partial negative charge at an appropriate distance from the onium head in phenylcholine ethers was essentials for their nicotinic activity. This negative charge was assumed to be in a position analogous to the partial negative charge assigned to the carbonyl oxygen in acetylcholine. It is noteworthy that 2- and 6-positions of phenyl ring in the phenyl choline ethers bear the same relation to the ether oxygen as does the carbonyl oxygen to the ether oxygen in the acetylcholine. Hence it must be the 2- and 6-positions that participate in the secondary binding. The participation of these positions in secondary binding has been confirmed by Kier (1968) also through the conformational studies on nicotine and acetylcholine.

Now the quantitative aspect is also not able to solve the dilemma whether it is the ether oxygen or the two ortho positions in the phenyl ring, which are responsible for the secondary binding. May be a more sophisticated MO method or experiment alone can solve this problem.

However, conclusively our quantitative study on the subject supports the idea of involvement of charge-transfer phenomenon in the activity of hallucinogens, local anesthetics, and nicotinic agents; and in the last case it also shows that the charge-transfer mechanism alone may not be solely responsible for the activity of drugs. Some secondary binding also contributes to the nicotinic activity of phenylcholine ethers.

Acknowledgement

The financial assistance of CSIR, New Delhi, in the form of a PDF to one of the authors (PS) is thankfully acknowledged.

References

Crow J, Wasserman O and Holland W C 1969 *J. Med. Chem.* **12** 764
Eckert T 1962 *Arzneim.—Forsch.* **12** 8
Fukui K, Nagata C and Imamura A 1960 *Science* **132** 87
Hey P 1952 *Br. J. Pharmacol.* **7** 117
Karreman G, Isenberg I and Szent-Györgyi 1959 *Science* **130** 1191
Kier L B 1968 *Mol. Pharmacol.* **4** 70
Ormerod W E 1956 *Br. J. Pharmacol.* **11** 267
Sekul A A and Holland W C 1961a *J. Pharmacol. Exp. Ther.* **132** 171
Sekul A A and Holland W C 1961b *J. Pharmacol. Exp. Ther.* **133** 313
Snyder S H and Merril C R 1965 *Proc. Nat. Acad. Sci. U.S.* **54** 258
von Muralt A 1958 *Neue Ergebuisse der Nervenphysiologie* (Berlin: Springer)
Yoneda F and Nitta Y 1965 *Chem. Pharm. Bull. Jpn* **13** 574