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Electron Densities in Neuroleptics by X-ray Photoelectron Spectroscopy, ^{13}C Nuclear Magnetic Resonance, and Quantum Calculations on Model Compounds

J. RIGA AND J. J. VERBIST

Laboratoire de Spectroscopie Electronique, Facultés Universitaires Notre-Dame de la Paix, B-5000 Namur, Belgium

J. DEGELAEN[1]

Laboratoire de Chimie Pharmaceutique, Université Catholique de Louvain, B-1200 Bruxelles, Belgium

J. P. TOLLENAERE AND M. H. J. KOCH

Research Laboratories, Janssen Pharmaceutica, B-2340 Beerse, Belgium

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SUMMARY

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Nitrogen 1*s* electron binding energies of a series of neuroleptics in the solid state have been obtained by X-ray photoelectron spectroscopy. The ^{13}C NMR data give a good correlation between the charges on the carbonyl carbons and the corresponding chemical shifts, thereby providing evidence for the internal consistency of the CNDO/2 (complete neglect of differential overlap) charge densities obtained for the *N*-ethyl analogues. An analogy between X-ray photoelectron spectroscopic results in the gas phase and in the solid state suggests that the nitrogen 1*s* shifts measured in the solid state can be related to the proton affinity of amines.

INTRODUCTION

The interactions of a series of similar drugs with their receptor are governed by their detailed structure and must be related to relatively small changes in the electronic properties. We have considered the nitrogen 1*s* electron binding energy as obtained by X-ray photoelectron spectroscopy and the ^{13}C NMR chemical shifts of the carbonyl carbons of a series of neuroleptics as a measure of these differences at potential pharmacophores. In addition, we have tried to correlate these data with the results of quantum chemical calculations on model compounds.

The structure of the compounds studied are shown in Fig. 1.

EXPERIMENTS AND RESULTS

X-ray photoelectron spectroscopy. Core-level photoelectron spectra were recorded

[1] Chargé de Recherches du Fonds National de la Recherche Scientifique (Belgium).

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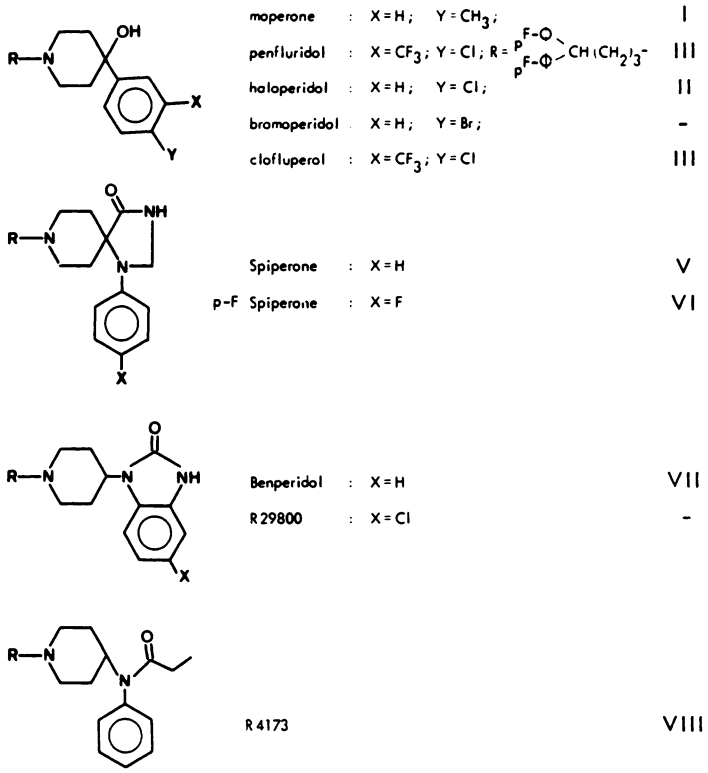


FIG. 1. *Structural formulae of the compounds*
Unless indicated otherwise, R = p-F$-\emptyset-$CO$-(CH_2)_3-$. The Roman numerals refer to Table 2.

on a Hewlett-Packard 5950A ESCA[2] spectrometer, using monochromatized AlK_α radiation ($h\nu$ = 1486.6 eV). The powdered samples were presented as pellets, and an electron "flood gun" was used to compensate for the surface charge buildup, which otherwise would have caused significant loss of resolution. The calibration was done by referencing the well-resolved fluorine 1s peaks (687.7 eV) to the carbon 1s peak of n-$C_{36}H_{74}$, which was carefully located at 284.7 eV with respect to the gold $4f_{7/2}$ level at 84.0 eV.

The complete experimental data are given in Table 1. Nitrogen 1s levels were observed with very good resolution (Fig. 2). A second derivative method (1) was used to locate the individual components when appropriate, as indicated by the dashed lines in the corresponding spectra. The carbon 1s peaks can be resolved into three main components, corresponding to aromatic carbons, carbonyl carbons, and carbons bound to fluorine. The relative intensities are in agreement with those expected from the structural formulae. Because of the number of overlapping peaks however, it is not reasonable to attempt a detailed deconvolution. No attempt was made to analyze the oxygen 1s peaks. Distinct chlorine 2p doublets (Fig. 3) were observed in the hydrochlorides of haloperidol and penfluridol. The low-energy peaks are attributed to the chloride ion, and the high-energy peak, to organic chlorine.

^{13}C nuclear magnetic resonance. The ^{14}C NMR spectra were recorded on a Varian CFT-20 spectrometer operated in the internal ^2H lock mode. The various compounds were dissolved in $CDCl_3$ in a 20% (w/v) concentration. All chemical shifts are expressed in parts per million downfield from

[2] The abbreviations used are: ESCA, X-ray photoelectron spectroscopy; CNDO/2, complete neglect of differential overlap.

TABLE 1

Positions of ESCA peaks binding energies relative to fluorine peak at 687.7 eV

N_b represents the basic nitrogen, and N_A, the amido and anilino nitrogens.

Compound	C 1s	N 1s		Cl $2p_{3/2}$	O 1s
		N_b	N_A		
	eV	*eV*		*eV*	*eV*
Spiperone	287.1, 284.7	398.9	400.0		531.8
Spiperone HCl	287.5, 286.0, 284.9	401.7	400.0	186.9	531.9
Benperidol	288.2, 287.3, 285.7, 284.6	399.4	400.2		531.7
Benperidol HCl	287.8, 287.0, 285.8, 284.6	401.8	400.1	187.1	531.9
Penfluridol	286.6, 284.6	399.3		200.4	532.1
Penfluridol HCl	286.5, 284.6	401.9		187.2, 200.3	532.4
Haloperidol	287.2, 286.0, 284.7	399.2		200.3	532.0
Haloperidol HCl	287.2, 286.1, 284.7	401.8		187.2, 200.0	532.3
R 4173	286.2, 284.7	398.7	399.9		
Bromoperidol	287.2, 285.8, 284.7	399.15			
Moperone	287.2, 285.7, 284.7	399.1			
Clofluperol	292.4, 287.0, 284.7	399.25			
p-Fluorospiperone	287.1, 285.8, 284.7	399.2	399.8		
R 29800	287.1, 285.7, 284.7	398.9	400.3		

tetramethylsilane used as internal reference.

Initially the spectra were recorded with complete proton noise decoupling. Assignment of the various resonances was made by single-frequency off-resonance decoupling.

Quantum chemical calculations. The calculations were performed using the CNDO/2 approximation (2). The molecular geometries were taken from previously reported X-ray diffraction data (3–7), but to save computing time the butyrophenone and diphenylbutyl side chains were replaced by a fully extended ethyl chain. The resulting charges[3] are given in Table 2. To make a direct comparison easier, the relevant values of the charges for the complete molecules of haloperidol and spiperone (8) are also included in this table. It is difficult to draw definite conclusions about the significance of the small differences between the two results, which may have arisen from various sources, such as replacement of a constant molecular fragment by another, or differences in the calculated coordinates of the hydrogen atoms or in the parameterization of the computer programs.

[3] The CNDO/2 charges are in fact valence shell electron populations.

DISCUSSION

Nitrogen 1s binding energies for the various compounds are given in Table 3. The peaks can be assigned by comparison of the spectra of the free base and the corresponding hydrochloride. The amido and anilino nitrogen peaks remain unchanged at 400 eV, while the difference between the binding energy of the basic nitrogen in the free base and the hydrochloride amounts to 2.6 eV, in agreement with values reported for piperidine derivatives (9, 11). The shifts (ΔE_b) are given relative to an arbitrary reference at 400.4 eV.

A simple electrostatic potential model (12) was used to obtain the calculated shifts (ΔE_b^Q):

$$\Delta E_b^Q = k\,\Delta Q_N + \Delta V_N \qquad (1)$$

where ΔQ_N represents the charge variation on the nitrogen atom, ΔV_N is the potential of the surrounding atoms in the molecule, and k is a constant (21.5 eV/unit charge).

The potential ΔV_N has been approximated by a point charge model; i.e.,

$$\Delta V_N = \sum_i \frac{Q_i e^2}{r_{N_i}}$$

In principle, ΔV_N should correspond to the crystal potential. However, it has been shown in a similar study (9) that the use of

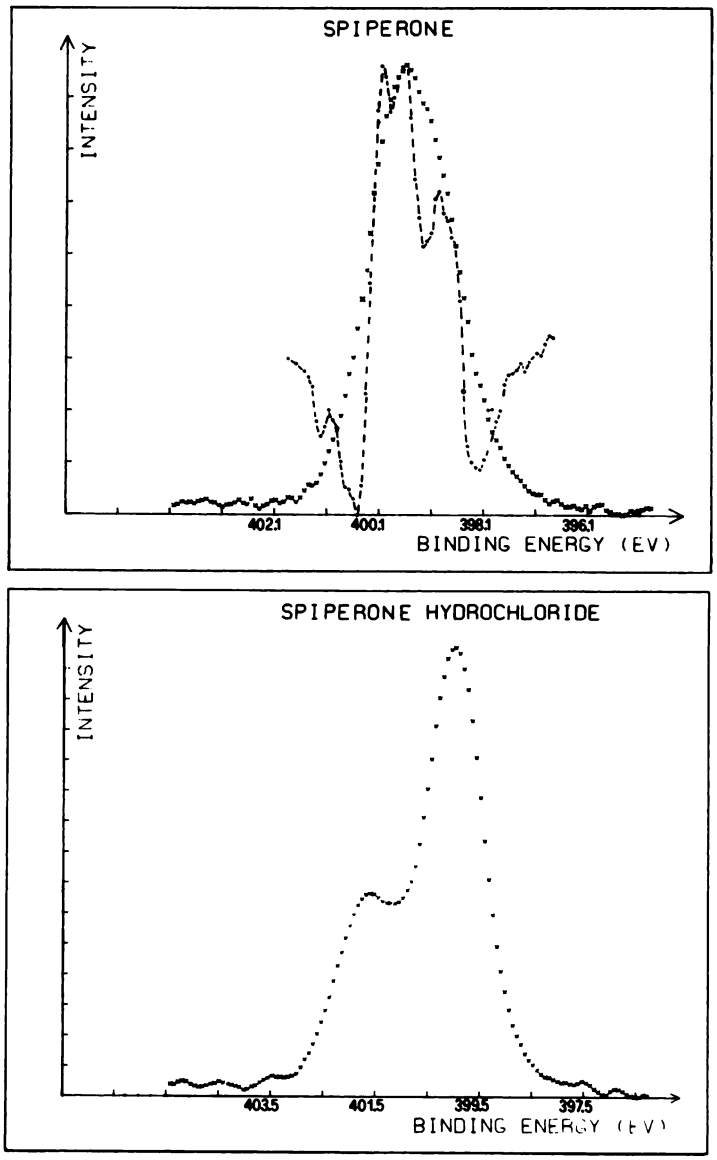


FIG. 2. *Nitrogen 1s photoelectron spectra for free base and hydrochloride of spiperone*
The dashed lines correspond to the components due to the different nitrogen atoms. Note the shift of the basic nitrogen to higher energies upon protonation.

the crystal potential does not lead to significant improvement of the calculated shifts. This is perhaps not surprising in view of the fact that the charges are calculated for isolated molecules anyway.

Hydrogen bonding is expected to increase the value of E_b. However, as indicated in Table 3, most of the compounds have only weak hydrogen bonds involving the piperidine nitrogen atoms.

The major assumption in the electrostatic potential model is that core-level binding energies can be equated to changes in the effective potential experienced by core orbitals. The calculation of shifts from CNDO/2 charges relies on initial state properties only, but it is known to give good agreement within a group of molecules of similar size and local environment, at least in gas-phase studies. In this

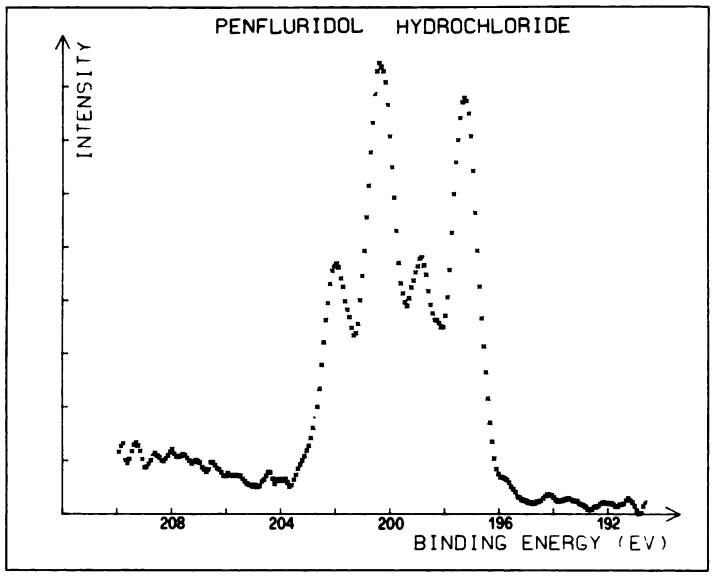


FIG. 3. *Chlorine 2p doublets in penfluridol HCl*
The low-energy peaks correspond to the chloride ion.

case the molecular reorganization energy can be neglected, and consequently the shifts reflect the charge distribution in the neutral molecule.

Although in the solid state the shifts are small and it is often difficult to find a suitable reference level, some interesting results can be obtained. The importance of the potential term (ΔV_N) in Eq. 1 is shown by the fact that a simple charge model (ΔV_N = constant) would predict the amido and anilino nitrogens to have lower binding energies than the piperidine nitrogens. Moreover, the charge on the piperidine nitrogen does not vary much in the present series of compounds, although one observes differences of more than 0.5 eV in the binding energies. Thus it is clear that simple charge models are likely to lead to erroneous conclusions even when considering atoms with a very similar local environment.

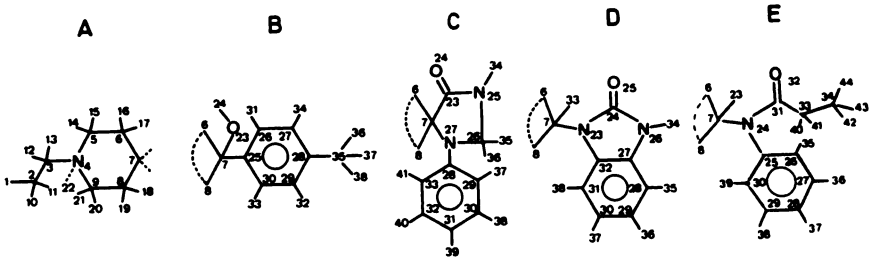
Equation 1 gives a satisfactory agreement between the observed and calculated shifts (Fig. 4). The largest deviation is observed for the basic nitrogen of benperidol, which is involved in a strong N–H···N hydrogen bond in the crystal (5). As expected for the influence of a hydrogen bond on the binding energy, the observed value (E_b) is larger than the calculated value by approximately 0.3 eV. The shifts for the hydrochlorides are not given. To evaluate these correctly, a precise description of the N–H···Cl interaction is required in order to calculate the charge distribution for the neutral ion pair rather than for isolated ions. In any case, as already pointed out (9), the fact that in the protonated forms the positive charge is delocalized and that 0.2 electron or less remains on the nitrogen atom raises some questions as to the nature of the anionic sites which are often proposed in receptor models.

Within a series of compounds which differ only by one substituent there is a good agreement between the observed shifts and Hammett substituent constants (13) (Fig. 5). A correlation of this type was found earlier for substituted benzene derivatives in the gas phase (14). The analogy between the observations in the gas phase and in the solid state suggests an interesting interpretation of the experimental results. It is known that ESCA nitrogen shifts in the gas phase correlate well with the proton affinity in a series of amines (15). The agreement between the shifts observed in the solid state and those calculated for isolated molecules implies

TABLE 2

CNDO/2 charges of N-ethyl analogues of neuroleptics

The Roman numerals correspond to the structures in Fig. 1. The numbering of the common fragment (A) is the same for all compounds. In series B atoms 36, 37, and 38 are bound to either atom 34 or 35, as indicated below. In series B, for compound I, 35 = C; 36, 37 and 38 = H; 34 = H; for compound II, 34 = H; 35 = Cl; compound II_b = haloperidol (8); for compound III, 34 = C; 36, 37, and 38 = F; 35 = Cl; IV = III; 22 = H^+. In series C, for compound V, 39 = H; compound V_b = spiperone (8); for compound VI, 39 = F. Series D applies to compound VII, and series F, to compound VIII.



atom	I	II	II_b	III	IV	V	V_b	VI	VII	VIII
1	0.9982	0.9963		0.9958	0.9384	0.9978		0.9973	0.9970	0.9930
2	4.0279	4.0281		4.0280	4.0421	4.0277		4.0278	4.0280	4.0253
3	3.8978	3.8977	3.8948	3.8977	3.9102	3.8985	3.8984	3.8984	3.8978	3.8919
4	5.1623	5.1617	5.1604	5.1610	4.9737	5.1584	5.1614	5.1584	5.1611	5.1620
5	3.9010	3.9012	3.8883	3.9012	3.9142	3.9137	3.8903	3.9137	3.9000	3.9001
6	4.0199	4.0191	4.0094	4.0193	4.0324	4.0029	3.9986	4.0026	4.0180	4.0098
7	3.8339	3.8363	3.8319	3.8358	3.8384	3.9348	3.9323	3.9351	3.8663	3.8613
8	4.0169	4.0161	4.0062	4.0164	4.0321	3.9913	3.9949	3.9914	4.0151	4.0095
9	3.9192	3.9195	3.8880	3.9196	3.9117	3.9271	3.8941	3.9272	3.9181	3.9012
10	0.9917	0.9917		0.9917	0.9691	0.9924		0.9923	0.9917	0.9930
11	0.9922	0.9914		0.9905	0.9632	0.9935		0.9932	0.9919	0.9963
12	1.0253	1.0244	1.0121	1.0242	0.9592	1.0193	1.0258	1.0191	1.0237	1.0262
13	1.0172	1.0155	1.0277	1.0145	0.9602	1.0170	1.0220	1.0166	1.0162	1.0190
14	1.0233	1.0218	0.9944	1.0215	0.9588	0.9964	1.0139	0.9959	1.0213	1.0187
15	1.0190	1.0152	0.9932	1.0131	0.9633	1.0189	1.0196	1.0181	1.0163	1.0162
16	0.9923	0.9980	1.0025	0.9972	0.9459	1.0038	1.0060	1.0036	1.0080	1.0028
17	1.0010	0.9913	1.0039	0.9904	0.9694	0.9895	1.0008	0.9915	0.9920	0.9981
18	0.9984	0.9916	1.0026	0.9963	0.9676	1.0058	1.0087	1.0053	0.9999	1.0031
19	0.9921	0.9971	0.9995	0.9903	0.9434	0.9980	1.0013	0.9984	0.9922	0.9984
20	1.0125	1.0062	1.0277	1.0108	0.9497	1.0062	1.0127	1.0054	1.0107	1.0194
21	1.0095	1.0111	1.0183	1.0041	0.9545	0.9851	1.0204	0.9848	1.0073	1.0184
22					0.8299					
23	6.2883	6.2869	6.2848	6.2869	6.2601	3.6523	3.6614	3.6519	5.1958	0.9938
24	0.8662	0.8612	*	0.8581	0.8705	6.3765	6.3313	6.3750	3.5636	5.1983
25	3.9928	3.9696	3.9829	3.9708	3.9819	5.2141	5.2147	5.2141	6.3962	3.8756
26	4.0085	4.0133	4.0049	3.9924	3.9894	3.8014	3.8074	3.8017	5.2155	4.0325
27	4.0138	3.9789	3.9847	4.0286	4.0238	5.1922	5.1963	5.1916	3.9039	3.9827
28	3.9454	3.9287	3.9167	3.9171	3.9109	3.8536	3.8619	3.8663	4.0308	4.0076
29	4.0182	3.9795	3.9793	3.9813	3.9771	4.0555	4.0636	4.0381	3.9974	3.9828
30	4.0023	4.0074	4.0131	3.9948	3.9863	3.9704	3.9643	4.0196	4.0020	4.0326
31	1.0174	1.0032	1.0028	0.9907	1.0000	4.0253	4.0163	3.8107	4.0211	3.6527
32	1.0182	0.9907	0.9860	0.9843	0.9678	3.9702	3.9682	4.0192	3.9225	6.3775
33	1.0019	0.9877	0.9958	0.9818	0.9766	4.0621	4.0565	4.0448	4.0012	4.0470
34	1.0144	0.9908	0.9837	3.4114	3.4094	0.8711	0.8733	0.8700	0.8681	3.9939
35	4.3868	7.1711	7.1793	7.1419	7.0988	1.0333	1.0246	1.0331	1.0034	0.9948
36	0.8442			7.2123	7.2043	1.0202	1.0234	1.0200	1.0050	1.0020
37	0.9612			7.2078	7.1978	1.0044	1.0008	0.9979	1.0044	1.0020
38	0.7689			7.2204	7.2179	1.0093	1.0129	0.9847	1.0027	1.0021
39						1.0086	1.0097	7.2157		0.9949
40						1.0096	1.0120	0.9851		0.9869
41						0.9915	1.0020	0.9844		0.9869
42										1.0086
43										0.9901
44										0.9901

* Not given in ref. 8.

that the ESCA shifts reported here are related to the proton affinities of the various amines. The differences between the proton affinities of compounds with comparable polarizability are ascribed to lone pair hybridization effects of the nitrogen atoms (16).

One should be very cautious however,

TABLE 3

Nitrogen 1s binding energy (E_b) for basic (N_b), anilino (N_{An}), and amido (N_{Am}) nitrogens

The shift is relative to an arbitrary reference at 400.4 ev. $k\ \Delta Q$N is the contribution of the charge to the shift; ΔV_N is the contribution of the electrostatic potential; $\Delta E_b{}^a$ is the calculated shift; and HB is the type of hydrogen bond involving the basic nitrogen in the solid state. pK_a values determined at 25° by J. Peeters (unpublished results).

Compound	Atom	E_b	ΔE_b	$k\ \Delta Q_N$	ΔV_N	$\Delta E_b{}^a$	pK_a	HB
		eV	*eV*			*eV*		
1. Moperone	N_b	399.1	−1.3	−3.49	1.98	−1.51	8.98	
2. Haloperidol	N_b	399.2	−1.2	−3.48	2.25	−1.22	8.06	OH···N
3. Bromoperidol	N_b	399.15	−1.25				8.82	
4. Clofluperol	N_b	399.25	−1.15	−3.46	2.36	−1.09	8.41	
5. Penfluridol	N_b	399.3	−1.1	−3.46	2.36	−1.09	8.75	OH···N
6. Benperidol	N_b	399.4	−1.0	−3.46	2.12	−1.34	7.99	NH···N
	N_{Am}	400.2	−0.2	−4.63	4.56	−0.07		
	N_{An}			−4.21	3.64	−0.57		
7. R 29800	N_b	398.9	−1.5					None
	$N_{Am/An}$	400.3	−0.1					
8. Spiperone	N_b	398.9	−1.5	−3.40	1.90	−1.50	9.09	None
	N_{Am}			−4.61	4.63	0.02		
	N_{An}	400.0	−0.4	−4.13	3.16	−0.97		
9. *p*-Fluorospiperone	N_b	399.2	−1.2	−3.40	1.98	−1.42		
	N_{Am}			−4.60	4.74	0.14		
	N_{An}	399.8	−0.6	−4.12	3.30	−0.81		
10. R 4173	N_b	398.7	−1.7	−3.48	1.90	−1.58	8.40	None
	N_{Am}	399.9	−0.5	−4.26	3.60	−0.66		
11. Morphine	N_b	398.7	−1.7[a]			1.74	7.93[b]	

[a] From ref. 9.
[b] From ref. 10.

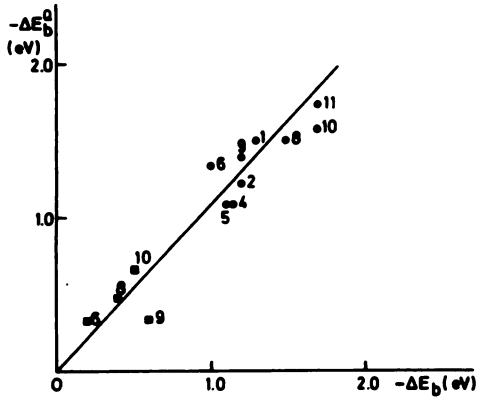


FIG. 4. *Experimental ESCA nitrogen 1s shifts vs. calculated values obtained from potential model for basic nitrogen atoms* (●) *and amido and anilino nitrogen atoms* (■)

The numbers correspond to those in Table 3.

when comparing atoms in different environments. A good example is provided by the *N*-ethyl analogue of spiperone. The percentage *s* character, defined as the 2*s* orbital density relative to total atomic charge density, is calculated in the CNDO/2 approximation to be 26%, 24%, and 23% for the basic nitrogen and the anilino and amido nitrogens, respectively. The small

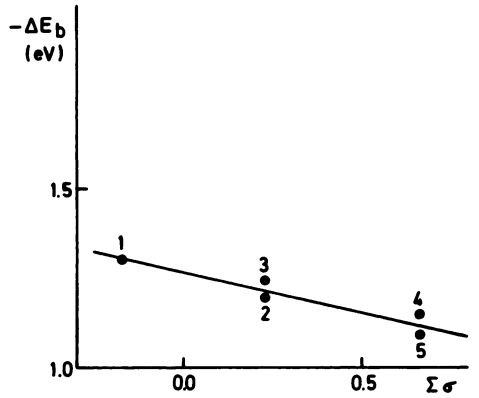


FIG. 5. *Relationship between Hammett substituent constants and ESCA nitrogen 1s shifts of basic nitrogen atoms*

The numbers correspond to those in Table 3.

difference between the binding energies for the anilino and amido nitrogen atoms is in keeping with their virtually identical *s* character. The nominally larger *s* character of the piperidine nitrogen would imply a lower proton affinity and consequently a higher E_b value than that of the other nitrogen atoms. This is contrary to the experimental results and can probably be attributed to the greater polarizability of the basic nitrogen atom, which leads to a lower value of E_b, although other factors, such as angle strain in the 5-membered ring, could conceivably play a role. There is no simple relationship between the pK_a of the basic nitrogens and the E_b shift. This is a well-known phenomenon that can be attributed to solvation effects, which mask the differences in proton affinity (17).

The trends observed here suggest an approach to a partial explanation of the often irregular order of biological responses in a series of compounds with very similar aqueous basicities (bulk pK_a values) or with regular changes in the neighborhood of a nitrogen atom. It is well established that the gas-phase basicity of amines increases regularly with increasing alkyl substitution at the nitrogen atom (16). Thus the fact that most neurotransmitters, e.g., dopamine, are primary amines while most of their antagonists are structurally related tertiary amines, suggests that, other things being equal, the latter bind more strongly to a receptor site involving the formation of a hydrogen bond. In developing this argument, one is of course left with the problem of the relevance of gas-phase phenomena to drug-receptor interactions.

Evidence supporting the link may be found in the fact that biologically active molecules should desolvate before interacting with their receptor, as indicated by the available structural data on protein-substrate and protein-inhibitor complexes (18). A reinterpretation of the data obtained for morphine and its antagonists (9) suggests, on the contrary, that the antagonists have a lower proton affinity than morphine, since they are characterized by a higher value of E_b. The difference between the E_b values of morphine and the mixed agonist-antagonist cyclazocine, which amounts to 0.5 eV (≅12 kcal/mole), is large enough to be considered a plausible explanation for their different pharmacological behavior.

To obtain a definitive confirmation of this hypothesis, one should compare the free bases of a series of congener narcotic agonist-antagonist pairs. Until now ESCA data have been available only for the morphine-nalorphine pair (9). The difference between the experimental nitrogen 1*s* binding energies of morphine and nalorphine is not significant (-0.1 ± 0.2 eV). However, the calculated difference (-0.1 eV) seems to confirm that the proton affinity of nalorphine is lower (≅3 kcal/mole) than that of morphine. Note also that R 4173, which is related to the potent analgesic fentanyl, has a low E_b value. Moreover, to obtain analgesic analogues of benperidol and spiperone, it is necessary to increase the alkyl substitution in the neighborhood of the piperidine nitrogen, which is expected to lower the E_b value or to increase the proton affinity of these compounds. Our interpretation depends, of course, on the validity and internal consistency of the CNDO/2 charges.

An independent verification of the consistency of the relative magnitude of these charges is provided by ^{13}C NMR measurements. The chemical shifts of the carbons bound to fluorine are constant for all molecules (163 ± 0.1 ppm). This further justifies our use of fluorine as internal standard for the ESCA measurements, since it is unlikely that major charge fluctuations would occur at these atoms.

The diamagnetic shift produced by the excess electronic charge on the carbonyl carbons is illustrated in Fig. 6. Since we did not include the butyrophenone chain in our calculations, the CNDO/2 charge on the carbonyl carbon of this moiety has been taken as the mean of the values published for the corresponding atom in haloperidol (3.7643) and in spiperone (3.7622) (8). The observed correlation, involving amide carbonyl groups ($\Delta\delta^{13}C = 200\ \Delta Q_{CNDO}$), is in agreement with the available data for ketones and oximes ($\Delta\delta^{13}C =$

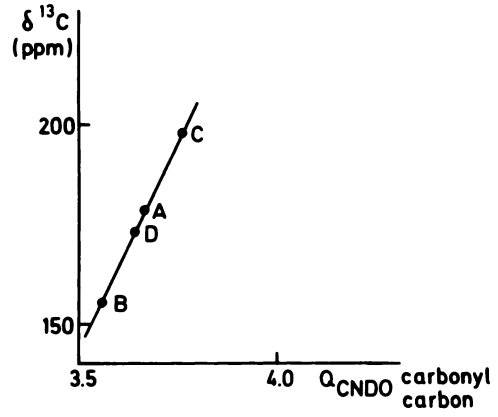


FIG. 6. ^{13}C *chemical shift for carbonyl carbons vs. CNDO/2 charge*

A, amido carbonyl of spiperone; *B*, amido carbonyl of benperidol; *C*, phenone carbonyl; *D*, amido carbonyl of R 4173.

220 ΔQ_{CNDO}) (19). Thus the CNDO/2 charges for the various compounds are consistent.

In conclusion, it appears that ESCA and ^{13}C NMR measurements can give useful information about the properties of possible pharmacophores for a series of drugs. It has been shown that within a series of related compounds it seems possible to obtain at least qualitative information about the proton affinity of amines from solid-state ESCA spectra. Although the procedures used are by no means ideal, it should be borne in mind that many biologically interesting compounds will not yield gas-phase spectra. The agreement between the theoretical results and the experimental data further justifies the interpretation which has been given. Since the vast majority of drugs, especially those acting on the central nervous system, are amines, a systematic study of their properties seems well worth undertaking. In this respect proton affinity certainly appears to be a property which has been relatively neglected from both the experimental and the theoretical point of view.

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