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Ultraviolet Photoelectron Spectroscopy of Cyclic Amidines. 1. Electronic Structure of Some α-Adrenergic Benzylimidazolines

A. P. de Jong*

Laboratorium voor Farmacie, Vakgroep Farmaceutische Scheikunde, Plantage Muidergracht 24

and H. van Dam

Anorganisch Chemisch Laboratorium, J. H. van't Hoff Instituut, Nieuwe Achtergracht 166, Universiteit van Amsterdam, 1018 WV Amsterdam, The Netherlands. *Received May 17, 1979*

Slight changes in the structure of the 2-benzylimidazolines are able to produce drastic changes in pharmacological action and potency. In order to determine whether electronic effects are involved, as well as to reveal some aspects of the electronic structure of these compounds, UV-photoelectron spectra of 2-benzylimidazoline and some substituted analogues, including naphazoline, oxymetazoline, tetrahydrozoline, and xylometazoline, have been recorded. Assignments of various ionization energies (IE's) to particular molecular orbitals have been made on the basis of correlation of IE's of similar molecules, substituent effects, differences in intensity between He(I) and He(II) spectra, and results of modified CNDO/s calculations. It turned out that there is no conjugative electronic interaction between the phenyl and imidazoline ring. The methyleneimidazoline substituent proved to be a weak electron-withdrawing group. The CNDO/s method in conjunction with Koopmans' theorem predicts rather well the energy levels of orbitals possessing predominant π character. The location of the energy levels of orbitals with mainly n_N character is not correctly estimated by CNDO/s. The electronic properties, measured with photoelectron spectroscopy, do not seem to be related to the qualitative pharmacological action of the 2-benzylimidazolines, but for the sympathomimetic compounds naphazoline, oxymetazoline, tetrahydrozoline, and xylometazoline a correlation has been found between first aromatic IE and potency of the drug on both the peripheral and central α-adrenergic receptor level.

In 1939, Hartmann and Isler[1] carried out an extensive investigation into the pharmacological activity of a great number of benzylimidazolines. It turned out that slight alterations in the chemical structure of these molecules were able to bring about drastic changes in pharmacological action and activity. Some compounds showed sympatholytic activity, e.g., 2-benzylimidazoline, whereas others, such as naphazoline, exerted sympathomimetic activity. Mujic and van Rossum[2] have shown that sympathomimetic activity of these compounds was the result of direct α-adrenergic receptor stimulation. Investigating the relationship between chemical structure and pharmacological activity, Struijker Boudier et al.[3] found that, in addition to the increase of molar volume, differences in the pK_a were playing an important role. Differences in the pK_a within a series of structurally narrow related molecules are known to be closely connected with differences in electronic structure. Although for benzylimidazolines much is known about the influence of substituents on the pharmacological activity in a variety of biological tests, little information is available regarding the effect of these substituents on the electronic structure. With the development of UV photoelectron spectroscopy (UPS), a new experimental method has come at our disposal to gain some insight into the electronic structure of molecules. According to Koopmans' theorem, the ionization energies (IE_i), which are directly measured with UPS, are related to the actual orbital energy levels (ϵ_i), as shown in eq 1.[4] In this approximation, relaxation and

$$IE_i = -\epsilon_i \quad (1)$$

correlation effects are not taken into account. Nevertheless, it is customary to regard the photoelectron spectrum as a direct representation of the molecular orbital energy diagram.

Quantum mechanical calculation provide considerable information about the electronic properties of molecules and are used as an aid in the interpretation of the photoelectron spectra. For this latter purpose, the semiempirical CNDO/s method has proven quite reliable.[5-7]

Recently, the UPS technique has been successfully applied to the determination of the electronic structure

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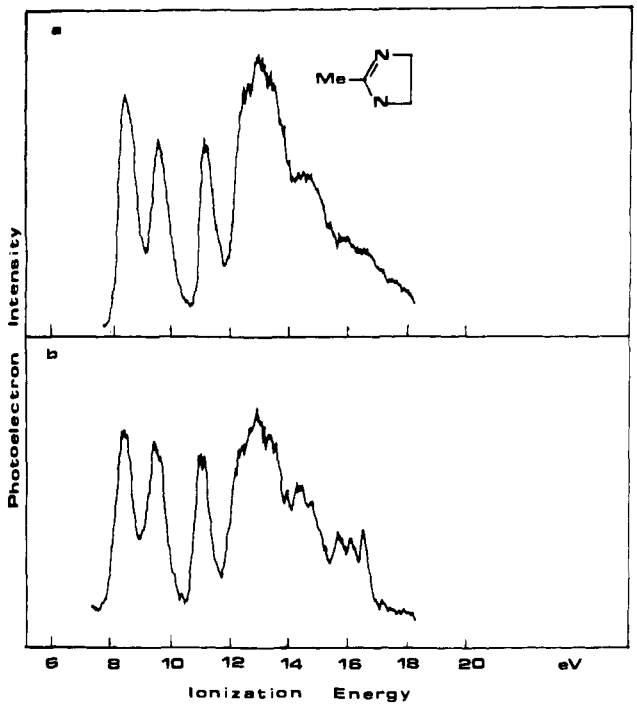

Figure 1. (a) He(I) and (b) He(II) photoelectron spectra of 2-methylimidazoline (1).

of some pharmacologically relevant drugs.[8-13] In a series of hallucinogenic phenethylamines and tryptamines, a reasonable correlation between ionization energies and hallucinogenic potency has been obtained.[8]

The purpose of this investigation is to elucidate the electronic structure of some benzylimidazolines and to determine how differences herein correlate with differences in biological activity.

Experimental Section

Photoelectron spectra were recorded on a Perkin-Elmer PS-18 spectrometer, modified with a Helectros He(I)/He(II) source. Peak positions were calibrated by simultaneously recording the spectra of the calibrants, xenon and argon, along with that of the sample. Vertical ionization energies were taken as the position of maximum intensity. Resolution, as measured on the argon peak at 15.76 eV, was 25–30 meV.

2-Methylimidazoline, 2-benzylimidazoline, naphazoline, oxymetazoline, and tetrahydrozoline were obtained from commercial sources. Purity was checked with TLC. The other compounds have been synthesized according to methods described in the literature[14-16] and purified by recrystallization. Identity and purity were verified by NMR, IR, mass spectroscopy, TLC, and by comparing the melting points with literature values. Molecular orbital calculations were performed using the CNDO/s method of Del Bene and Jaffe.[17] The parametrization was taken from work by Kuehnlenz and Jaffe.[18] The two-electron two-center integrals were approximated using the Nishimoto–Mataga formulas.[19]

Input to the CNDO/s program consisted of Cartesian coordinates of the atoms, which were calculated from standard bond lengths and angles.[20] The conformation chosen for naphazoline was the most stable one according to PCILO calculations.[21] The other compounds were calculated from a similar conformation.

Results

Photoelectron Spectra. The photoelectron (PE) spectra of the various imidazolines are shown in Figures 1–3, and the observed vertical ionization energies (IE's) with their assignments are listed in Table I.

2-Benzylimidazoline. The orbitals of 2-benzylimidazoline can be constructed from those of benzene and 2-methylimidazoline. 2-Benzylimidazoline has five low-

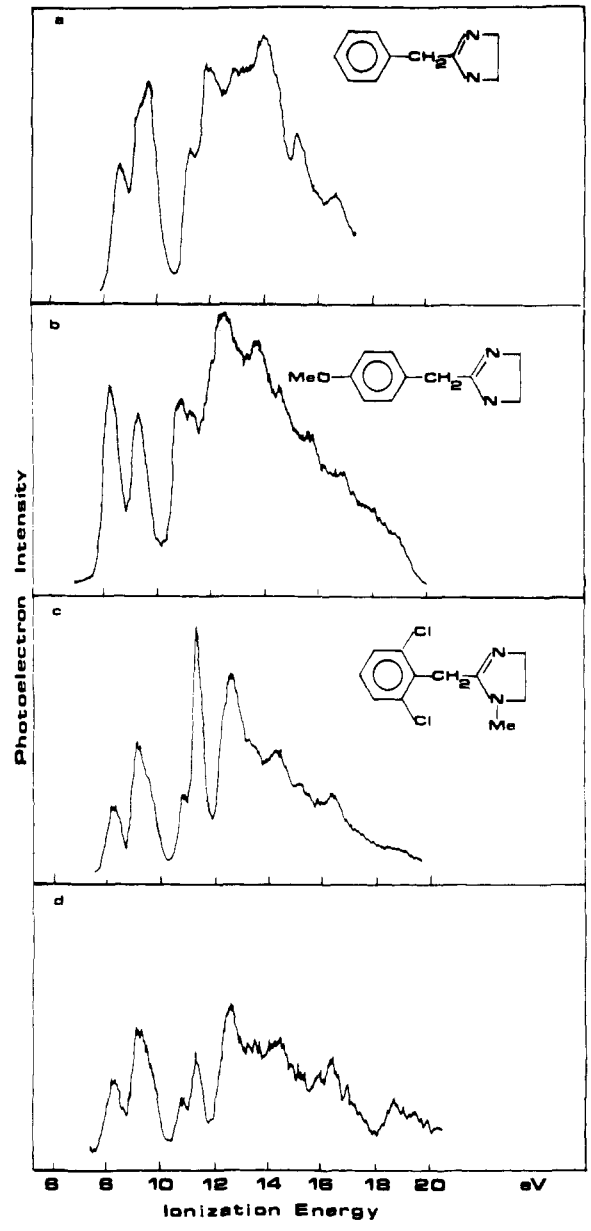

Figure 2. He(I) photoelectron spectra of (a) 2-benzylimidazoline (**2**), (b) 2-(4-methoxybenzyl)imidazoline (**4**), and (c) 2-(2,6-dichlorobenzyl)-1-methylimidazoline (**6**). (d) He(II) photoelectron spectrum of 2-(2,6-dichlorobenzyl)-1-methylimidazoline.

energy ionizations arising from five high-level molecular orbitals. Two of these orbitals are mainly localized on the aromatic ring, while the other three are chiefly situated on the imidazoline moiety. In 2-benzylimidazoline, interaction between phenyl and imidazoline π orbitals is hardly to be expected, because of the strong insulating character of the methylene group. It is therefore permitted to consider the PE spectra of the separate ring systems for the interpretation of the spectrum of 2-benzylimidazoline.

The photoelectron spectra of substituted benzenes have been extensively studied.[6,22-27] In benzene, the twofold degenerate e_{1g} orbital has an IE of 9.25 eV, but this degeneracy is removed by monosubstitution. This is evident from an examination of the symmetries of the highest occupied π orbitals in benzene. At the point of substitution, one of the benzene orbitals (b_1 in C_{2v} symmetry) has its maximum electron density, whereas the other orbital (a_2 in C_{2v} symmetry) has a node. Since the b_1 orbital is symmetric and the a_2 orbital is antisymmetric with respect to the vertical plane in the assumed C_{2v} group, these orbitals are referred to as Ph_S and Ph_A, respectively.

Table I. Ionization Energies[b] (eV) and Assignments[a]

no.	compd	π_-	Ph_S	Ph_A	n_{Nim}	π_+
1	2-methylimidazoline	8.56			9.65	11.33
2	2-benzylimidazoline	8.50	9.28	9.50	9.59	11.20
3	2-(2-methylbenzyl)imidazoline	8.60	8.95	9.19	9.49	11.15
4	2-(4-methoxybenzyl)imidazoline	8.60	8.39	9.39	9.55	11.00, 11.18 (n_O)
5	2-(2,6-dichlorobenzyl)imidazoline	8.42	9.20		9.50	11.26, 11.26 (n_{Cl})
6	2-(2,6-dichlorobenzyl)-1-methylimidazoline	8.21	9.12	9.24	9.50	10.86, 11.33 (n_{Cl})
7	tetrahydrozoline	8.33	8.78	9.01	9.33	10.62
8	xylometazoline	8.49	8.27		9.60	11.27, 10.59 (a_1)
9	oxymetazoline	8.36	8.04		9.51	
10	naphazoline	8.46			9.72	11.02

[a] The π_-, n_{Nim}, and π_+ orbitals are primarily located on the imidazoline ring; the Ph_S and Ph_A orbitals are mainly localized on the phenyl ring. For a detailed description of the character of the orbitals, see the text. [b] IE's from naphthalene ring: 8.24, 8.88, and 9.89 eV.

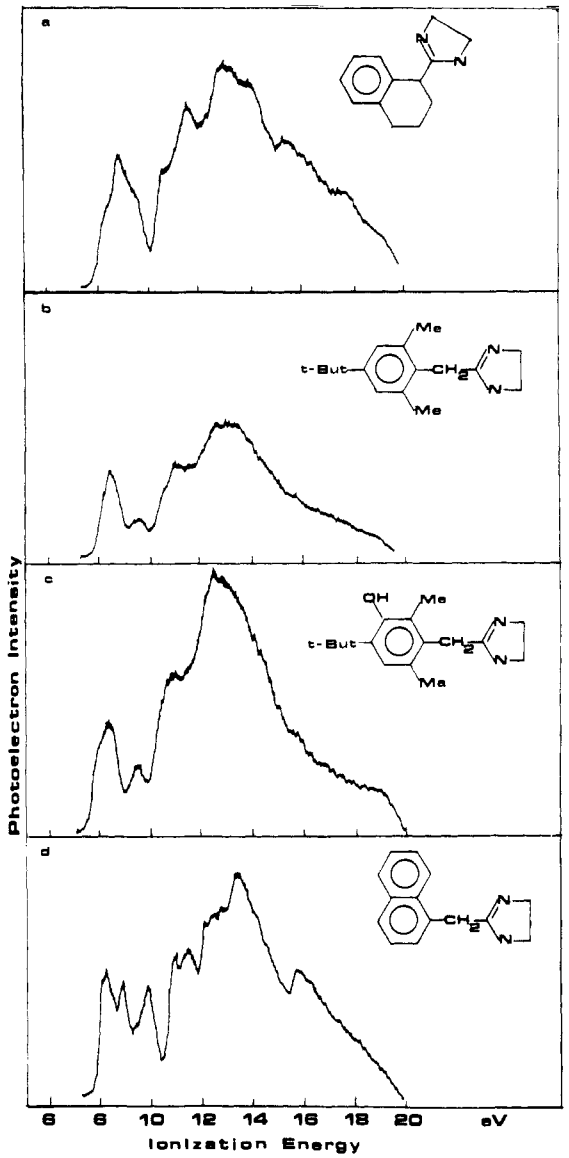

Figure 3. He(I) photoelectron spectra of (a) tetrahydrozoline (7), (b) xylometazoline (8), (c) oxymetazoline (9), and (d) naphazoline (10).

Electron-donating substituents destabilize the Ph_S orbital, while electron-withdrawing substituents tend to stabilize this orbital. Substituents with large inductive effects tend to shift both Ph_S and Ph_A orbitals.

To facilitate assignment of the ionizations of the bands arising from the imidazoline moiety of 2-benzylimidazoline (2), the He(I) and He(II) PE spectra of 2-methylimidazoline (1) have been recorded (Figure 1).

In the low-energy region, three distinct peaks are observed at 8.56, 9.65, and 11.33 eV, respectively. According to CNDO/s calculations, the first band arises from ionization of a π orbital, which is the negative combination of the $\pi_{C=N}$ and amino N lone pair orbital (π_-). This orbital has predominant $\pi_{C=N}$ character. The second band originates from ionization of the lone pair on the imino N atom (n_{Nim}), whereas the third is assigned to the positive combination of the $\pi_{C=N}$ and amino N lone-pair orbital (π_+) which possesses predominantly nitrogen lone-pair character. The He(II) spectrum (Figure 1b) shows an intensity increase of the second and third band in comparison with the He(I) spectrum. Since it is known that N lone-pair ionization increases with incident photon energy,[28] the He(II) spectrum confirms the assignment given by the CNDO/s calculation.

The lowest IE of **2** occurs at 8.50 eV. This corresponds to the first IE of **1** and is attributed to ionization of the π_- orbital. The second band in the spectrum of **2** (Figure 2a) has its maximum at 9.59 eV and a shoulder at 9.28 eV. The intensity of this band suggests that three ionizations are involved. The maximum at 9.59 eV is assigned to the n_{Nim} ionization, because of the resemblance with the 9.65-eV band in **1**. The other two ionizations have to arise from the Ph_S and Ph_A orbitals. The shoulder at 9.28 eV is attributed to the Ph_A orbital because it is less influenced by substitution, whereas ionization of the Ph_S orbital occurs at about 9.5 eV. As both ionization energies are shifted to higher values with respect to benzene, it is concluded that the methyleneimidazoline substituent has an electron-withdrawing character. This is confirmed by population analysis carried out with CNDO/s. Shifts in the spectra of the 2-methyl (**3**) and 4-methoxy (**4**) derivatives of **2** confirm the assignment of the bands in the 2-benzylimidazoline spectrum.

2-(2-Methylbenzyl)imidazoline (3). In the spectrum of **3**, the maximum of the second band shifts from 9.59 to 8.95 eV. The IE's at 8.60 and 9.50 eV originate from ionizations of the π_- and n_{Nim} orbitals of the imidazoline ring, which are hardly influenced by substitution in the phenyl moiety.

2-(4-Methoxybenzyl)imidazoline (4; Figure 2b). The stronger electron-donating character of the 4-methoxy group causes in **4** a larger destabilization of the Ph_S orbital, whereas there is practically no influence of the Ph_A IE. The respective IE's are found at 8.36 and 9.39 eV. The imidazoline IE's are not shifted after *p*-OCH_3 substitution. In the He(II) spectrum, the third band is split. As the higher energetic part of this band shows a higher intensity with respect to the He(I) spectrum, this ionization is attributed to the n_O orbital of the OCH_3 group, because the intensity of the oxygen lone-pair ionization increases with incident photon energy.[28] The n_O ionization occurs

at 11.18 eV. In anisole the analogous IE is found at 11.06 eV.[25]

Ionization of the π_+ orbital in **1** occurs at 11.33 eV. In the spectra of **2–4**, bands are observed at 11.20, 11.15, and 11.00 eV, respectively. These bands do not seem very sensitive to substitution in the phenyl ring and are therefore assigned to the π_+ ionization. Additional evidence for the location of this orbital ionization is provided by the shift after N-methylation in the dichloro compound **5**, which will be discussed later.

2-(2,6-Dichlorobenzyl)imidazoline (5). In analogy with 2-benzylimidazoline, the orbitals of **5** can be made up of the orbitals of 1,3-dichlorobenzene and 2-methylimidazoline. The PE spectrum of 1,3-dichlorobenzene shows peaks at about 9.3 and 9.7 eV arising from benzene π-orbital ionizations and a third band at 11.7 eV originating from ionization of Cl 3p orbitals.[22,29] For **5**, π_- ionization takes place at 8.42 eV. The second band in the spectrum is broad. Its maximum is located at 9.20 eV and a shoulder is observed at 9.50 eV. Ionizations of Ph_S, Ph_A, and n_{Nim} orbitals are involved with this band. Moreover, a broad band with a maximum at 11.26 eV is observed in the low-energy region. The He(II) spectrum of **5** shows a dramatic decrease in intensity of this band, which is characteristic for Cl 3p electrons.[28] The π_+ IE is also located inside the 11.26-eV band. This is made plausible by the shift observed after N-methylation. The π_+ ionization appears at 10.86 eV in the PE spectrum of the *N*-methyl derivative **6** (Figure 2c). The expected decrease of about 0.4 eV is in accordance with the shift observed for Me_3N (8.50 eV) with regard to Me_2NH (8.94 eV).[30] In **6**, π_- ionization occurs at 8.21, which means a 0.21-eV decrease in comparison to **5** due to the electron-donating methyl group. The n_{Nim} IE remains unchanged. Also for **6**, the comparison of the relative intensities of the bands with incident photon energy proves to be a useful assignment criterion for Cl 3p orbitals. The He(I) intensity of the band at 11.33 eV is drastically reduced in the He(II) spectrum of **6** (Figure 2d).

Tetrahydrozoline (7; Figure 3a). The PE spectrum of tetrahydrozoline shows much resemblance with the spectrum of **3**. The second band is shifted toward the first one with the result that a broad band without resolved structure is observed. The sequence in the assignment of the bands is identical with **3**. π_- ionization occurs at 8.33 eV. The maximum at 8.78 eV arises from ionization of the Ph_S orbital, whereas Ph_A ionization is observed as a shoulder at 9.0 eV. n_{Nim} lone-pair ionization is observed as a shoulder at 9.33 eV, while the peak at 10.62 eV is attributed to ionization of the π_+ orbital. When IE's of tetrahydrozoline are compared with those of 2-benzylimidazoline, it can be concluded that the *n*-propyl group connecting the phenyl moiety with the bridge C atom decreases both the phenyl and imidazoline IE's. The phenyl orbitals are destabilized by 0.5 eV, whereas the n_{Nim} and π_+ IE's are decreased by 0.26 and 0.58 eV, respectively. The destabilization of the π_- orbital amounts only to 0.1 eV.

Xylometazoline (8; Figure 3b). In the PE spectrum of xylometazoline, the first two bands observed in **2** coincide. The electron-donating capacity of *tert*-butyl and methyl groups is responsible for overlapping of the phenyl IE's with the π_- IE. As expected, the orbitals primarily located on the imidazoline moiety do not prove to be sensitive to substitution in the phenyl ring. The IE's of the n_{Nim} and π_+ orbitals are located at 9.60 and 11.27 eV, respectively. The shoulder at 10.50 eV originates probably from ionization of the totally symmetric π orbital of the phenyl ring (a_1). This value is comparable to the a_1 IE of *tert*-butylbenzene (10.5 eV), whereas in benzene the a_1 ionization occurs at 11.5 eV.[22]

Oxymetazoline (9; Figure 3c). The only structural difference of oxymetazoline in comparison with xylometazoline is the 3-OH group. In benzene, the electron-donating character of an OH substituent causes a decrease of the Ph_S IE, whereas the Ph_A is much less influenced. This behavior is also observed in the PE spectrum of oxymetazoline. In comparison with the spectrum of **8**, a shoulder appears at 8.04 eV reflecting the position of the Ph_S orbital ionization. The other characteristics of the oxymetazoline spectrum are essentially identical with that of **8**. The oxygen lone-pair ionization (n_O) is expected at about 10.5 eV (cf. 10.60 eV for 2-*tert*-butylphenol[31] and 11.00 eV for 2.4-dimethylphenol[25]). The unresolved structure of the bands in this region of the spectrum, however, prevents the recognition of the n_O ionization.

Naphazoline (10; Figure 3d). The analysis of bands in the naphthalene spectrum has been given by Eland and Danby[32] and has been confirmed by Brundle et al.[33] with the aid of perfluoro effect. The first three ionizations are attributed to ionizations from π orbitals and are located at 8.13, 8.88, and 10.01 eV, respectively. In naphazoline, the naphthalene and imidazoline moieties appear to be electronically separated by the insulating methylene bridge.

The naphthalene ionizations occur at 8.24, 8.88, and 9.89 eV, whereas the imidazoline ionizations are found at 8.46 (π_-), 9.72 (n_{Nim}), and 11.02 (π_+) eV. There is hardly any difference with the IE's of the model compounds.

CNDO/s Calculations. Semiempirical molecular orbital calculations employing the CNDO/s method were used to confirm the assignment of the PE spectra.

Calculations were carried out for the compounds **1–4**, **7**, and **10**. Panel A of Figure 4 shows vertical ionization energies of these molecules, whereas panel B presents energy levels that were obtained when results from CNDO/s calculations were used in conjunction with Koopmans' theorem and corrected by Bigelow's correction formula.[34] This formula is capable of adjusting the CNDO/s eigenvalues for systematic errors in the calculation scheme. Although the correction formula was developed for benzene only, it appears to also give reasonably good results for other molecules.[35,36]

The corrected calculated orbital energy levels reflect rather well the experimental IE values. A closer examination of the results in Figure 4 demonstrates that ordering and spacing of the π levels, predicted by the calculations, are in reasonable agreement with the results of the PE spectra. The CNDO/s method, however, does not estimate correctly the position of the energy levels of orbitals with mainly n_N character with respect to the π levels. This also occurred in the case of the isoalloxazines.[36] Furthermore, the CNDO/s method overestimates the energy levels of two σ orbitals in the calculated molecules which appear between the n_{Nim} and π_+ orbital energy levels and are not taken up in Figure 4B.

The reason for this is still uncertain. Possibly, there exists a large difference in relaxation between the n_N, σ, and π orbitals. This will lead to errors when one uses Koopmans' theorem with CNDO/s, since then no allowance is made for relaxation effects, but also errors made in the resonance integral approximation in the CNDO formalism may account for this divergence.[37]

Discussion

The photoelectron spectra combined with the CNDO/s MO calculations provided more details about the electronic

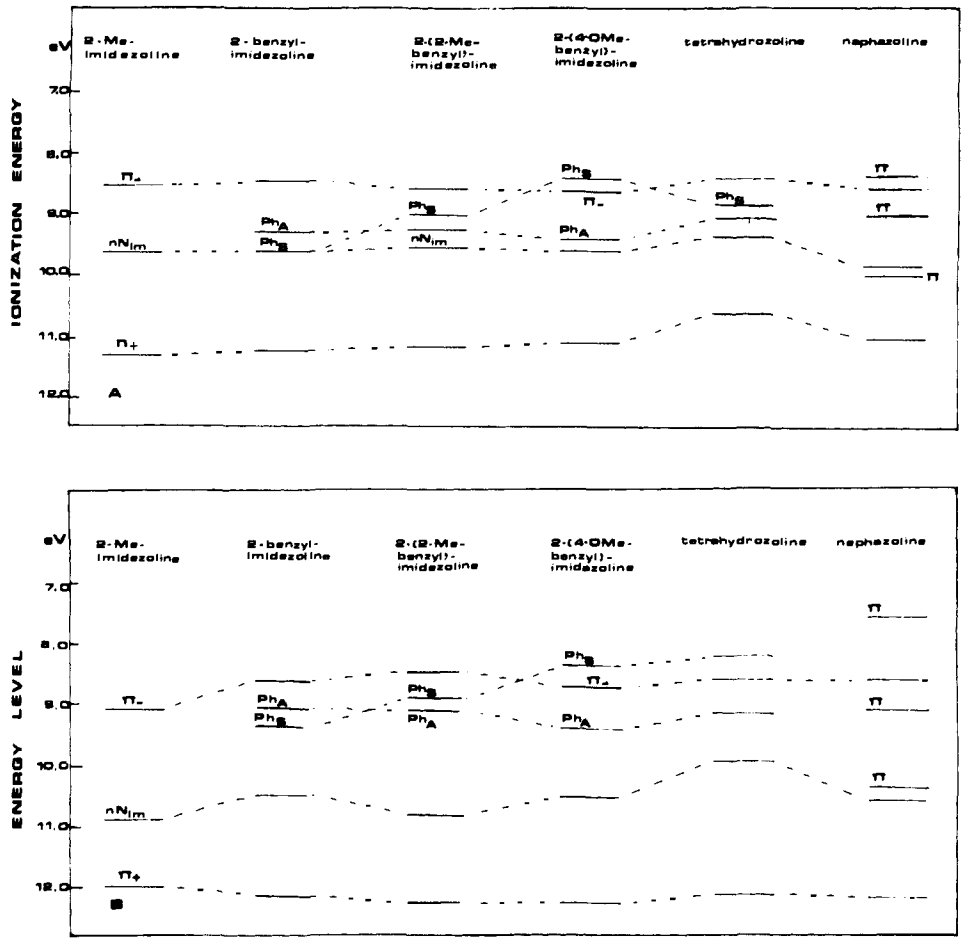

Figure 4. Energy-level diagrams showing the π_-, Ph_S, Ph_A, n_{Nim}, and π_+ orbital energy levels of 2-methylimidazoline, 2-benzylimidazoline, 2-(2-methylbenzyl)imidazoline, 2-(4-methoxybenzyl)imidazoline, tetrahydrozoline, and naphazoline. Panel A shows experimental results obtained from vertical ionization energies. Panel B shows energy levels obtained from CNDO/s molecular orbital calculations, which were corrected with the aid of Bigelow's formula.[34]

structure of the benzylimidazolines than was previously available. The major electronic properties of these compounds are the following: (1) the methyleneimidazoline substituent has an electron-withdrawing character and shows an inductive effect on both Ph_S and Ph_A orbitals of benzene; (2) there is no specific electronic interaction between benzene and the imidazoline ring. Substitution in one ring does not influence the electronic character of the other ring; (3) the first IE arises from a π orbital localized on the imidazoline ring, with the exception of 2-(4-methoxybenzyl)imidazoline, naphazoline, oxymetazoline, and xylometazoline in which the first IE originates from an orbital, mainly localized on the aromatic ring.

When one tries to correlate the electronic data with the biological activity, one has to be very careful. Generally, the biological activity is expressed as a dose in milligrams per kilograms for intact animals. The effective dose, however, is not only determined by drug–receptor complex formation but also by a host of other factors as, e.g., uptake, elimination, distribution, and biotransformation of the drug. In in vitro experiments, most of these processes are eliminated, with the result that a more likely picture of the events on receptor level is obtained. Furthermore, it has to be verified that the various drugs act on the same receptor population.

The effect on the blood circulation of 1, **5**, and **6** is not known. Experiments on isolated rabbit jejunum indicate that **5** is acting as a partial α-adrenergic agonist.[3]

In cats, 2-benzylimidazoline (**2**) brings about a fall in arterial blood pressure, but in reserpinized animals it increases the blood pressure.[38] This suggests a direct sympathomimetic action in addition to a sympatholytic effect and, therefore, **2** is considered a partial agonist.

2-(4-Methoxybenzyl)imidazoline (**4**) brings about a decrease in blood pressure, but the 3,4,5-trimethoxy derivative causes a rise.[1] One should not expect much difference between the first IE of **4** and that of the 3,-4,5-trimethoxy compound. For instance, 4-methoxyphenethylamine and 3,4,5-trimethoxyphenethylamine (mescaline) have practically the same value.[8] This suggests that electronic properties, as measured with UPS, are not related to the qualitative pharmacological action of the benzylimidazolines.

Of the various α-adrenergic receptor models, the isolated rabbit jejunum is claimed to contain the most specific α-adrenergic receptors.[2,39,40] In this preparation, the sympathomimetic imidazolines used in this study all showed an intrinsic activity of 1.[3,41] Since the dose–response curves were all parallel with respect to the dose–response curve of (−)-noradrenaline,[41] it can be concluded that these compounds act in the same way on the same receptor. Oxymetazoline proved to be the most potent drug, followed by naphazoline, xylometazoline, and tetrahydrozoline. It is shown in Table II that the first IE originating from an aromatic orbital parallels the trend in pD_2. Because the first IE is a measure of the ability of a compound to act as an electron donor, this relationship supports Belleau's suggestion[42,43] that electron donation of the aromatic ring may play an important role in the engagement of agonists with the α-adrenergic receptor. Though the UPS data cannot be used to predict the qualitative pharmacological action of the benzylimida-

Table II. Affinities for the α-Adrenergic Receptor in Isolated Rabbit Intestine (pD_2) from Reference 41, Abilities to Displace Specifically Bound [^{3}H]Clonidine in Rat Brain Homogenate (K_i) from Reference 44, and First Aromatic Ring Ionization Energies (IE_1)

	pD_2	K_i, nM	IE_1, eV
oxymetazoline	9.8	1.9 ± 0.3	8.04
naphazoline	7.1	5.7 ± 2.1	8.24
xylometazoline	7.1	4.8 ± 1.4	8.27
tetrahydrozoline	6.5	11 ± 4	8.78

zolines, there seems to exist a relationship between the first IE and the potency of the sympathomimetic compounds. Such a relationship between ionization energy and biological activity, stressing the role of the aromatic ring, has been earlier described for hallucinogenic tryptamines and phenethylamines.[8]

Although there are only four compounds involved, the similar trend in the ability of a drug to displace specifically bound [^{3}H]clonidine in rat brain homogenate[44] and the first aromatic ring IE (Table II) also suggests the importance of the aromatic moiety in the interaction with central α-adrenergic receptors. To establish whether IE's are valid indicators of drug activity, UPS and binding studies on a greater variety of imidazolines are in progress.

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