Application of Photoelectron Spectroscopy to Biologically Active Molecules and Their Constituent Parts. II. (1) 1,4-Benzodiazepines

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The HeI photoelectron (PE) spectra of 5-phenyl-7-chloro-2H-1,4-benzodiazepin-2-one (1), its 1-methyl derivative (2), 3-hydroxy derivative (3), 1-methyl-3-hydroxy derivative (4), 3-(S)-methyl derivative (5), and 1-methyl-3-(S)-methyl derivative (6) have been recorded. The electronic structure of these compounds is discussed on the basis of the observed ionization energies, and of the semiempirical CNDO/2 calculations on model compounds 1a-6a, which have a hydrogen instead of the phenyl group in the 5-position. As a result the character of the seven highest occupied orbitals in 1-6 have been assigned.

1,4-Benzodiazepines and their derivatives have been objects of extensive investigations during the last years. These compounds are of special interest because of their psychopharmacologic activity, having use as tranquilizers. Compounds as diazepam (2), desmethyldiazepam (1), oxazepam (4), temazepam (3) are some of the best known. Most work as yet has been done on the synthesis (2), investigation of pharmacologic activity and chemical properties (3), less on the structure and stereochemistry (4,5), but negligible on the electronic structure of these compounds. In the present work we report the PE spectra of compounds 1-4, and the newly prepared (6) chiral substances 5 and 6 as well. Gas phase uv-photoelectron spectroscopy (UPS) allows, besides the exact determination of the ionization energies of molecules, also insight into their electronic structure. Namely, within the validity of Koopmans' theorem, the observed energies of electronic systems in the PE spectra can be assigned to ionizations from discrete molecular orbitals describing the distribution of electron pairs in the molecule. PE spectra in combination with results of quantum chemistry calculations represent a powerful tool for investigation of the relationship between electronic structure and molecular properties. Such investigation is particularly interesting for biologically highly active molecules, such as 1,4-benzodiazepines, offering better insight into electronic structure-activity relationship. This is of prime importance for explanation of mechanism of their activity on the molecular level.

Compounds 1-4 form three pairs which differ by substitution (R₁) at the 3-position, i.e., instead of one

hydrogen at C_3 in prochiral compound 1 and 2, compounds 3 and 4 (chiral, racemic) bear a hydroxy group, and compounds 5 and 6 (chiral, S-configuration) methyl group. Two compounds forming a pair differ in the hydrogen (compounds 1, 3 and 5) or methyl group (compounds 2, 4 and 6) at the nitrogen in the 1-position.
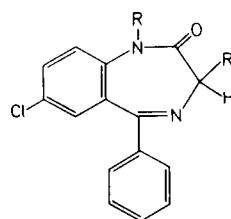
	R	R₁
1	H	H
2	CH₃	H
3	H	OH
4	CH₃	OH
5	H	CH₃ (S-configuration)
6	CH₃	CH₃ (S-configuration)

Results.

Photoelectron Spectra.

The low resolution (about 35 meV) PE spectra have been recorded on a Vacuum Generators UVG3 instrument (7) using HeI (21.22eV) excitation and inlet system temperatures of 160°, 160°, 180°, 200°, 170° and 170° for 1 to 6, respectively. For calibration small amounts of nitrogen and argon were added to the sample flow during the measurement. The compounds were of high purity, recrystallized and prepared as described in references 2, 6 and 8.

The PE spectra of 1-6 are reproduced in Figures 1-6. Since the compounds have very low vapour pressure and enhanced inlet temperatures of up to 200° (at which they tend to decompose) have been used, the PE spectra are of relatively poor quality. The observed adiabatic (I_A) and
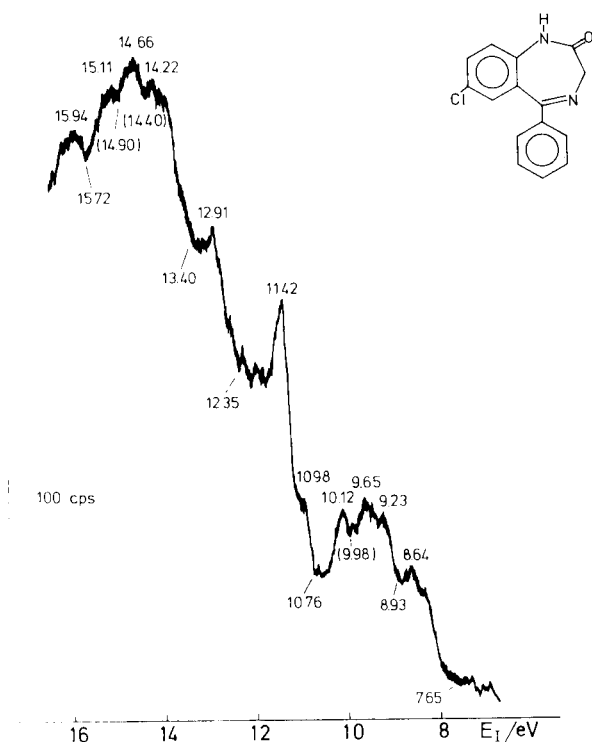
Figure 1. The HeI PE spectrum of **1** at 160°. The observed adiabatic and ventical ionization energies (EI/eV) of the proposed electron energy systems are indicated on bottom and top, respectively (doubtful values are given in parenthesis).

Figure 2. The HeI PE spectrum of **2** at 160°; assignment is performed as described for Figure 1.

vertical (I_V) ionization energies (in eV) of the proposed electron energy systems are indicated on their bottom and top, respectively. Doubtful values are given in parenthesis. Because of the rather diffuse character of the observed systems, the accuracy of the quoted ionization energies is 0.02 eV.

CNDO/2 Calculations.

Although CNDO/2 calculations proved to be of little value for intrepreting PE spectra (1) this semiempirical method has been chosen because it takes into account all valence electrons and the actual geometry of the studied molecule. The atomic coordinates of **2** necessary for the CNDO/2 calculation are from reference 9. For compounds **2-6** standard bond lengths have been chosen for the substituents and the same basic geometry as for **2**. Since complete CNDO/2 calculations on **2** would require 97 basic functions (and even more for others) we performed calculations on model compounds **1a-6a**, *i.e.*, such without the phenyl group in the 5-position. These calculations within the framework of the standard CNDO/2 method (10) yielded the following results:
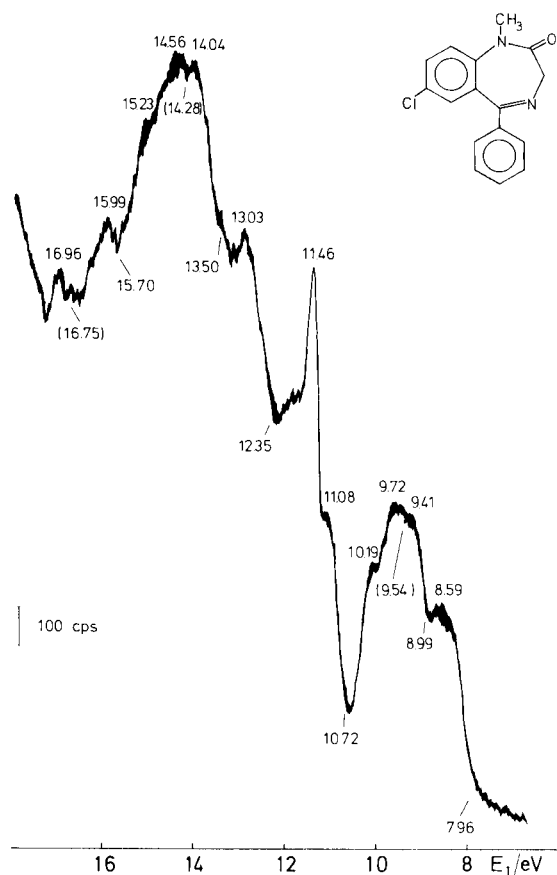
i) The first two highest occupied ψ_1 and ψ_2 in **1a-6a** are of π-type.

ii) They are followed by an orbital ψ_3 which mainly describes the lone pair electrons at 4-nitrogen.

iii) The orbital ψ_4 is of π-type including the p-electron of oxygen, and is

iv) followed by orbitals ψ_5, ψ_6, ψ_7 which more or less contain the electrons of chlorine.

v) The energies of the orbitals ψ_1 to ψ_5 do not vary much for the model compounds **1a-6a** (ψ_1:11.4-11.7, ψ_2: 12.0-12.4, ψ_3: 12.7-12.8, ψ_4: 13.4-13.6 and ψ_5: ionization energies observed in PE spectra of **1-6** (where six ionization energies are lower than 12 eV).

Discussion

In order to get some insight into the electronic structure of **1-6** from their PE spectra in comparison with CNDO/2 calculations on model compounds **1a-6a**, one has to take into account the differences between both series and the weakness of the CNDO/2 method to predict the correct orbital sequences, as well.
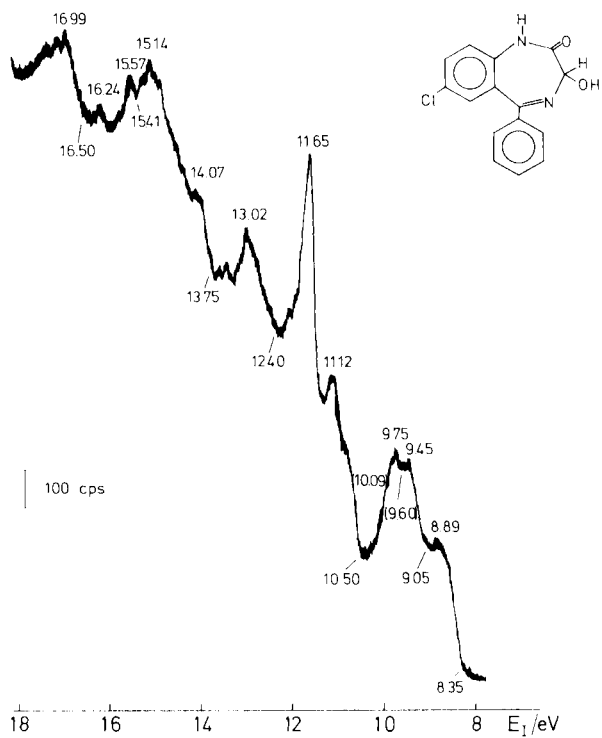
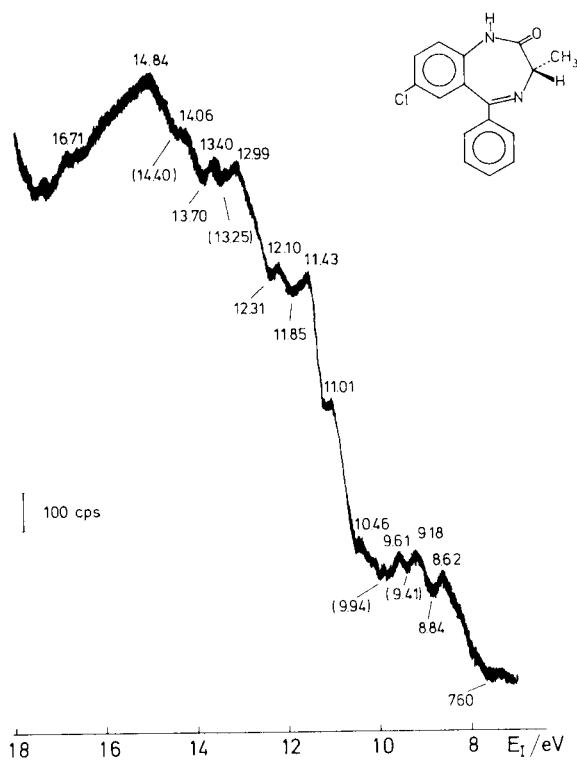Figure 3. The HeI PE spectrum of **3** at 180°; assignment is performed as described for Figure 1.

Figure 5. The HeI PE spectrum of **5** at 170°; assignment is performed as described for Figure 1.
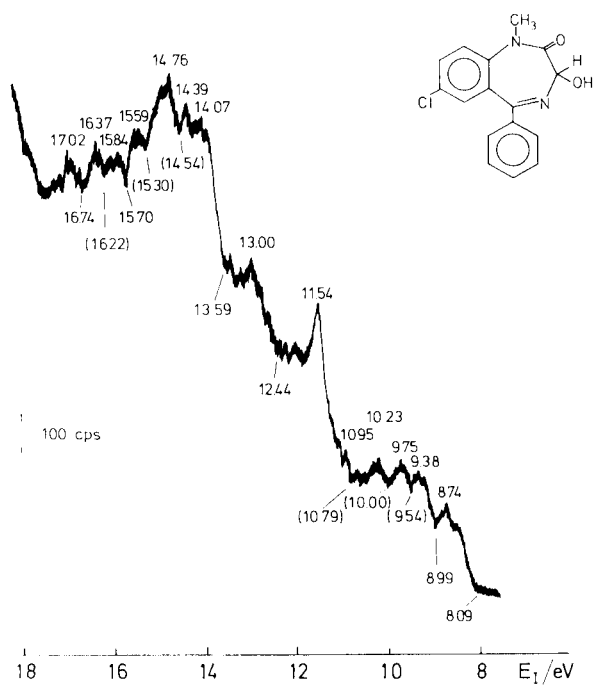

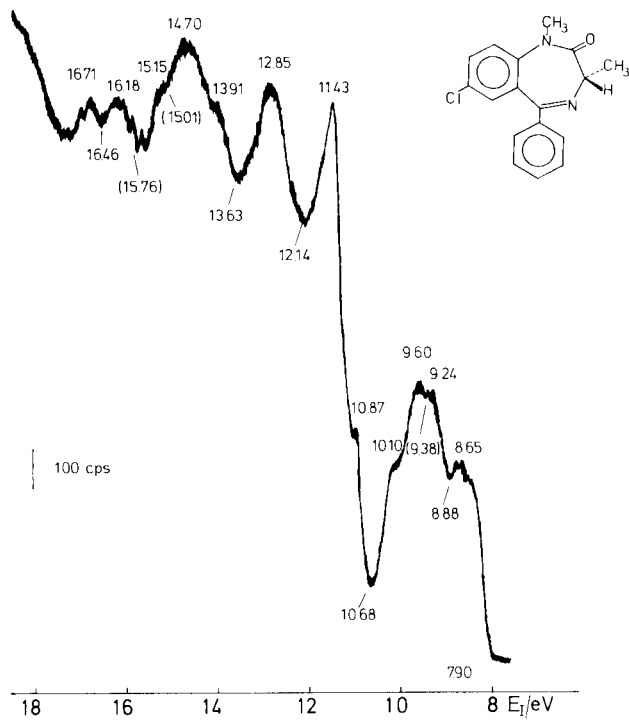Figure 4. The HeI PE spectrum of **4** at 200°; assignment is performed as described for Figure 1.

Figure 6. The HeI PE spectrum of **6** at 170°; assignment is performed as described for Figure 1.

Concerning the first, it is to be expected that the phenyl group in the 5-position will yield two additional electron systems at low energy, which correspond to ionizations from the originally degenerate benzene orbitals. Their energy is expected to be between 9 and 10 eV. From the spectra it is easily recognized (pronounced peak) that the ionization energy which could be attributed to the lone pairs of chlorine appears at a nearly constant value of about 11.5 eV, and is the sixth observed electron energy system. Thus, only the nitrogen lone pair orbital, n_N, seems to be between the four highest π-orbitals and the lone pair of orbitals of chlorine, n_{Cl}. In conclusion, on the basis of CNDO/2 calculations and the reported PE spectra one would suggest the following ordering of the seven highest occupied orbitals in compounds **1-6**:

$$4\pi > n_N > n_{Cl} > \pi\ (n_O) \text{ or } 3\pi > n_N > \pi > n_{Cl} > \pi\ (n_O)$$

On the other hand, in PE spectra of aliphatic amino acids (11) (glycine and (S)-alanine are in fact incorporated in the studied molecules **1, 2, 5** and **6**) the nitrogen lone pair ionization energy is in the region of 9.5-10.0 eV (1_V) and is followed by the oxygen lone pair (10.7-11.2) and π_{CO} ionizations (11.3-12.1) thus indicating that some of the systems assigned as π ionizations might arise from lone pairs.

REFERENCES AND NOTES

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