On the Proton Affinity of Pteridine

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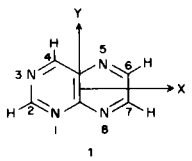
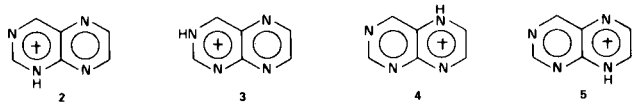
Received September 11, 1973

All-valence-electron and perturbation calculations suggest that pteridine may preferably be protonated at the pyrazine moiety. Correlation between these results and some experimental data is presented.

Attention has recently been devoted to the problem of protonation of heterocyclic bases which embody more than one site for proton attachment (2). We have previously reported (3) application of SCF-LCAO-all-valence-electron calculations for purine and its mono-protonated forms, using the CNDO/2 algorithm (4). A reasonable agreement was obtained between the theoretical computations and the experimental evidence available. Here we present some results regarding pteridine (**1**) (5) and its four-mono-protonated forms **2-5** (Scheme I). In

SCHEME I



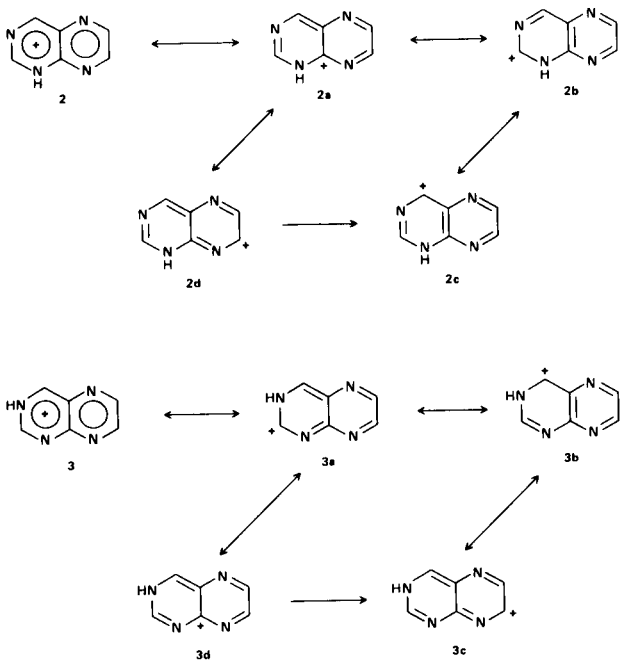


order to eliminate as much as possible the influence of the particular algorithm chosen, we have carried out the calculations both with CNDO/2 and the modified INDO (MINDO/1) (6) methods. MINDO/1, which includes both σ and π valence electrons, has proven valuable (7) in estimation of relative stabilities and heats of formation or related isomers. Also, energy profiles, which are overestimated by CNDO/2 (8), are "closer" to reality within MINDO/1, due to the inclusion of some one-center core integrals, the latter being ignored in CNDO/2 due to ZDO approximation.

Method of Calculations.

Cartesian coordinates were calculated on the basis of an X-ray study of pteridine (free base) (9a). Unfortunately, this work does not include data for the C-H bonds and we have assumed the latter to have a length of 1.08 Å (9b). For $\overset{+}{N}$-H bonds in forms **2-5** we choose a length of 0.9 Å. It was also assumed that no drastic deviations in the C-N=C bond angles do occur upon quaternization (*cf.* ref. 10). Likewise, calculations were based on a "bisector approach" of the attacking proton towards the nitrogen atoms. Clearly, our geometry may not necessarily represent a minimum in the potential surface. However, the rather large basis-set, composed of 48 valence electrons in 24 doubly-occupied molecular orbitals, precluded any extensive minimization attempts of the geometry as function of energy, due to the extreme

SCHEME II



time-consuming feature of such calculations (11).

Computations were performed using FORTRAN programs obtained through the QCPE (No. 100 and 137 for CNDO/2 and MINDO/1 respectively). Modifications were made in the diagonalizing routines (Householder's method).

TABLE I

Energy Profiles for Pteridine and *N*-Monoprotonated Derivatives

	CNDO/2		MINDO/1	
No.	Electronic energy (eV)	Total energy (eV)	Electronic energy (eV)	Total energy (eV)
1	-8912.453	-2524.300	-7035.781	-1654.041
2	-9208.774	-2536.882	-7282.220	-1664.899
3	-9190.856	-2536.863	-7266.251	-1664.777
4	-9204.236	-2536.903	-7278.574	-1664.752
5	-9209.510	-2537.171	-7282.683	-1665.039

Results and Discussion.

In columns 2 and 3 of Table I we present the energy profiles for the parent base (**1**) and its *N*-mono-protonated forms **2-5**, as computed by CNDO/2. Total energies (E_T) are expressed as sum of total valence-shell electronic energies (E_E) and the nuclear repulsion terms (E_N). The order of stability, as judged from E_T of the mono-protonated forms **2-5** is: H^+ (N-8) > H^+ (N-5) > H^+ (N-1) > H^+ (N-3). Thus, a division into two classes is observed where class a comprises the pyrazine-protonated forms **4**, **5**, which are more stable than their pyrimidine-protonated companions **2**, **3** (class b) by an average value of 3.8 Kcal/mole. Within class a, form **5** is more stable by 6.2 Kcal/mole than **4**, while within class b, **2** differs only insignificantly from **3** by 0.4 Kcal/mole. The last result is reminiscent of a previous CNDO/2 calculation (3) where it was found that protonation at position 3 of purine, in its NH-7 tautomeric form, would not differ significantly (0.3 Kcal/mole) from its H^+(N-1) companion (note that position 1 and 3 in purine correspond to position 3 and 1, respectively, in pteridine).

The valence-shell electronic energy (E_E) is in line with the prediction regarding the preference of form **5** over its companions. Here the computed order of stability is: H^+(N-8) > H^+(N-1) > H^+(N-5) > H^+(N-3). If one assumes (12) that the size of an N-H group is smaller than that of an N-lone pair, the order to E_E is reasonable: the mutual electronic interaction between the *peri* lone pairs ($2P_y$ in our geometrical notation) at positions 1 and 8 is relieved upon protonation at either N-1 or N-8, with a preference of *ca.* 17 Kcal/mole in favor of the latter site (13).

Judged from E_E considerations, **3** is the least stable form (*cf.* calculation of E_E for protonation at N-1 in the pyrimidine moiety of purine (3)). If one observes the four canonical structures (Scheme II) associated with **2** and **3**, it is evident that the latter has one *ortho*-quinoid resonance form and one "aromatic" structure (**3a**, **3b** respectively). In contrast, **2** has one *ortho*-quinoid form (**2a**) but two "aromatic" forms (**2b**, **2c**) (15). One would, therefore, expect some preference of isomer **2** over **3** in accord with both E_E and E_T computations.

Columns 4 and 5 of Table I present some results obtained by MINDO/1. Qualitative similarity is evident between this method and CNDO/2, the order to stability being maintained for both E_E and E_T. As already mentioned above, the absolute values of the profiles associated with MINDO/1 are lower than those of CNDO/2 as the result of a different parametrization and inclusion of some core integrals.

Another approach for the determination of the most probable position for proton attachment is the calculation of the proton affinity index Δ_{BE^+-BE}, defined as the absolute difference between the binding energies of the protonated and non-protonated species: the smaller its magnitude, the more reactive the position of protonation denoted (16). The results in Table II suggest that form **5**, *i.e.* protonation at N-8, has the lowest value and, therefore, the highest probability to dominate among its isomers.

TABLE II

Binding Energies, Proton Affinities and Heat of Formations

	CNDO/2		MINDO/1		
No.	Binding energy (eV)	Δ_{BE^+-BE}	Binding energy	Δ_{BE^+-BE}	Heat of formation Kcal/mole
1	-243.180	– – –	-70.313	– – –	+64.250
2	-238.386	4.794	-67.576	2.737	+179.479
3	-238.367	4.813	-67.454	2.859	+182.299
4	-238.407	4.773	-67.429	2.884	+182.864
5	-238.675	4.505	-67.716	2.597	+176.251

CNDO/2 suggests the order of preference to be: H^+(N-8) > H^+(N-5) > H^+(N-1) > H^+(N-3), while MINDO/1 leads to an exchange of position 1 and 5, the order being: H^+(N-8) > H^+(N-1) > H^+(N-3) > H^+(N-5).

In column 6 of Table II we present heat of formations of compounds **1-5**. Although MINDO/1 is known to be less accurate for charged species than its recent variant MINDO/2 (17), we are interested here in comparing the *relative* stabilities of isomers **2-5** and not their absolute values. Again, form **5** is predicted to be the most stable one, the order being: H^+(N-8) > H^+(N-1) > H^+(N-3) > H^+(N-5), *i.e.* in parallelism with the order of proton affinities computed by the same algorithm.

TABLE III

Atom-atom Self-polarisabilities ($\pi_{i,j}$)

Coulomb integral (a)	Position of attack	$\pi_{1,1}$	$\pi_{3,3}$	$\pi_{5,5}$	$\pi_{8,8}$
h = 0.4		0.417	0.389	0.433	0.428
h = 0.6	N-1	0.392	0.387	0.433	0.426
	N-3	0.415	0.370	0.434	0.428
	N-5	0.418	0.390	0.416	0.433
	N-8	0.414	0.388	0.435	0.408
h = 0.8	N-1	0.362	0.385	0.433	0.423
	N-3	0.413	0.347	0.434	0.428
	N-5	0.420	0.392	0.391	0.437
	N-8	0.411	0.388	0.436	0.381
h = 1.0	N-1	0.330	0.383	0.434	0.420
	N-3	0.411	0.321	0.435	0.427
	N-5	0.421	0.394	0.361	0.440
	N-8	0.408	0.387	0.437	0.349
h = 1.2	N-1	0.296	0.382	0.434	0.417
	N-3	0.408	0.293	0.436	0.427
	N-5	0.423	0.396	0.329	0.443
	N-8	0.404	0.387	0.437	0.316
h = 1.4	N-1	0.264	0.380	0.434	0.415
	N-3	0.406	0.265	0.437	0.426
	N-5	0.424	0.398	0.296	0.444
	N-8	0.401	0.386	0.437	0.283
h = 1.6	N-1	0.234	0.378	0.435	0.412
	N-3	0.404	0.238	0.438	0.425
	N-5	0.426	0.400	0.263	0.445
	N-8	0.398	0.386	0.436	0.251
h = 1.8	N-1	0.206	0.377	0.435	0.410
	N-3	0.403	0.213	0.439	0.425
	N-5	0.427	0.402	0.233	0.446
	N-8	0.396	0.385	0.436	0.222
h = 2.0	N-1	0.181	0.375	0.435	0.407
	N-3	0.401	0.190	0.440	0.424
	N-5	0.429	0.404	0.205	0.447
	N-8	0.393	0.385	0.436	0.195

(a) Coulomb integral defined as: $\alpha_N = \alpha_0 + h\beta_0$, where $\alpha_0 = 0$.

Perturbation Calculations.

The all-valence-shell profiles presented above apply to molecules in their "frozen" (static) ground state. Chemical reactions are actually dynamic processes in which activated states play the most important role. Unfortunately, such type of computations are not yet feasible owing to lack of information regarding the geometry of the transition state. However, one of the most useful methods for gaining insight into chemical reactions is the perturbation method (PMO) (18), as developed by Coulson and Longuet-Higgins (19). Within this approach we have chosen to calculate the atom-atom self-polarizabilities defined as:

$$\pi_{i,i} = 4 \sum^{occ.} \sum^{unocc.} \frac{a_{\mu i}^2 \; a_{\nu i}^2}{E_\mu - E_\nu}$$

where $a_{\mu i}$ and $a_{\nu i}$ denote the coefficientes of the i-th atom at the ϕ_μ and ϕ_ν MO's possessing energies of E_μ and E_ν: summation is carried out over the occupied and unoccupied levels, respectively. The coefficients $a_{\mu i}$ and $a_{\nu i}$ may be obtained from π-electronic SCF or Huckel wave functions: we have preferred the latter for simplicity. $\pi_{i,i}$ indices calculated for the four nitrogen atoms of pteridine (**1**) give some idea regarding the ability of these atoms to develop a negative charge and thus to accept an electrophile (H^+,R^+). The larger the absolute $\pi_{i,i}$ value, the greater is the gain in negative charge at the particular position. In order to make our calculations independent of the parameters chosen, we worked with Coulomb integrals for the nitrogen atoms: $\alpha_N = \alpha_0 + h\beta_0$, where h was continuously varied from the commonly used value of 0.4 to 2.0 (sp^2-hybridized nitrogen atom in its neutral and quaternary forms, respectively) (20,21). The resonance integrals: $\beta_{C=X} = k\beta_0$ were kept constant using k = 1.0 for both C=N and C=C bonds. In Table III we present the results; the largest $\pi_{i,i}$ values have been underlined. It is evident that the largest index is always associated with positions 5 and 8 of the pyrazine moiety, these values being independent of the particular h value. Also, variation at position **1** or **3** of the pyrimidine ring of **1** still shows that the largest $\pi_{i,i}$ value is associated with positions 5 and 8.

The theoretical calculations presented here suggest that protonation of pteridine may involve the pyrazine ring preferably. Consequently it became desirable to gain some experimental evidence regarding this problem. In analogy (22) to the pmr spectrum of purine, we have anticipated that if protonation at N-3 of **1** would occur, the symmetry of the electric field gradient at this particular atom would become more shperical and consequently

the quadrupole moment would be reduced to permit observation of the long-range spin-spin coupling between H-2 and H-4 (23). Conversely, if protonation would occur at the pyrazine moiety, one should observe some significant changes in the chemical shifts of H-7 and H-8. Unfortunately, at room temperature and under strict anhydrous conditions, pteridine turned to be so unstable in acidic media such as trifluoroacetic acid (TFA) or deuteriochloroform containing deuterium sulfate (*cf.* ref. 26 for instability of **1** in aqueous acid) that no clear conclusion could be drawn from these pmr experiments regarding the preferred site of protonation of **1** (27).

It should be noted that Albert has tentatively assumed pteridine to undergo protonation at N-3 in aqueous acidic media (*cf.* formula 35 in ref. 29). We feel that this suggestion does not contradict the present calculations since the above-mentioned reaction is actually in acid-catalysed addition of water (30) across the azomethine 3,4 N=C bond (31). Such an addition-reaction may be subject to kinetic control, while our MO computations refer to an anhydrous thermodynamically-stabilized species. Therefore, a direct comparison in such a case would, in our opinion, be illegitimate.

EXPERIMENTAL

Pteridine was a gift from Prof. D. J. Brown and was crystallized from a small volume of benzene (charcoal). TFA, deuterium sulfate and deuteriochloroform were Merck products. Pmr measurements were recorded on a Jeol MH-100 instrument operating at 100 MHz. Tetramethylsilane was used as internal standard.

Acknowledgment.

The author wishes to thank the Alexander von Humboldt Foundation for a scholarship. Thanks are also due to Prof. W. Pfleiderer for comments and kind hospitality, to Prof. D. J. Brown, Australian National University, Canberra, for the pteridine and the helpful correspondence, to Drs. I. Tamir and D. Lichtenberg for the pmr spectra and valuable comments, and to Prof. F. Bergmann for stimulating discussions and constant encouragement.

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