Application of the MINDO Method to the Tautomers of Purine

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The four purine tautomers are compared by two all-valence electron methods: CNDO/2 and MINDO. The experimental ionization potential of purine is in good agreement with the value calculated by MINDO, while dipole-moment measurements agree better with those calculated by CNDO/2 Markedly different results are obtained when charge distributions are calculated by the two methods.

PULLMAN *et al.*[1,2] have calculated some electronic properties of the four purine tautomers using the SCF–PPP and the CNDO/2 methods. The results obtained agreed moderately well with experimental evidence because the CNDO/2 theory is known to emphasize ground-state properties such as heat of formation, total energies, and ionization potentials, while the SCF–PPP method is probably unsuitable for such determinations owing to neglect of the whole σ framework.

A method which would include all valence electrons (*viz.*, both σ and π electrons), and could reproduce ground-state properties better than the CNDO/2

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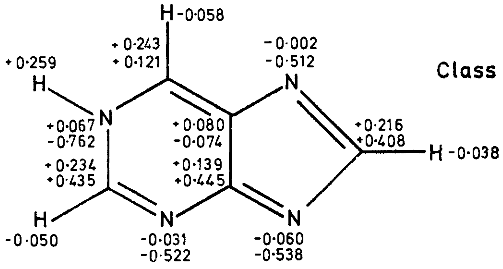
[1] B. Pullman, E. D. Bergmann, H. Weiler-Feilchenfeld, and Z. Neiman, *Internat. J. Quantum Chem.*, 1963, III, **5**, 103.

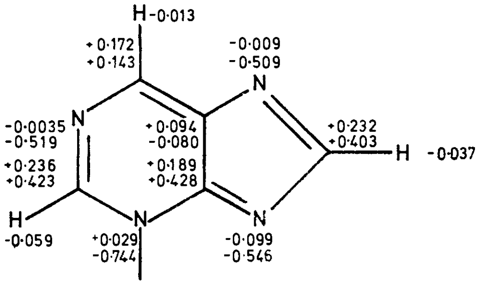
[2] B. Pullman, H. Berthod, F. Bergmann, Z. Neiman, H. Weiler-Feilchenfeld, and E. D. Bergmann, *Tetrahedron*, 1970, **26**, 1483.

method, is the recently developed theory called 'modified INDO' (MINDO) by Baird and Dewar.[3] This is similar to the CNDO/2 treatment of the valence electrons and differs only in that the one-centre monoatomic integrals are retained as parameters while in CNDO/2 all such integrals vanish owing to the ZDO approximation. Baird and Dewar[3] showed that the MINDO algorithm gives good estimates of ground-state properties for both hydrocarbons and heterocycles, and therefore it seemed worthwhile to adopt it for the purine tautomers. It must be stressed that both methods are highly approximate and their predictions are not insensitive to changes in parameter values and geometries. The relative merits of the theories have been discussed elsewhere[3] and the MINDO method, which includes one-centre exchange integrals, seems to be theoretically more realistic.

Class *a*

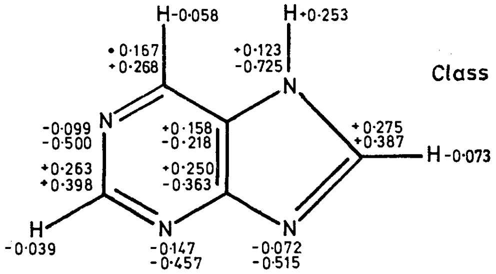


(I)

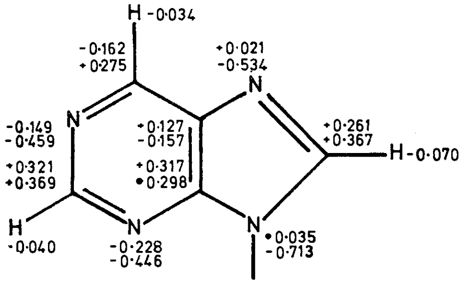


(II)

Class *b*



(III)



(IV)

Upper number, σ charge; lower number, π charge.

Our basic problem for these calculations was to design a proper geometry for the isomers. These tautomers can be divided structurally into two classes: class *a* comprise the 1- and 3-NH-tautomers (I) and (II) which have in common the 'fulvene-like' π-deficient imidazole moiety[4] and a *para*- or *ortho*-quinoid structure in the pyrimidine ring. Class *b* comprises 7- and 9-NH-purine (III) and (IV) which share the aromatic pyrimidine moiety and the π-excessive imidazole ring.[4]

Accurate data on geometry are available only for the 7-NH-purine since crystalline purine was found by *X*-ray crystallography to exist in this form.[5] As this does not imply that the tautomers would bear a geometry similar to the 7-NH-analogue we adopted the values for bond lengths and angles suggested by Pullman *et al.*:[2] therefore the results will facilitate a direct comparison between the CNDO/2 and the present MINDO algorithms. We stress that the geometry here was only tentative and no attempt was made to minimize the total energy as a function of it (as recently done in the MINDO/2 version[6]). However it will be shown that some of the present results have a logical meaning and do go parallel to the expected trend in the purine tautomers.

Method of Calculation.—The MINDO and CNDO/2 programmes were made available through the QCPE (programmes #137 and 91). The original MINDO programme was modified only in the diagonalizing subroutine and the results were checked against the original data of Baird and Dewar.[3] Co-ordinates were calculated by Dewar's programme (QCPE #136). About 24 iterations were necessary in order to obtain convergence; the time required for each calculation was about 720 s on a CDC 6400 digital computer. All calculations were carried out at the computation centre of the Hebrew University of Jerusalem.

RESULTS

(1) The values for heat of formation, obtained by the MINDO method (Table 1), permit a clear-cut separation of the two classes: Class *a* differs from *b* not only in the

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[3] N. C. Baird and M. J. S. Dewar, *J. Chem. Phys.*, 1969, **50**, 1262; N. C. Baird, M. J. S. Dewar, and R. Sustmann, *J. Chem. Phys.*, 1969, **50**, 1275.

[4] A. Albert, 'Heterocyclic Chemistry,' The Athlone Press, London, 1959, pp. 39—241.

[5] D. J. Watson, R. M. Sweet, and R. Marsh, *Acta Cryst.*, 1965, **19**, 573.

[6] M. J. S. Dewar and E. Haselbach, *J. Amer. Chem. Soc.*, 1970, **92**, 590.

absolute numerical values, but also in the sign. Thus for class *a*, an endothermic and for *b* an exothermic heat of formation is indicated. The values also predict the order of stability in each class as (II) > (I) and (III) > (IV), the difference in the heats of formation being much larger for the first pair.

(2) The values for the total energy, obtained either by CNDO/2 or by MINDO, show that class *b* is more stable. According to the MINDO method, only a slight difference exists between the total energy of (III) and (IV) (0·02 eV = 0·46 kcal mol^{-1}), while CNDO/2 calculations lead to a 10 times greater difference (0·2 eV = 4·6 kcal mol^{-1}). Both methods predict that form (II) is more stable than (I). This corresponds to the experimental observation that 1-methylpurine is unstable while the 3-methyl analogue can be kept for several months without decomposition.[7] Similarly, 9-methylpurine is unstable;[8,9] this however is not borne out by the small difference between (III) and (IV), according to MINDO.

TABLE 1

Energy/eV and heat of formation/kcal mol^{-1} of the tautomers of purine

	CNDO [a]				MINDO					
Compd.	Total energy	HOMO	LEMO	Δ (HOMO–LEMO)	Total energy	Total bonding energy	Heat of formation	HOMO	LEMO	Δ (HOMO–LEMO)
(I)	−2310·2	−11·0	1·9	9·1	−1526·7	−63·8	+42·7	−9·4	2·1	7·3
(II)	−2310·4	−11·3	1·7	9·6	−1527·1	−64·3	+33·0	−9·5	2·1	7·4
(III)	−2312·1	−11·9	3·0	8·9	−1532·05	−69·22	−81·5	−9·3	1·7	7·6
(IV)	−2311·9	−11·3	3·2	8·1	−1532·03	−69·20	−81·0	−9·2	1·8	7·4

[a] Taken from ref. 2.

The values of total energy, obtained by MINDO, are considerably lower than those furnished by CNDO/2. This well known difference is due to the fact that the one-centre repulsion integrals and the one-electron resonance integrals are estimated by SAO (split-atomic-orbital) rather than by values derived from atomic spectra.

The MINDO method yields also values for the total *bonding* energy (defined as the difference between *total* energy and the sum of the energies of the individual atoms in the system). Again, the division between class *a* and *b* is manifest; tautomer (II) is more stable than (I), and (III) is slightly more stable than (IV).

(3) Both methods predict that the dipole moment of tautomers (I) and (III) should be larger than the moment of (II) and (IV); the last two compounds should possess about the same moment (Table 2). The result for tautomer (IV), as calculated by the CNDO/2 method ($\mu_D = 4{\cdot}19$ D) is in good agreement with the value 4·3 D found by DeVoe and Tinoco[10] for 9-methylpurine. In general, the values of dipole moments calculated by the CNDO/2 method for the four tautomers agree better with the experimental results, at least in the series of 8-phenylpurines.[2] However, a phenyl group may behave differently when attached to a π-deficient (class *a*) or a π-excessive ring (class *b*) so that the good agreement between experiment and the values calculated by the CNDO/2 method may be accidental.

The angles of the dipole moment, obtained by either method, show reasonably good agreement.

(4) The ionization potential of purine, measured by the electron bombardment method, is 9·7 eV.[11] This method always gives higher values than 'adiabatic' procedures, such as photoelectron spectroscopy.[12] Dewar *et al.*[13] found an excellent correlation between ionization potentials obtained experimentally by photoelectron methods and the values calculated by MINDO, assuming the validity of Koopmans' theorem.[14] The value found experimentally for purine[11] is therefore in good correlation with the average value for all four tautomers (9·35 eV) calculated by the MINDO method (see the values of HOMO in Table 1). The average value, obtained by CNDO/2, is higher (11·4 eV).

(5) The charge distribution in the ground state, obtained by the two methods, shows qualitative and quantitative differences. The numerical values calculated by MINDO are always higher than those obtained from CNDO/2, a fact that was explained in the original paper on the MINDO method.[3] The following points should be noted. (*a*) Hydrogen atoms attached to carbon atoms are always negatively charged while in CNDO/2 no uniform trend can be noted. Although it has been suggested[15] that the polarization of the carbon–hydrogen bond may exist as $\overset{\delta+}{\mathrm{C}}$–$\overset{\delta-}{\mathrm{H}}$, the results obtained here by the MINDO method do not substantiate or contradict this hypothesis. The geometry for our calculation was only tentative and small differences in it may cause reversal of the above observed phenomena.

TABLE 2

Dipole moments of the tautomers of purine

	CNDO [a]		MINDO	
Tautomer	μ_{total}	Angle (°) [b]	μ_{total}	Angle (°) [b]
1-NH (I)	6·75	241	5·30	243
3-NH (II)	4·19	320	3·21	295
7-NH (III)	6·08	150	5·36	150
9-NH (IV)	4·19	45	3·37	47

[a] Taken from ref. 2. [b] Counterclockwise from C(4)—C(5) axis.

(*b*) In both methods, a hydrogen atom attached to nitrogen bears a positive charge, in accord with the fact that nitrogen is more electronegative than hydrogen (Figure).

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[7] L. B. Townsend and R. K. Robins, *J. Heterocyclic Chem.*, 1966, **3**, 241.

[8] A. Bendich, P. J. Russell, and J. J. Fox, *J. Amer. Chem. Soc.*, 1954, **76**, 6073.

[9] A. G. Beaman and R. K. Robins, *J. Org. Chem.*, 1963, **28**, 2310.

[10] H. DeVoe and I. Tinoco, *J. Mol. Biol.*, 1962, **4**, 500.

[11] C. Lifschitz, E. D. Bergmann, and B. Pullman, *Tetrahedron Letters*, 1967, 4583.

[12] M. J. S. Dewar, 'The Molecular Orbital Theory of Organic Chemistry,' McGraw-Hill, New York, 1969, p. 273.

[13] M. J. S. Dewar, E. Haselbach, and S. D. Worley, *Proc. Roy. Soc.*, 1970, *A*, **315**, 431.

[14] T. Koopmans, *Physica*, 1933, **1**, 104.

[15] P. M. E. Lewis and R. Robinson, *Tetrahedron Letters*, 1970, 2783.

(*c*) Calculation of the total charge on the nitrogen atoms by the two methods gives different results: in CNDO/2 the most ' basic ' (negative) atom in compounds (I)—(III) is N(9), while in compound (IV) it is the nitrogen atom at position 7. According to MINDO calculations, in compounds (I), (II), and (IV) the most negative nitrogen atom is the one bearing the proton, while in (III) it is N(3) (see Figure).

(*d*) Among the three positions available for substitution in purine [C(6), C(2), and C(8)], the highest positive charge (*i.e.*, the greatest electrophilicity), as judged from MINDO, is found at C(2) for tautomers (I), (II), and (IV), while in (III) C(2) and C(8) have practically identical charges. On the other hand, CNDO/2 calculations place the largest positive charge at C(8) for tautomers (II), (III), and (IV), while in (I) no difference is observed between positions 2 and 8. Both methods, however, assign the smallest positive charge to C(6) (see Figure).

(*e*) MINDO predicts C(5) to bear a positive charge in class *a* and a negative one in class *b*. In contrast, CNDO/2 predicts a positive charge for C(5) in both classes.

According to the MO theory developed by Fukui *et al.*,[16] the highest-occupied and the lowest-empty molecular orbitals (HOMO and LEMO) are important in determining the pathway of the chemical reaction (frontier theory). It is noteworthy that the CNDO/2 and the MINDO method give different results regarding the type of these orbitals. Thus in the CNDO/2 formalism (see Table 3) all these orbitals are of a π type; in the MINDO algorithm LEMO is of a σ symmetry while HOMO is divided into both σ and π types, contrary to the division according to chemical structures (class *a* and *b*): The 1- and 7-NH-tautomers have a σ symmetry of its highest-occupied MO while the 3- and 9-NH-isomers are of a π type. It would be impossible to deduce which of the methods gives the ' correct ' answer. Information regarding orbital structure has recently become available through photoelectron spectroscopy, but not yet for such complex compounds as purine tautomers.

TABLE 3

Orbital symmetries for the purine tautomers

	CNDO/2		MINDO	
Tautomer	HOMO	LEMO	HOMO	LEMO
1-NH (I)	π	π	σ	σ
3-NH (II)	π	π	π	σ
7-NH (III)	π	π	σ	σ
9-NH (IV)	π	π	π	σ

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