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Relatio

Amine-Imine Tautomerism in Adenines*

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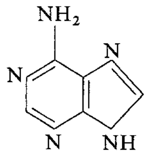
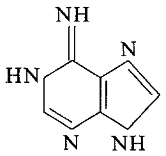
CNDO/2 calculations predict that while the amine form of adenine should be the most stable one for the N(9)H, N(7)H and N(3)H tautomers of this substance, the imine form should on the contrary be the most stable for the N(1)H tautomer. The prediction is verified by experiment.

Adenine is generally represented in the amine form, I, a conclusion based on a large number of physicochemical studies by a variety of methods [1]. The tautomerization of adenine to the imine form, II, has nevertheless been postulated to be of possible significance in spontaneous mutagenesis as the imine form is no longer able to couple with thymine but may, on the other hand, form a hydrogen-bonded pair with cytosine [2]. Calculations carried out for these two forms (in their N(9)H configuration i.e. in the configuration in which the imidazole ring proton is fixed at N_9), by a combination of a refined Hückel procedure for the π electrons and a refined Del-Re procedure for the σ electrons, have confirmed the greater stability of the amine form [3]. This result has presently been reconfirmed with the use of the CNDO/2 method [4] which treats simultaneously all the valence electrons. As can be seen in Table 1, the amine form is calculated to be about 27 Kcal/mole more stable the imine one (the imine form, II, is being designated in this table as the N(1)H–N(9)H one, a notation which specifies the position of the two ring protons). A very similar result is obtained if the N(7)H tautomer of the amine form of adenine, III, and the corresponding N(1)H–N(7)H tautomer of the imine form, IV, are being considered.



I



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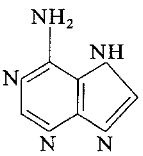

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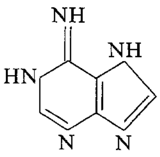

IV

The problem may nevertheless be raised whether the greater overall stability of the amine form is a general property of all possible pairs of amine-imine

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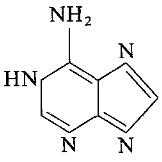
tautomers of adenine or whether a pair may be found in which the imine form would be the most stable one, Thus, it may in fact be observed that following certainly a very approximate but nevertheless significant way of reasoning, frequently used with success in resonance theory [5], the sum of the bond energies being practically nearly the same in a pair of amine-imine tautomers, the greater stability of the amine form of the N(9)H and N(7)H tautomers may probably be attributed in a large extent to the great π-electron delocalization energy of this form due to the presence of a Kékulé-type resonance in their pyrimidine ring. Such resonance will, however, no longer be present in the amine forms of the two remaining possible tautomers, the N(1)H and the N(3)H ones, V and VI, in which the π-electrons delocalization energies may therefore be of a comparable order of magnitude in the amine and the corresponding imine forms, in which case no *a priori* guess may then be easily made as to the preminence of one or the other form. The imine forms corresponding to the N(1)H adenine, V, are II and IV, those corresponding to the N(3)H adenine, VI, are VII and VIII. It may be worthwhile stressing that in the two amine forms no hydrogen is present at N_7 or N_9 of the imidazole ring. This hydrogen has moved over to N_1 or N_3. On the contrary, a hydrogen is attached to N_9 or the N_7 in the imine forms.



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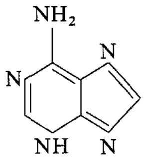

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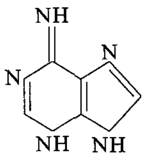

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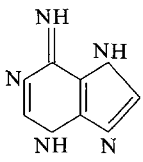


VIII

Calculations for all these forms have been performed within the framework of the CNDO/2 method, as applied previously in this laboratory to a large series of biological purines [6–9] including the corresponding forms of purine itself in relation to a number of recent experimental studies on such tautomers. The results are summarized in the Table, which includes beside the total molecular energies, some other useful physicochemical characteristics of the molecules studied.

A glance at the table indicates then a positive answer to our problem. Thus, it shows that while the amine form of the N(3)H tautomer of adenine, VI, is predicted to be more stable than the associated imine forms VII or VIII, the

Table. *Electronic properties of adenines*

No.	Tautomer	Dipole moment (Debyes)	Highest occupied MO (eV)	Lowest empty MO (eV)	Total energy (Kcal/mole)
I	Amine, N(9)H	3.0	−10.1	3.8	−61226
III	Amine, N(7)H	7.4	−10.7	2.9	−61224
VI	Amine, N(3)H	4.2	−10.7	2.4	−61196
V	Amine, N(1)H	8.9	−10.7	2.7	−61190
II	Imine, N(1)H–N(9)H	5.9	− 9.2	3.0	−61199
IV	Imine, N(1)H–N(7)H	3.8	− 9.5	3.1	−61200
VII	Imine, N(3)H–N(9)H	10.6	− 9.4	3.4	−61187
VIII	Imine, N(3)H–N(7)H	3.2	− 9.5	3.3	−61193

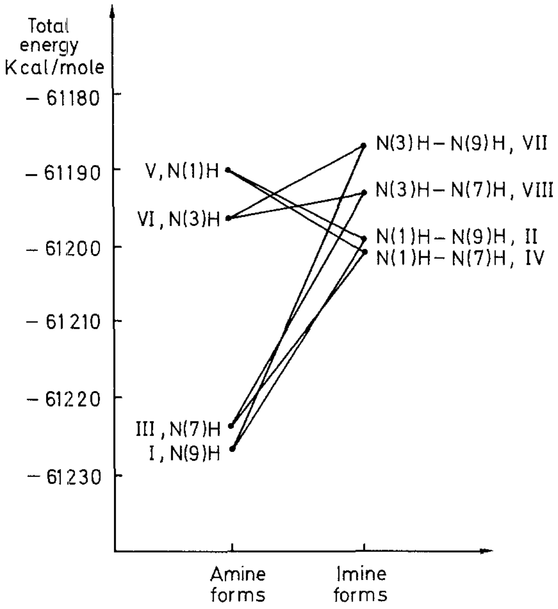
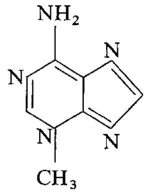


Fig. 1. Relative stabilities of the associated amine and imine forms of adenine tautomers

reverse is true for the two corresponding forms of the N(1)H tautomer. The imine forms of this tautomer, II or IV, are predicted to be more stable than the associated amine form V. The situation may be traced back to the fact that while the amine form of the N(1)H tautomer is *the least stable* of the amine forms of the four tautomers, its imine forms are *the most stable* among the imine forms, sufficiently stable in fact to lie below the corresponding amine form. The overall relationship between the different tautomeric forms is illustrated schematically in Fig. 1.

Now, it is particularly remarkable that this delicate theoretical result is confirmed by experiment. Thus, chemical evidence indicates that while 3-methyladenine exists in the amine form IX [10, 11], derived from VI, 1-methyladenine exists, on the contrary, in the imine form X [12], derived from II. In fact, our calculations do not preclude the existence of X as a derivative of IV rather than II. The determination of the dipole moment of this substance should be able to solve this detail, the difference between the N(7)H and the N(9)H forms of purines being generally quite appreciable from the viewpoint of their dipole moments and representing therefore a very useful tool for distinguishing between such otherwise very close tautomers [7, 8].



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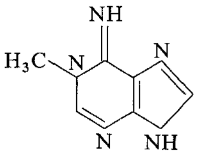

X

It certainly is a strong argument in favour of the use of the CNDO method in problems of tautomerism, that it is able to account so satisfactorily for the state of affairs described here. It may be added that in order to obtain information about other properties of the tautomers, for which the CNDO/2 method in its usual form is not particularly suitable e.g. transition energies, the compounds considered here have also been studied by the semi-empirical SCF method. The results obtained ate quite satisfactory [9].

References

1. Pullman, B., and A. Pullman: Quantum biochemistry. New York: Wiley-Intersciences 1963.
2. Pullman, A.: In: Electronic aspects of biochemistry, B. Pullman Ed., p. 135. New York: Academic Press 1964.
3. Berthod, H., and A. Pullman: J. Chim. physique **62**, 942 (1965).
4. Pople, J. A., and G. A. Segal: J. chem. Physics **43 S**, 136 (1965).
5. Pullman, B., and A. Pullman: Les théories electronique de la chimie organique. Paris: Masson 1952.
6. Giessner-Prettre, C., and A. Pullman: Theoret. chim. Acta (Berl.) **9**, 279 (1968).
7. Pullman, B., H. Berthod, and J. Langlet: C. R. Acad. Sci. (Paris) **266**, 1063 (1968).
8. —, —, E, D. Bergmann, F. Bergmann, Z. Neiman, and H. Weiler-Feilchenfeld: C. R. Acad. Sci. (Paris) **267**, 1461 (1968).
9. Pullman, B.: In: Quantum aspects of heterocyclic compounds in chemistry and biochemistry. Jerusalem: Israel Academy of Sciences and Humanities 1969.
10. Jones, J. W., and R. K. Robins: J. Amer. chem. Soc. **84**, 1914 (1962).
11. Pal, B. C., and C. A. Horton: J. chem. Soc. (London) **1964**, 400.
12. Brookes, P., and P. D. Lawley: J. chem. Soc. (London) **1960**, 539.

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