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On the Crystal Structure of Purine*

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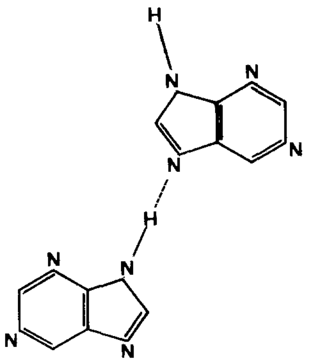
In the crystal structure of purine the molecules are linked together by single hydrogen bonds. The tautomer present has a proton linked to N$_{(7)}$ and not to N$_{(9)}$. Calculations indicate that the two tautomers have equal stabilities but that the N$_{(7)}$H tautomer has a dipole moment much greater than the N$_{(9)}$H one. The driving force for the presence of the N$_{(7)}$H tautomer in the purine crystal is the greater electrostatic interaction energy obtained with this tautomer with respect to the one which would be obtained with the N$_{(9)}$H one.

Der Purinkristall besteht aus der tautomeren Form des Moleküls, bei dem ein Proton am N$_{(7)}$ und nicht am N$_{(9)}$ gebunden ist. Die Rechnungen ergeben für beide tautomere Formen dieselbe Stabilität, aber das Dipolmoment der Form N$_{(7)}$H ist wesentlich größer, als das der tautomeren Form N$_{(9)}$H. Auch aus dem höheren Wert der elektrostatischen Wechselwirkungsenergie der Form N$_{(7)}$H kann auf die Anwesenheit dieser Form im Kristall geschlossen werden.

Le cristal de la purine contient la forme tautomère de la molécule dans laquelle un proton est fixé sur N$_{(7)}$ et non sur N$_{(9)}$. Les calculs montrent que les deux formes tautomères ont la même stabilité mais que le moment dipolaire du tautomère N$_{(7)}$H est nettement plus grand que celui du tautomère N$_{(9)}$H. La présence du tautomère N$_{(7)}$H dans le cristal peut alors être attribuée à la plus grande valeur de l'énergie d'interaction électrostatique par rapport à celle qui serait obtenue avec le tautomère N$_{(9)}$H.

The crystal structure of purine [9] involves long chains of molecules, linked together by single hydrogen bonds, in the way illustrated in I for a dimer. The surprising feature of this configuration is that *a proton is attached to* N$_{(7)}$ *rather than to* N$_{(9)}$ *of the purine skeleton*, while in most biological derivatives of purines including the nucleosides and nucleotides the substituent is fixed at N$_{(9)}$.

II



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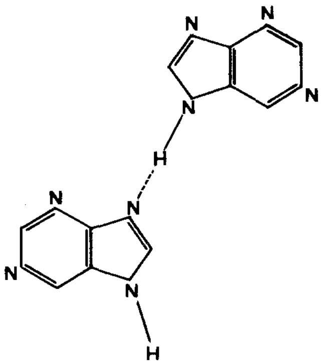

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Quantum-mechanical calculations on the relative stabilities of the two tautomeric purines, one with a proton attached to $N_{(7)}$ and the other with a proton attached to $N_{(9)}$, indicate practically undistinguishable stabilities. Thus, Hückel-type calculations of the delocalization energies of the π electrons yield practically identical results for the two tautomers [7] and so do also similar more recent calculations carried out in our laboratory by a semi-empirical self-consistent field procedure. Similar results are also obtained by extended Hückel calculations involving all valence electrons (unpublished results to be described separately).

On the other hand these different calculations indicate a difference in one of the electronic characteristics of the tautomers which may possibly account for the presence of the $N_{(7)}H$ tautomer rather than the $N_{(9)}H$ one in the purine crystal. This characteristic is the electronic distribution in the two forms, illustrated in Fig. 1 and 2. The two distributions are sufficiently different to lead to a prediction that *the dipole moment of the two forms should be appreciably different, too.* In a refined Hückel approximation (following Berthod and Pullman [2]) the predicted dipole moment is 4,1 D for the $N_{(9)}H$ form and 6,3 D for the $N_{(7)}H$ form. In the SCF approximation (following Berthod, Giessner and Pullman [3]) the two dipole moments are respectively 3,6 D and 5,5 D. The moment predicted for the $N_{(9)}H$ form is in satisfactory agreement with the moments known for related compounds: 4,3 D in 9-methylpurine [6], 3,8 D in 6,9-dimethylpurine [1]. The dipole moment of the $N_{(7)}H$ form may therefore be expected to be appreciably greater than that of the $N_{(9)}H$ form.

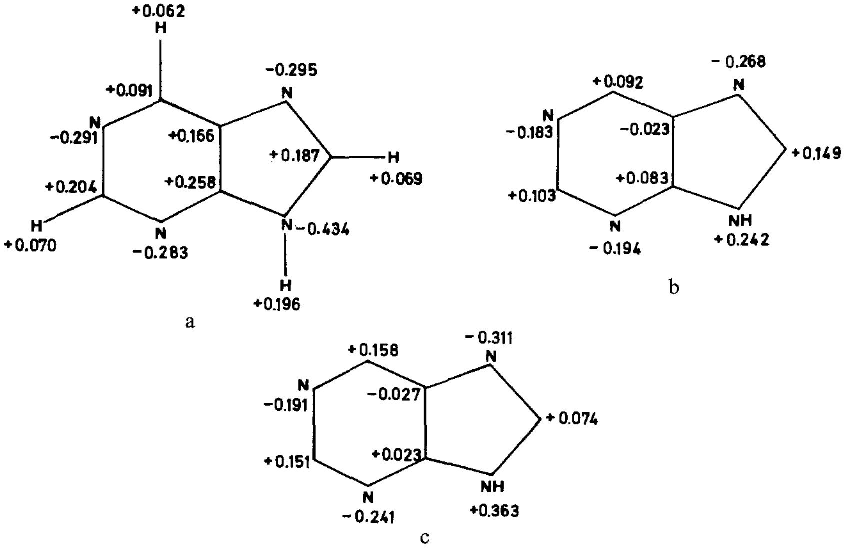

Fig. 1a—c. Net electronic charges in the $N_{(9)}H$ tautomer of purine. a σ-electrons; b π-electrons (Hückel approximation); c π-electrons (Pariser-Parr-Pople approximation)

In these circumstances it appears probable that the Van der Waals-London forces (and in this case their electrostatic component in particular), which appear to be responsible for the major part of the interaction energies in hydrogen bonded structures, whether in crystals or in solution [4], should also be greater in the crystals involving the $N_{(7)}H$ tautomer. It is expected on the basis of previous experience that this conclusion should hold even when the calculations of the interaction energies are carried out in the "monopole" rather than in the "dipole" approximation.

In order to check this hypothesis calculations have been performed on the Van der Waals-London interaction energies for the dimer I and for the hypothetical dimer II which differs from the dimer I only in the shift of the proton from $N_{(7)}$ to $N_{(9)}$ of the bases involved. The results of the calculations, carried out in different approximations (for their detailed description see [5]) are indicated in the table. It is believed that they are listed in the order of increasing refinement [the charges utilized for these calculations are those of a) and b) of Figs. 1 and 2; very similar results are obtained with the charges a) and c) of these figures].

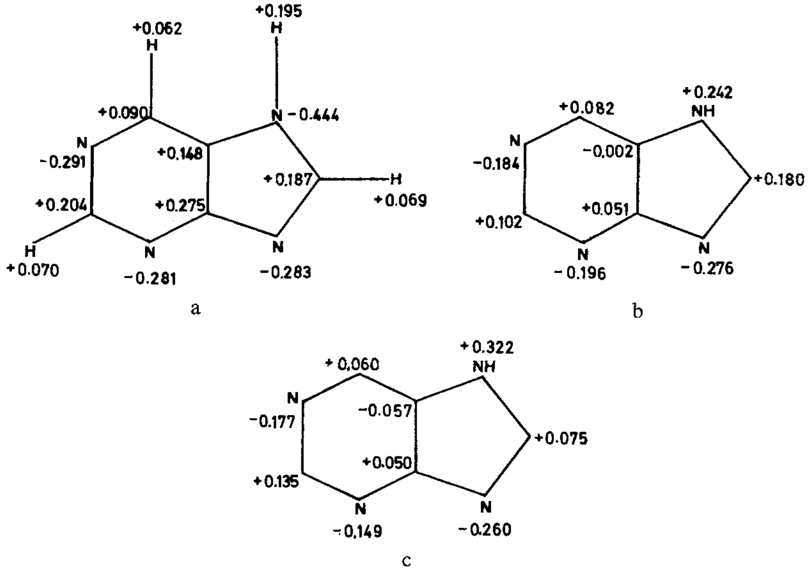

Fig. 2 a—c. Net electronic charges in the $N_{(7)}H$ tautomer of purine. a σ-electrons; b π-electrons (Hückel approximation); c π-electrons (Pariser-Parr-Pople approximation)

The results of the table indicate, as expected, that *the intermolecular interaction energies are significantly greater in the dimer I than in the dimer II*. It may certainly be extrapolated that the same situation would prevail in higher polymers of the two kinds.

On the other hand, in the crystal the purines, besides being hydrogen bonded, are also packed on top of one another (stacked). It may be estimated however, that the part of the interaction energy which corresponds to this aspect of the crystal structure would not be very different for the two possible configurations. The predominant component in the stacking type of interaction is the dispersion energy [4] and this may be expected to be similar for both configurations.

It appears therefore plausible to admit that the driving force for the occurence of the $N_{(7)}H$ tautomer of purine in the crystal of this substance resides in the relatively high dipole moment of this tautomer, (higher than the dipole moment of the $N_{(9)}H$ tautomer) and in the corresponding aspects of the electronic charge distribution, which lead to greater electrostatic interaction energy than would have been obtained with the $N_{(9)}H$ tautomers.

Table. *Interaction energies in purine dimers (Kcal/mole)*

Compounds	Approximation	Components				Total
		Electrostatic	Inductive	Dispersion	Repulsion	
Dimer I (observed)	Dipole-induced dipole	−1.12	−0.30	−0.39		−1.81
	Monopole-induced dipole	−6.84	−0.73	−0.39		−7.96
	Monopole-bond polarisabilities	−6.84	−1.36	−1.32		−9.52
	Monopole-bond polarisabilities + repulsion	−6.84	−1.36	−1.32	+2.42	−7.10
Dimer II (hypothetical)	Dipole-induced dipole	−0.21	−0.12	−0.37		−0.69
	Monopole-induced dipole	−5.68	−0.43	−0.37		−6.48
	Monopole-bond polarisabilities	−5.68	−1.03	−1.34		−8.05
	Monopole-bond polarisabilities + repulsion	−5.68	−1.03	−1.34	+4.37	−3.68

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