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ELECTRONIC STRUCTURE OF PURINE TAUTOMERS

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Abstract—The electronic properties of the four tautomers of purine have been studied theoretically by the PPP-DPB and by the CNDO/2 methods. The dipole moments and UV absorption spectra of simple derivatives of the different purine forms have been determined experimentally. On the whole, they are in good agreement with the predictions. In particular the N(1)H and N(7)H tautomers have moments higher by several Debyes than the N(3)H and N(9)H tautomers; the electronic spectra show a bathochromic shift from the N(9)H to the N(7)H to the N(1)H to the N(3)H form, in this order.

INTRODUCTION

THE molecule of purine is generally represented in the form in which an H atom is attached to the N_9 nitrogen; this form will be called the N(9)H tautomer. However, other tautomeric forms may be considered in which the hydrogen would be attached to the other nitrogens of the molecule, yielding the N(7)H, N(3)H and N(1)H tautomers (Fig. 1). In fact, although the majority of biological purines exist essentially as derivatives of the N(9)H tautomer, the crystal of purine itself, which consists of long chains of these molecules linked by single H-bonds, involves the N(7)H tautomer,[1] a situation which has been studied and accounted for theoretically by Pullman *et al.*[2] Moreover, unambiguous Me derivatives of the four tautomeric forms (with the Me replacing the N-bound hydrogen) have been prepared: the derivatives of the N(7)H and N(9)H tautomers by Bendich *et al.* already in 1954[3] and those of the N(1)H and N(3)H tautomers in 1962 and 1966, respectively, by Townsend and Robins.[4,5]

The present paper deals with the theoretical investigation, by quantum-mechanical methods, of the principal electronic characteristics of the four tautomers of purine and compares the results with a certain number of physicochemical properties determined experimentally in relatively simple derivatives of these compounds.

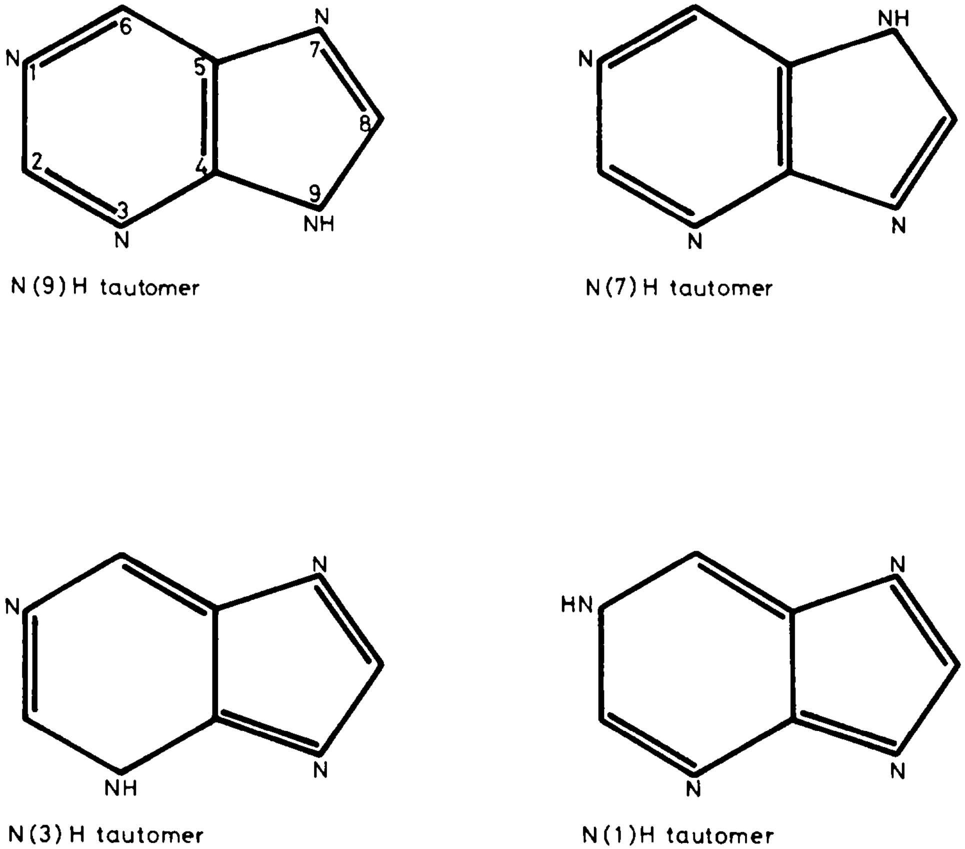
THEORY

The electronic structure of the four fundamental tautomers of purine has been studied by two quantum-mechanical procedures:

1. A combination of a Pariser–Parr–Pople semi-empirical SCFCI treatment for the π-electrons with a Del Re-Berthod-Pullman type procedure for the σ-electrons, already described in detail[6] and designated here as the PPP-DBP method.

2. An all-valence electrons CNDO/2 treatment[7] applied previously to the purine and pyrimidine bases of the nucleic acids.[8]

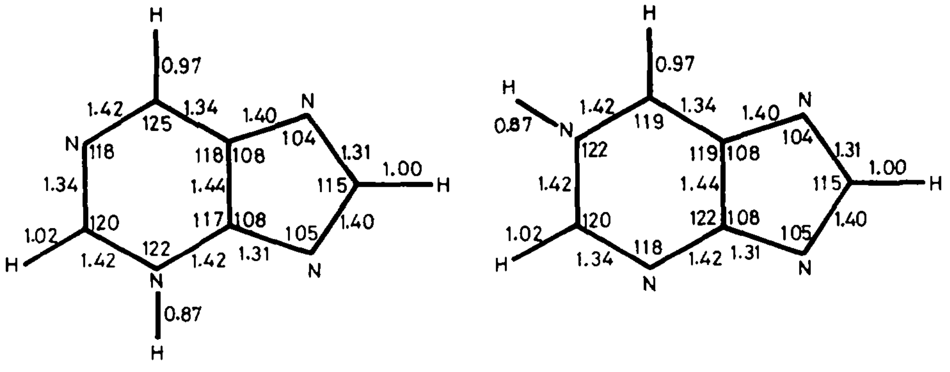
As is well known, the results of calculations carried out by these methods depend to some extent on the geometries adopted.[9] The only directly available geometry is that of the N(7)H tautomer.[1] That of the N(9)H may be deduced relatively easily;[9] because of the particular importance of this most common tautomer, the calculations have been carried out for two geometries: (1) one deduced from that of the N(7)H tautomer[1] by inverting the lengths of the 7–8 and 8–9 bonds, those of the 5–7 and 4–9 bonds and the corresponding angles (inverted Watson's geometry) and (2) one established by Spencer[10] on the basis of a general study of purine derivatives (Spencer's geometry). The geometries of the N(3)H and N(1)H tautomers are more difficult to ascertain; the guiding line in this respect was the observation that, because of the possibility of writing only one Kékulé-type structure for these tautomers, the "resonance" of their mobile electrons must be more restricted than in the N(9)H and N(7)H tautomers, and that, therefore, the bond localization should be more pronounced in them; it is obvious, however, that the geometries assumed for these particular tautomers are subject to caution. The geometries adopted in the calculations are represented in Fig. 2.



N(9)H tautomer N(7)H tautomer

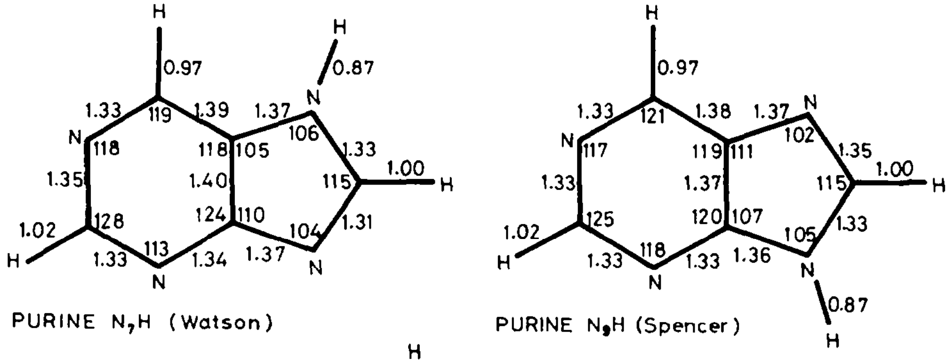
N(3)H tautomer N(1)H tautomer

FIG. 1. Tautomeric forms of purine



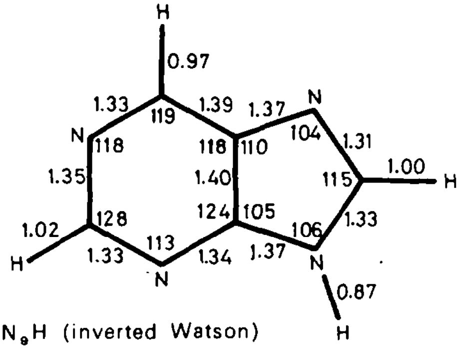
PURINE N_3H

PURINE N_1H



PURINE N_7H (Watson)

PURINE N_9H (Spencer)



PURINE N_9H (inverted Watson)

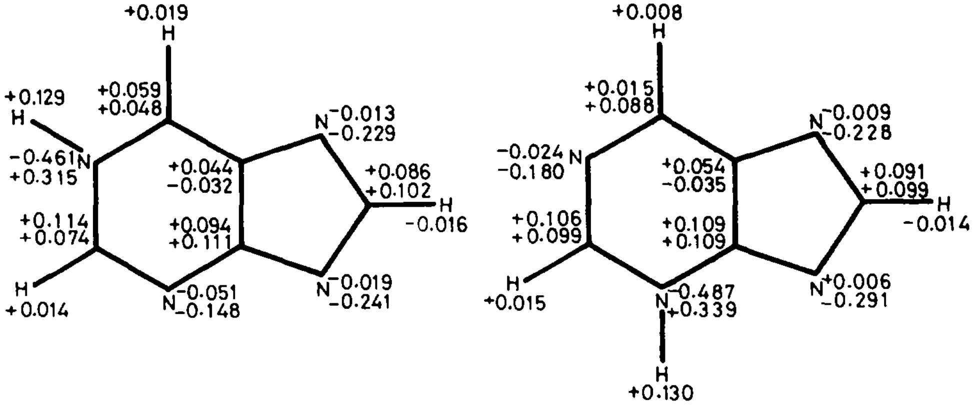
FIG. 2. The adopted geometries.

The principal results of the computations, summarized in Tables 1 and 2 and in Fig. 3, are the following:

(1) *Dipole moments* (Table 1)

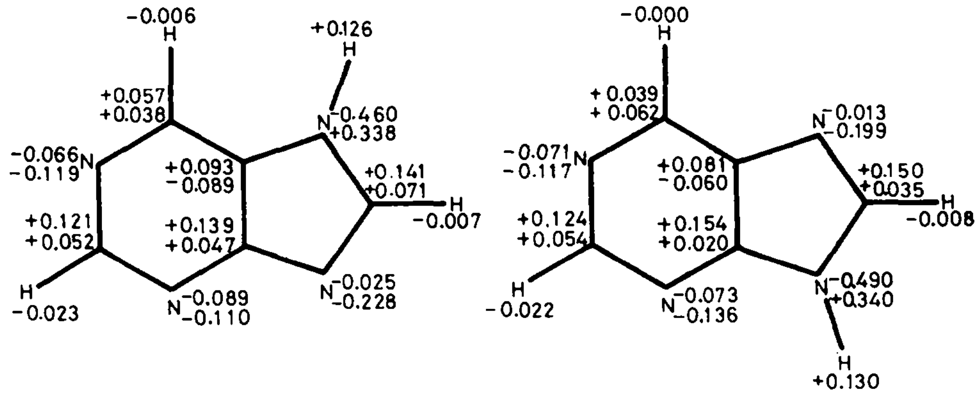
The values of the total dipole moments predicted by the two procedures are similar. Both procedures indicate that the tautomers may be divided, from that point of view, into two groups: tautomers N(1)H and N(7)H which should possess relatively high dipole moments, of the order of 5–7 D, and tautomers N(3)H and N(9) which should possess significantly smaller dipole moments, of the order of 3–4 D.

From the previously known[11] value of 4·3 D for the dipole moment of 9-methylpurine it may be assumed that the CNDO results are somewhat more satisfactory on the absolute scale. Table 1 indicates also the different components which make up the total moments and the angle of the dipole moment with the C_4—C_5 bond; the constancy of this angle in the two procedures is worth stressing. Fig. 3 indicates the distribution of the σ and π charges obtained by the CNDO method; the distribution obtained by the PPP-DBP procedure is analogous. For the same reason only one diagram, corresponding to results obtained with the inverted Watson geometry, is given for the N(9)H tautomer.



N(1)H tautomer of purine

N(3)H tautomer of purine



N(7)H tautomer of purine

N(9)H tautomer of purine

FIG. 3. Net electronic charges in purine tautomers evaluated by the CNDO/2 method.
upper number: σ charges
lower number: π charges

(2) *Highest occupied* (*HOMO*) *and lowest empty* (*LEMO*) *molecular orbitals* (Table 2)

Both methods predict that the four tautomers should have remarkably, and somewhat surprisingly, similar electron donating properties (ionization potentials). As may be judged from the experimentally known ionization potential of the N(9)H tautomer (9·7 eV[12]), the PPP-DBP method somewhat underestimates and the CNDO method appreciably overestimates the values of the ionization potentials (the last situation is common to CNDO calculations in general).

TABLE 1. DIPOLE MOMENTS (DEBYE UNITS)

Purine tautomer	PPP-DBP method				CNDO method				
	μ_σ	μ_π	μ_{total}	$\measuredangle^a$	μ_σ	μ_π	μ_{sp}^b	μ_{total}	$\measuredangle^a$
N(1)H	1·44	4·21	5·38	241°	2·11	5·98	3·02	6·75	241°
N(3)H	0·29	3·24	3·37	320°	1·90	4·72	1·68	4·19	320°
N(7)H	1·82	3·79	5·50	153°	1·20	3·94	3·38	6·08	150°
N(9)H (inverted Watson)	0·44	2·86	3·27	48°	1·58	3·29	2·00	3·75	49°
N(9)H (Spencer)	0·64	3·05	3·68	46°	1·43	3·60	2·02	4·19	45°

[a] Angle of the dipole with the C_4-C_5 axis (counted counterclockwise).

[b] Hybridization moment.

As concerns the electron accepting properties (electron affinities) of the tautomers both methods predict that these should be greater for the N(1)H and N(3)H tautomers than for the N(7)H and N(9)H ones. These properties are probably also overestimated in the CNDO procedure.

TABLE 2. SOME ENERGY CHARACTERISTICS (IN EV)

Purine tautomer	PPP CI method						CNDO method			
	HOMO	LEMO	E_π	ΔE_1		λ_{max}	HOMO	LEMO	$E_{electr.}$	E_{total}
				eV	mμ	mμ				
N(1)H	− 9·0	0·5	− 373·2	4·50	276	275	− 11·0	1·9	− 7859·9	− 2310·2
N(3)H	− 9·2	0·3	− 376·1	4·45	279	277	− 11·3	1·7	− 7871·1	− 2310·4
N(7)H	− 9·1	1·1	− 381·8	4·73	262	266·5	− 11·9	3·0	− 7983·2	− 2312·1
N(9)H (inverted Watson)	− 9·0	1·2	− 382·2	4·81	258	264	− 11·5	3·2	− 7982·9	− 2312·2
N(9)H (Spencer)	− 8·9	1·1	− 382·5	4·93	251		− 11·3	3·2	− 7996·0	− 2311·9

(3) *Electronic and total energy* (Table 2)

In this respect, the CNDO results are *a priori* particularly significant. They indicate that from the point of view of both the electronic energy and the total energy (electronic energy + nuclear repulsion) the N(7)H and the N(9)H tautomers should be more stable than the N(1)H or N(3)H ones. According to the values of the total energies this excess of stability should be of the order 2 eV or 46 kcal/mole.

(4) *The longest wavelength of absorption* (λ_{max}) (Table 2)

In this respect the PPPCI results on the π-electron system should *a priori* be considered. They enable one to predict that the N(1)H and N(3)H tautomers should be bathochromic by about 10 nm with respect to the N(7)H and N(9)H ones. The comparison of the theoretical evaluation of the energy of the first singlet transition (E_1) with the experimental values of λ_{max} in the methylated derivatives of the tautomers[3-5] indicates a satisfactory agreement both in the ordering of all four tautomers and in the absolute values for most of them (the N(9)H tautomer showing a slight deviation).

EXPERIMENTAL RESULTS AND DISCUSSION

As already reported in a preliminary note,[13] measurements of the dipole moments and electronic spectra of suitably substituted purines were carried out in order to confirm these calculations. It is impossible to study the different tautomers separately because their solution might contain equilibria mixtures of the various forms; therefore, each tautomer was "stabilized" by methylation of the purine at the corresponding nitrogen atom, and the isomeric 1-, 3-, 7- and 9-methylpurine were studied instead of the N(1)H, N(3)H, N(7)H and N(9)H tautomers; the introduction of a methyl group was expected to have only a small influence on the dipole moments and absorption bands of the molecules.

A. *Dipole moments*

The different N-methylpurines are practically insoluble in the non-polar solvents used for dipole moment determinations. Their solubility was increased by the introduction of additional substituents into the molecules, viz. a phenyl group at the 8 position, or an alkylthio group at the 6 position, or both of them together. While substitution of purine by a phenyl group is not expected to influence appreciably the value of the electric moment, the same cannot be true for the introduction of an alkylthio group; moreover, the influence of the alkylthio substituent will vary in the different methylpurines because the moments of the tautomers of purine are expected to have different directions. It was assumed that these perturbations would be small enough not to affect the large predicted differences between the moments of the isomers. Because of difficulties in the synthesis of some N-Me derivatives no single series containing all four isomers was available. Nevertheless, the rather good agreement between the experimental data (Table 3) and the predicted values (Table 1) shows the above assumption to be justified.

In the 8-phenyl series, which should have the moments closest to the values of the purine tautomers, the 1-Me compound has a high moment, the 3- and 9-Me derivatives low moments, as expected from the theoretical calculations. In the 6-methylthio series it is interesting to see that the 7-Me compound has a moment larger by 2·5 D than the 9-Me one, but the moment of the 3-Me derivative is higher than expected. In the 6-methylthio-8-phenyl series the moment of the 1-Me derivative is larger than those of 3- and 9-methylpurine, in agreement with prediction (Table 1). In all three series, the unmethylated compound has a moment somewhat higher than that of the 9-Me derivative. This indicates that the unmethylated purines are not purely in the N(9)H form, as is usually assumed, but may consist of a mixture of tautomers.

The direction of the moment of the unmethylated purine was determined by vector addition from the experimental moments of 6-chloropurine (5·34 D) and 2,6-dichloro-purine (5·62 D)[14] and the calculated moment of purine (4·20 D) assumed to be in its N(9)H form (the moment of unsubstituted purine has not been determined experimentally because of its low solubility, but the theoretical value is in good agreement with the experimental moment of 4·3 D found for 9-methylpurine). An angle of 52° between the $C_4 \rightarrow C_5$ axis of the molecule and the direction of the purine moment fits these experimental data best (calculated for 6-chloro- and 2,6-dichloro-purine, 5·33 D and 5·58 D, respectively). This value is in good agreement with the angle of 45–49°, predicted for the N(9)H form.

TABLE 3. EXPERIMENTAL DATA ON DIPOLE MOMENTS
(in dioxane, 30°)

Compound	α'	β'	$P_{2\infty}$	RM_{calc}	μ(D)
8-Phenylpurine	34·06	− ·61	538·09	52·87	4·91 ± 0·10
1-Methyl-8-phenylpurine	67·50	− ·85	1025·48	57·53	6·94 ± 0·10
3-Methyl-8-phenylpurine	27·73	− ·65	448·02	57·53	4·40 ± 0·05
9-Methyl-8-phenylpurine	29·21	− ·72	468·77	57·53	4·52 ± 0·05
6-Methylthiopurine	21·32	− ·73	340·01	41·96	3·85 ± 0·10
3-Methyl-6-methylthiopurine	38·84	− ·71	601·24	46·55	5·25 ± 0·10
7-Methyl-6-methylthiopurine	44·29	− ·72	680·06	46·55	5·61 ± 0·10
9-Methyl-6-methylthiopurine	13·18	− ·48	228·23	46·55	3·01 ± 0·05
6-Decylthio-8-phenylpurine*	28·70	− ·22	516·79	105·95	4·52 ± 0·05*
1-Methyl-6-methylthio-8-phenylpurine	60·16	− 1·04	925·20	69·66	6·52 ± 0·10
3-Methyl-6-methylthio-8-phenylpurine	34·90	− ·89	555·16	69·66	4·91 ± 0·03
9-Methyl-6-methylthio-8-phenylpurine	24·58	− ·83	409·73	69·66	4·11 ± 0·10

* In this case the non-methylated compound was the 6-decylthio, not the 6-methylthio derivative; there should be no significant difference between the moments of these two substances.

Unfortunately the experimental data are too scarce to permit similar determinations of the directions of the moments of the N(1)H, N(3)H and N(7)H tautomers. Dyer *et al.*[15] have recently reported the moments of 6-chloro-7-benzyl- and 6-chloro-9-benzyl-purine as 5·03 and 4·91 D respectively. A vectorial calculation of the above type (assuming the quantum-mechanically calculated directions of the moments of the N(7)H and N(9)H tautomers to be correct) leads to 4·8 and 5·4 D for these two compounds, respectively. The difference between these values is larger than the difference between the experimental moments and of opposite direction, indicating the necessity for more work on this problem.

B. *Electronic spectra*

As already mentioned, the absorption spectra of the four N-methylpurines have been measured previously[3–5] and the agreement between the experimental and theoretical values is good. Table 4 gives the absorption bands of the more complicated derivatives studied here. As expected, the additional substituents cause pronounced shifts in the spectrum; however, the *sequence* of increasing wavelength from 9-methyl- to 7-methyl- to 1-methyl- to 3-methyl-purine is in good agreement with the predictions.

TABLE 4. EXPERIMENTAL ABSORPTION BANDS (IN ETHANOL)

Substance	λ_{max} (ε_{mol})*		
8-Phenylpurine	233 (13200)	292sh (23500), 299 (25000), 313sh (16500)	356 (800)
1-Methyl-8-phenylpurine	219 (26000), 246 (23500)	310 (24000), 321sh (20000)	
3-Methyl-8-phenylpurine	235 (22000)	310sh (30000), 322 (38000), 336sh (30000)	
9-Methyl-8-phenylpurine	231 (13700)	284 (18400)	
6-Methylthiopurine	217 (9900), 226sh (8000)	282 (13500), 288 (13600)	
3-Methyl-6-methylthiopurine	238 (11200)	313 (17000)	
7-Methyl-6-methylthiopurine	222 (10500)	285sh (10500), 293 (13300), 301 (11100)	
9-Methyl-6-methylthiopurine	219 (12500), 227sh (11000)	284 (16800), 291 (15800)	
6-Decylthio-8-phenylpurine	250 (17000)	309sh (24000), 318 (25500), 332sh (14500)	
1-Methyl-6-methylthio-8-phenylpurine	217 (16400), 258 (23000)	339 (2000)	
3-Methyl-6-methylthio-8-phenylpurine	233 (14600), 251 (17000)	342 (33500), 358 (32000)	
9-Methyl-6-methylthio-8-phenylpurine	221sh (4000)	278 (3600)	

* λ_{max} in nm.

EXPERIMENTAL

Materials. 6-Methylthiopurine was prepared according to the Lit,[16] 3-methyl-6-methylthiopurine according to Jones and Robins,[17] 7-methyl-6-methylthiopurine according to Prasad and Robins,[18] 9-methyl-6-methylthiopurine according to Robins and Lin.[19] 8-Phenylpurine was obtained by the method described;[20] all other 8-phenylpurine derivatives are *new compounds* and their synthesis will be described elsewhere.

Electronic spectra. The UV absorption curves were determined, in analytical grade ethanol, on a Unicam SP 800 spectrophotometer.

Dipole moments. The dipole moments were determined at 30·0 ± 0·1° in spectroscopic dioxane. Most compounds, though not very soluble, allowed a normal determination of the moment, with a somewhat higher experimental error than usual (Table 3).

The dielectric constants of the solns were measured with a heterodyne beat apparatus (500 kc) and the specific volumes with a Sprengel–Oswald pycnometer; the results were computed according to Halverstadt and Kumler.[21]

In some cases the refractive indices of the solns were determined with a Bellingham and Stanley Pulfrich Refractometer. As the molar refractions thus measured did not differ markedly from those calculated from the bond refractions proposed by LeFèvre and Steel,[22] and as some of the substances were too little soluble to permit a reliable measurement of the molar refraction, the calculated values were used throughout in the computation of the dipole moments. No correction for atomic polarization was made.

REFERENCES

[1] D. G. Watson, R. M. Sweet and R. E. Marsh, *Acta Cryst.* **19**, 573 (1965).

[2] B. Pullman, H. Berthod and J. Caillet, *Theoret. Chim. Acta* **10**, 43 (1968).

[3] A. Bendich, P. J. Russell and J. J. Fox, *J. Am. Chem. Soc.* **76**, 6073 (1954).

[4] L. B. Townsend and R. K. Robins, *J. Org. Chem.* **27**, 990 (1962).

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

[6] A. Pullman and B. Pullman, *Adv. Quantum Chem.* **4**, 267 (1968).

[7] J. A. Pople and G. A. Segal, *J. Chem. Phys.* **44**, 3289 (1966).
[8] C. Giessner-Prettre and A. Pullman, *Theoret. Chim. Acta* **9**, 279 (1968).
[9] B. Pullman, H. Berthod and J. Langlet, *C. R. Acad. Sci. Paris* **266**, 1063 (1968).
[10] M. Spencer, *Acta Cryst.* **12**, 59 (1959).
[11] H. DeVoe and I. Tinoco, *J. Mol. Biol.* **4**, 500 (1962).
[12] Ch. Lifschitz, E. D. Bergmann and B. Pullman, *Tetrahedron Letters* No. 46, 4583 (1967).
[13] B. Pullman, H. Berthod, E. D. Bergmann, F. Bergmann, Z. Neimann and H. Weiler-Feilchenfeld *C. R. Acad. Sci. Paris* C: **267**, 1461 (1968).
[14] H. Weiler-Feilchenfeld and E. D. Bergmann, *Israel J. Chem.* **6**, 823 (1968).
[15] E. Dyer, R. E. Farris, C. E. Minnier and M. Tokizawa, *J. Org. Chem.* **34**, 973 (1969).
[16] G. B. Elion, E. Burgi and G. H. Hitchings, *J. Am. Chem. Soc.* **74**, 411 (1952).
[17] J. W. Jones and R. K. Robins, *Ibid.* **84**, 1914 (1962).
[18] R. N. Prasad and R. K. Robins, *Ibid.*, **79**, 6401 (1957).
[19] R. K. Robins and H. H. Lin, *Ibid.*, **79**, 490 (1957).
[20] F. Bergmann, Z. Neiman and M. Kleiner, *J. Chem. Soc.* (C), 10 (1966).
[21] I. F. Halverstadt and W. D. Kumler, *J. Am. Chem. Soc.* **64**, 2988 (1942).
[22] R. J. W. LeFèvre and K. D. Steel, *Chem. & Ind.*, 670 (1961).