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Relationes

Conformational Studies on Substituted Purines

CNDO/2 Calculations on 9-Methyl-8-Phenyl-6-Thiopurine

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CNDO/2 calculations are performed on 9-methyl-8-phenyl-6-thiopurine in order to determine the molecular equilibrium conformation. The two methyl hydrogens are found to be staggered to the ortho hydrogen on the phenyl ring, and the dihedral angle between the phenyl group and the purine system was found to be equal to 30°, in good agreement with experimental data.

The results are discussed in relation to other conformational analyses performed with the CNDO/2 method.

Key words: Purines, conformations of ~

Introduction

The structure of 9-methyl-8-phenyl-6-thiopurine has been determined by X-ray investigations [1]. UV, NMR and mass spectrometric measurements on several compounds of this type have been reported by Bergmann and coworkers [2]. Methylation at N7 or N9 in 8-phenyl purines produces a large hypsocromic shift indicating a twist of the phenyl group. In the crystal structure determination, the phenyl group is twisted 28.8° relative to the purine ring. A steric hindrance induced by aromatic substitution prevents the phenyl group from lying in the purine plane. The purpose was to examine, by means of semi-empirical methods, if the orientation found for the methyl group and the phenyl group in the crystal structure is the same as for the free molecule or if the configuration is determined by solid state effects.

Molecular Geometry

The coordinates of the atoms were calculated from ordinary bond distances and angles obtained from experimental data [1], when not explicitly mentioned in the following. The actual transformation to coordinates were performed by a special program COORD [3]. For the methyl group we adopted a "standard geometry" with the three C–H bonds equal to 1.0 Å and NCH = 109.47° (tetrahedral angles). In the crystal structure, the methyl bonds C9–H91, C9–H92 and C9–H93 were 1.03(3) Å, 0.96(3) Å, and 1.00(3) Å respectively, and the angles N9C9H91, N9C9H92 and N9C9H93 were found equal to 104(2)°, 110(2)°, and 109(2)° respectively. (See Fig. 1 for nomenclature.) The

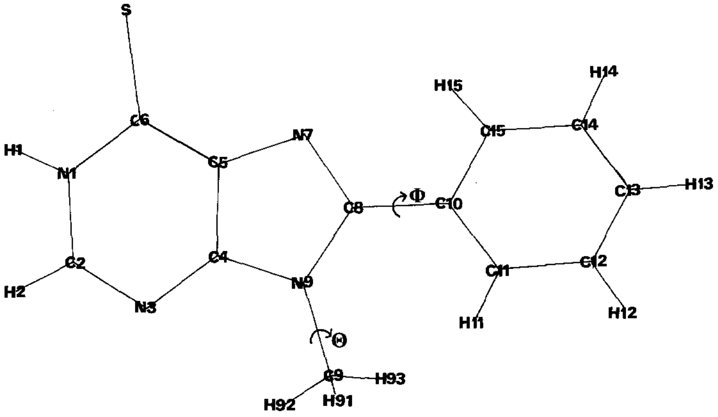

Fig. 1. The nomenclature of 9-methyl-8-phenyl-6-thiopurine

pyrimidine ring and the imidazole ring is found slightly twisted around the bond C4–C5, while in the calculation the purine system was assumed to be planar.

Calculations

One of the most applied semi-empirical methods is the complete neglect of differential overlap (CNDO) approximation introduced by Pople *et al.* [4–6]. The calculations were performed with a slightly modified CNDO/2 program [7]. The program uses *s* and *p* Slater orbitals on all atoms except for hydrogen where only *s* orbital is used. All parameters were taken from the original papers [5, 6] without any modifications.

The rotation of the two groups were studied step by step, assuming that the geometrical parameters remain invariable during rotation. In the first calculations the phenyl group was placed in the same plane as the purine system. In this conformation the methyl group was rotated about the C9–N9 bond. The energies were calculated varying Θ from 0° to 60°. The angle Θ is set equal to 0° when H92 lies in the same plane as the purine system, pointing away from the phenyl group. The orientation of the methyl group was then fixed in the position giving minimum energy, and the phenyl group rotated about the bond C8–C10. Φ equal to 0° corresponds to the phenyl ring lying in the purine plane. The positive orientations of the angles Θ and Φ are shown in Fig. 1. Further on the energy was calculated and plotted for different values of Θ and Φ. Near the minimum, the energy was calculated with intervals of 1° in Θ and Φ. The results are given in Table 1 and in Fig. 2 where a two-dimensional map of iso-energy curves is drawn.

Results

The calculations show that the minimum energy gives a conformation where $\Theta = 23°$ and $\Phi = 30°$. In the crystal structure the angle Φ is found equal to 28.8°, and the methyl hydrogens H91 and H93 were found to be staggered

Table 1. Calculated CNDO energies for different conformations on 9-methyl-8-phenyl-6-thiopurine

θ	Φ	-E(eV)	θ	Φ	-E(eV)
23	30	4082.581573	40	30	4082.571106
24	30	.581299	20	20	.569794
22	30	.581268	15	20	.569733
22	31	.580963	45	45	.568756
22	29	.580902	30	45	.568420
24	31	.580872	10	20	.567871
25	30	.580811	25	20	.566071
23	29	.580536	35	25	.566010
24	29	.580505	25	45	.565796
27	30	.580414	15	15	.565704
21	30	.580048	45	30	.565674
25	28	.579773	10	40	.565399
23	31	.579742	15	45	.561829
20	30	.579681	20	15	.560608
27	25	.579346	35	50	.560120
27	23	.579315	0	30	.560089
30	30	.579193	25	50	.558136
23	35	.578705	30	20	.556946
25	35	.578339	10	10	.556244
25	37	.578308	15	50	.556183
25	32	.578217	0	45	.555298
35	35	.578186	0	15	.551819
23	32	.578186	30	55	.551239
25	33	.577881	25	15	.550659
27	35	.577606	20	55	.548004
21	32	.577209	20	10	.541840

Table 1, continued

θ	Φ	-E(eV)	θ	Φ	-E(eV)
27	37	4082.577179	30	60	4082.540405
23	37	.577179	25	60	.538910
30	35	.576843	20	60	.538330
20	25	.576294	0	60	.537964
35	30	.576263	30	15	.536591
25	25	.576141	0	0	.524750
20	35	.576019	15	0	.515350
15	30	.575867	30	10	.505127
15	25	.575625	45	15	.472504
30	40	.575012	40	10	.452057
25	40	.574554	30	0	.436127
30	25	.572754	45	0	.331390
20	40	.571655	60	0	.261773
10	30	.571259			

relative to the ortho hydrogen H 11. The distances H 11...H 91 and H 11...H 93 are 2.36 Å and 2.38 Å respectively. These distances are equal within the standard deviations. In the calculated minimum energy conformation these distances were both equal to 2.35 Å. The two bonds C9–H91 and C9–H93 were both equal 1.0 Å in the calculation while in the crystal structure they were found with slightly different lengths.

The calculated gross atomic charges are given in Table 2. C2, C4, C6, and C8 have all higher positive gross atomic charges than expected for carbon, looking at an isolated carbon atom. In this case this is due to the high negative gross charges on the heteroatoms in the rings. C2, C4, and C8 have all electronegative nitrogen atoms, drawing electrons from both sides. C8 has in addition to a nitrogen atom, a strongly electronegative sulphur as neighbouring atom. The other carbon atoms in the molecule have relatively small charges. H1 which is bound to nitrogen has relatively strong positive gross charge while the charges on the other hydrogen atoms are small. Giessner-Prettre and Pullman have reported CNDO calculations of the bases of DNA [8]. The

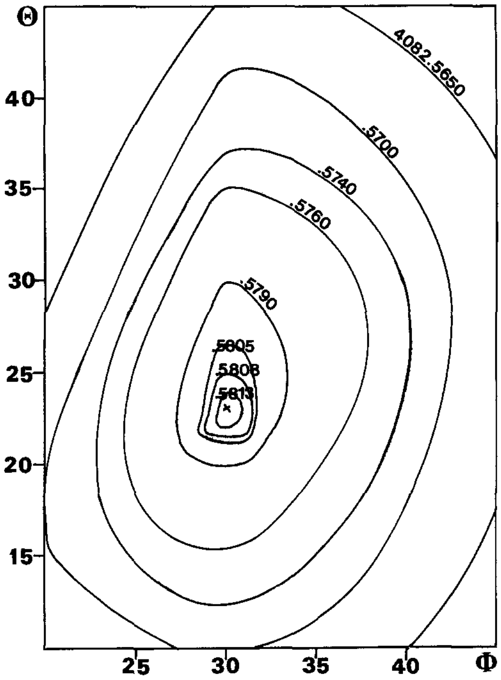

Fig. 2. Calculated potential surface for 9-methyl-8-phenyl-6-thiopurine

calculated charge densities of one of these e.g. adenine, is compared to the charge densities calculated in this work. Table 2 shows that the gross atomic charges in 9-methyl-8-phenyl-6-thiopurine are in good agreement with those on adenine.

Discussion

The CNDO calculations reproduce the experimental data for this molecule satisfactorily. The orientation of the methyl and phenyl group found in the crystal structure corresponds remarkably well to the minimum in the potential surface. In contrast to the present results, Gropen and Seip have reported on the failure of the CNDO/2 method in predicting molecular conformations in certain conjugated systems [9]. Glyoxal, 1,3-butadiene, benzaldehyd, biphenyl and 2,2′-difluorobiphenyl were all found to be twisted than found experimentally, and the authors assume that this discrepancy seems to indicate that the CNDO method underestimates the conjugation effect. They used the same parametrization as in this paper. Perahia and Pullman have applied the PCILO (perturbative configuration interaction using localized orbitals) method to the same compounds as Gropen and Seip, and this result is quite satisfactory as concerns the selection of the most stable conformation [11]. Their examination of the various contributions to the PCILO results shows that it is the delocalization com-

Table 2. Gross atomic charges calculated by CNDO/2

Atom	9-methyl-8-phenyl-6-thiopurine	Adenine (8)
S	-0.447	
N1	-0.105	-0.264
C2	0.224	0.207
N3	-0.212	-0.257
C4	0.195	0.197
C5	0.022	-0.039
C6	0.200	0.266
N7	-0.190	-0.223
C8	0.168	0.170
N9	-0.093	-0.123
C9	0.064	
C10	0.011	
C11	0.011	
C12	-0.001	
C13	0.003	
C14	0.003	
C15	0.003	
H1	0.139	
H2	-0.001	
H91	0.012	
H92	0.016	
H93	0.010	
H11	0.004	
H12	0.007	
H13	0.005	
H14	0.005	
H15	0.011	

ponent of the energy which favors the planar forms over the perpendicular one.

The most pronounced difference between e.g. biphenyl and 9-methyl-8-phenyl-6-thiopurine lies in the substituted methyl group on the purine ring. To examine if this steric effect is dominant in the determination of the conformation of minimum energy, the methyl group on C9 was removed and

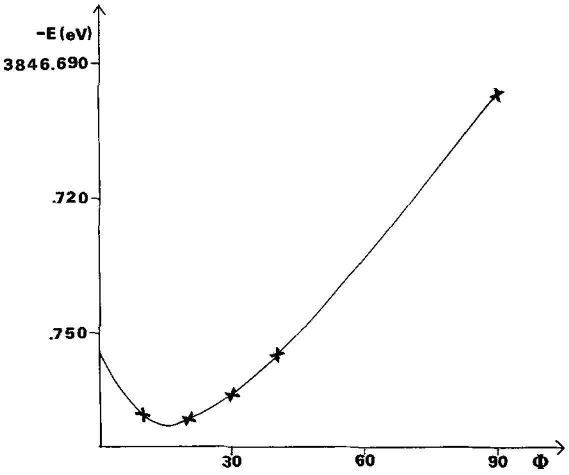

Fig. 3. Energy curves for 8-phenyl-6-thiopurine

replaced by a hydrogen atom. The N9–H distance was set equal to the $N1-H1=0.92$ Å, all other geometrical parameters as before. The phenyl group was rotated and the energy calculated for $\Phi=0°$, 10°, 20°, 30°, 40°, and 90°. The result is shown in Fig. 3. The minimum energy corresponds to a dihedral angle slightly less than 20° between the phenyl group and the purine ring. Thus the removal of the methyl group has decreased the dihedral angle significantly due to reduced steric interaction. The nature of the steric interaction in biphenyl is closely related to the present case. However, CNDO calculations on biphenyl give a dihedral angle of 90°. The experimental value for biphenyl in the gas phase is about 42° [10]. It is not readily explained why a large discrepancy occurs for the biphenyl molecule while the same type of calculation yields excellent results for the analogous purine system.

CNDO calculations on azobenzene and stilbene compared with experimental data are reported by Ljunggren and Wettermark [12, 13]. The experimental data indicate a planar conformation while the CNDO calculations give minimum energy when both phenyl rings are perpendicular to the plane involving the double bond. A comparison of *ab initio* versus CNDO barrier calculation are reported on N_2H_4, N_2F_4, P_2H_4, and P_2F_4 [14]. *Ab initio* results are in agreement with existing experimental predictions, but CNDO underestimates the magnitude of the barriers and gives fallacious values for the dihedral angle.

In other cases the CNDO method seems to give good correlations with experimental data as in this work. The calculations on anisole and ethylbenzene e.g. are reported to give good quantitative results [15]. The results for formaldimine and related compounds are in satisfactory agreement with *ab initio* results [16]. One may notice that the latter type of molecules are asymmetric while the molecules for which the method gives poor agreement are all symmetric.

Evidently it is necessary to develop the method further in order to predict *a priori* for which type of molecules the CNDO method will give correct conformations.

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