having the structure. Successive cycles of least-squares full matrix refinements, followed by difference Fourier synthesis, allowed location of the remainder non-H atoms. Refinements of scale factor, positional, and anisotropic thermal parameters for all non-hydrogen atoms was carried out to convergence, minimizing the function $\sum w(|F_o| - |F_c|)^2$. Some hydrogen atoms were located at geometric positions and the others from a final difference Fourier and isotropic thermal parameters. H atoms were not refined. The final cycle of refinements led to a final agreement factor, $R = 0.06$, $R = \sum(|F_o| - |F_c|)/\sum|F_o|$, using unit weight $R_w = 0.06$.

Atomic scattering factors from *International Tables for X-ray Crystallography*,[14] all calculations carried out with the XRAY system;[15] maximum residual density in the final difference map = ±0.3 eA.

Acknowledgment. We are indebted to the Comisión Asesora de Investigación Científica y Técnica (Grant number 85/354 and PR 84-0163-C03-02) for financial support. We also thank to the MS Service of the Facultad de Química (Universidad de Sevilla, España) for the mass spectra.

Registry No. **1a**, 16885-21-5; **1b**, 93125-33-8; **1c**, 93125-35-0; **1d**, 24580-90-3; **1e**, 24916-29-8; **1f**, 14965-56-1; **2a**, 123540-53-4; **2b**, 123540-54-5; **2c**, 123540-55-6; **2f**, 123540-56-7; **3a**, 123540-57-8; **3b**, 123540-58-9; **3c**, 123540-59-0; **3d**, 123540-60-3; **3e**, 107127-16-2; **3f**, 107127-18-4.

Supplementary Material Available: Table III listing crystallographic data (1 page). Ordering information is given on any current masthead page. [A listing of calculated and observed structure factors is available from A.L.]

(14) *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, 1974; Vol. IV, pp 202-207 (Present distributor D. Reidel, Dordrecht).

(15) Stewart, J. M.; Kundell, F. A.; Baldwin, J. C. *The* XRAY *System*; Computer Science Center, University of Maryland: College Park, MD, 1970.

Ab Initio Study of the Protonation and the Tautomerism of the 7-Aminopyrazolopyrimidine Molecule

Modesto Orozco, Enric I. Canela, Josefa Mallol, Carme Lluis, and Rafael Franco*

Departamento de Bioquímica y Fisiología, Facultad de Química, Universidad de Barcelona, Martí i Franquès 1, Barcelona 08028, Spain

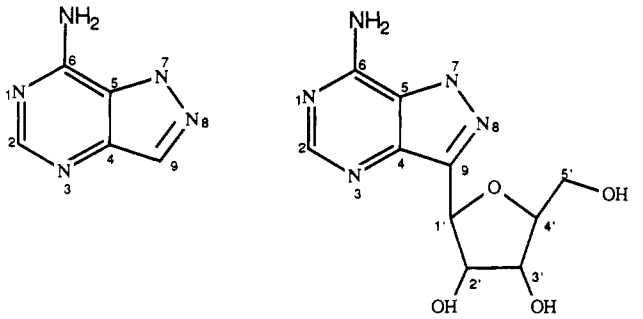
Received April 10, 1989

Introduction

7-Aminopyrazolo[4,3-*d*]pyrimidine[1] (see compound Ia in Scheme I) is an aromatic moiety present in several nucleosides of both biological and synthetic origins. Among them, formycin (7-amino-3β-D-ribofuranosyl pyrazolo[4,3-*d*]pyrimidine) is of particular interest (see compound Ib in scheme I). Formycin is a C-nucleoside analogue of adenosine, which was first isolated from cultures of Norcardia Interforma.[1b] This nucleoside has been extensively studied due to its antiviral,[2-4] antibiotic,[1b] immunodepressant,[5] antitumor,[5,6] and antimetabolic[4] properties. Nevertheless, its clinical use is hampered by its ease of deamination by adenosine deaminase (E.C.3.5.4.4),[7] the enzyme catalyzing the hydrolytic conversion of adenosine (and analogues) to inosine (and analogues).

* To whom all the correspondence should be addressed.

Scheme I. Schematic Representation of the 7-Aminopyrazolopyrimidine (IA) and Formycin (IB) Molecules[a]



I A I B

[a] Atom numbering follows the purine nomenclature system.

From an structural point of view, formycin is very similar to adenosine, but two differences exist: (i) The N-ribose bond of adenosine is replaced by a C-ribose bond in formycin; (ii) The imidazole ring of adenosine is replaced by a pyrazolo ring in formycin. The presence of a C-ribose bond instead of the N-ribose bond has consequences for the conformation of formycin, which have been discussed elsewhere (see ref 8 and references therein). Moreover, the existence of a pyrazolo ring in formycin leads to the existence of possible N7-H—N8-H tautomerism, an interesting phenomenon that cannot occur for adenosine.

The biological relevance of the N7H-N8H tautomerism has been recently pointed out by our laboratory.[9] Our theoretical results suggest that the N8-H tautomer of formycin can be deaminated by adenosine deaminase, while the N7-H tautomer is not a substrate for the enzyme. Since the deamination reaction is one of the most important interfering reactions accompanying the in vivo pharmacological use of formycin, accurate analysis of the pyrazolo tautomerism seems to be of major importance.

Several experimental (spectrophotometric, NMR, and X-ray) results have been reported in the literature concerning the structure, tautomerism, and protonation of pyrazolo pyrimidines. Thus Prusiner[10] reported the X-ray structure of formycin, Koyama et al.[11] that of formycin hydrobromide, and McKenna et al.[7] that of 3'-deoxy-

(1) (a) In this paper (although the rigourous IUPAC name of the aminopyrazolopyrimidine molecule is used) atom numbering has been done according to the purine nomenclature system. This is preferred to the use of the specific IUPAC nomenclature for pyrazolopyrimidine rings, in order to clarify the discussion. The purine nomenclature system has been used extensively in several studies about pyrazolopyrimidine derivatives, which are referenced and discussed in this paper. (b) Hori, M.; Ito, E.; Takita, T.; Koyama, T.; Takeuchi, T.; Umezawa, A. J. *J. Antibiot. Ser. A* **1964**, *17*, 96.

(2) Ishida, N.; Honiura, K.; Ksmegui, Y.; Schimizu, Y.; Matsumoto, S.; Izawa, A. *J. Antibiot. Ser. A* **1967**, *20*, 49.

(3) Takeuchi, T.; Iwanaga, J.; Aogaiad, T.; Umezawa, H. *J. Antibiot. Ser. A* **1966**, *19*, 286.

(4) Giziewicz, J.; De Clerq, M.; Luczak, M.; Shugar, D. *Biochem. Pharmacol.* **1975**, *24*, 1813.

(5) Odaka, T.; Takizawa, K.; Yamaura, K.; Yamamoto, T. *Jpn. J. Exp. Med.* **1969**, *39*, 327.

(6) Suhadolnik, R. J. In *Nucleosides as Biological Probes*; Willey: New York, 1979.

(7) McKenna, R.; Neidle, S.; Serafinowski, P. *Acta Crystallogr.* **1987**, *C43*, 2358.

(8) Birnbaum, G. I.; Shugar, D. In *Topics in Nucleic Acids Structure*; Macmillan Press: London, 1987; Part III, Chapter 1.

(9) Orozco, M.; Canela, E. I.; Franco, R. *Mol. Pharmacol.* **1989**, *35*, 257-264.

(10) Prusiner, P.; Brennan, T.; Sundaralingam, M. *Biochemistry* **1973**, *12*, 1196.

(11) Koyama, G.; Umezawa, H.; Iitaka, Y. *Acta Crystallogr.* **1974**, *B30*, 1511.

0022-3263/90/1955-0753$02.50/0

formycin hydrochloride. X-ray results are surprisingly heterogeneous since while McKenna et al. and Prusiner et al. detect the N7H tautomer, Koyama and co-workers detect the N8H tautomer.

Since the early NMR studies of the pyrazolo tautomerism reported by Krugh in 1973,[12] several other NMR studies of formycin and other pyrazolo pyrimidines have been reported.[8,13,14] All the studies clearly demonstrated the existence of a N7–H—N8–H tautomerism in solution, the N7–H tautomer being the most abundant.[8,12-14] The N7–H—N8–H change can easily occur upon acid or base catalysis.[15,16] According to temperature jump experiments of Cole and co-workers,[16] the N7–H—N8–H tautomeric change can also occur for the protonated forms of formycin. Finally, Chenon et al.[14] clearly demonstrated that the pyrazolo tautomerism is very dependent on the nature of the 6-substituent (7-substituent group according to IUPAC nomenclature) but is not related to the nature of the 9-substituent (3-substituent according to IUPAC nomenclature).

The site of protonation of formycin is also obscure, although experimental evidences[8,16] suggest that the protonation occurs not on the pyrazolo nitrogen but on one of the pyrimidine nitrogens. Experimental spectrophotometric data[8] suggest that the protonation can occur at either N1 or N3, but the relative percentages of the protonated species are unknown.[8] Moreover, important discrepancies exist in the X-ray data existent for protonated formycin. Thus, Koyama et al.[11] found protonation at N1, while McKenna et al. reported protonation at N3.[7]

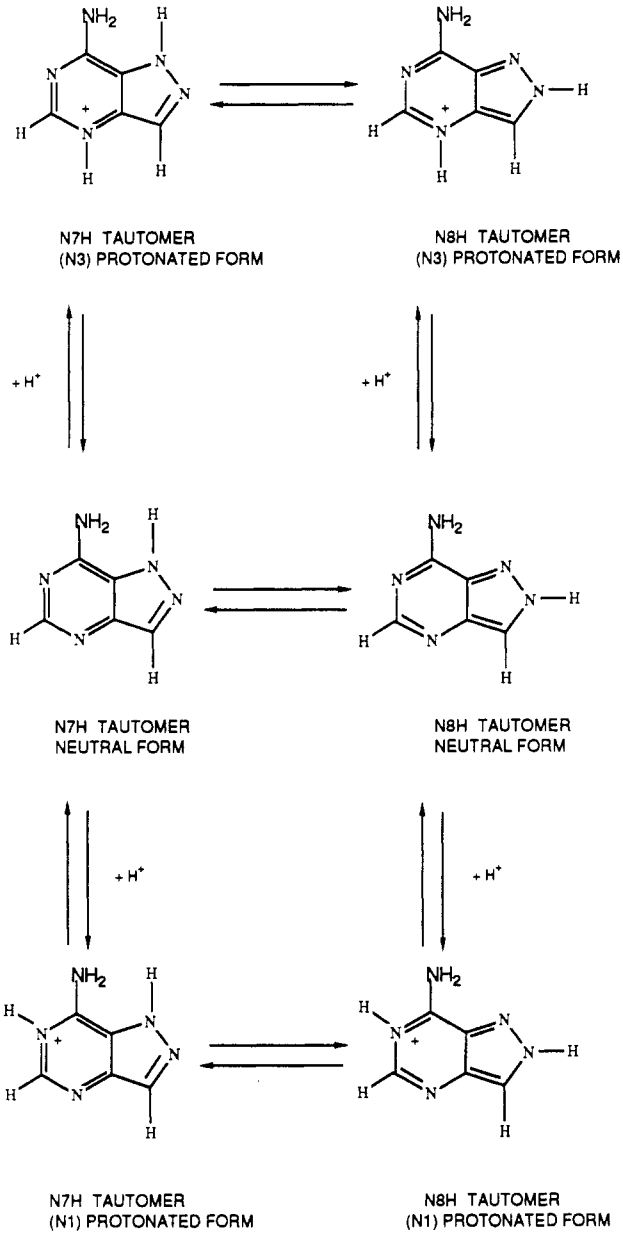
In the present paper a quantum chemical study is presented, in which both the protonation and the tautomerism of 7-aminopyrazolo[4,3-*d*]pyrimidine are studied by using ab initio methodology. To our knowledge, only the early CNDO studies of Ceasar and Greene[17] and our previous semiempirical AM1 and MNDO and ab initio STO-3G results[9] have been reported on the tautomerism and/or protonation of pyrazolo pyrimidine compounds.

Computational Details

Both AM1[18] and MNDO[19] semiempirical methods fail in the correct prediction of the N7–H—N8–H tautomeric preference of formycin.[9] Nevertheless, both methods provide accurate geometries, and it is clear from several studies that similar results are obtained from ab initio geometry optimization and from ab initio wave function calculation on the semiempirical full optimized geometry.[20,21] Thus, in the present work all the geometries were fully optimized using the AM1 method.

To test the influence of the basis set quality on the results, ab initio calculations were carried out at three different levels of sophistication: (i) STO-3G minimal basis set;[22] (ii) 3-21G split valence basis set;[23] (iii) mixed basis sets. For these latter (iii) calculations two different mixed basis sets were defined: the first, named MIXED 1 (4-31G* (N7,N8):3-21G:STO-3G (H)), defined

Scheme II



the two pyrazolo nitrogen atoms (where the tautomerism occurs) by means of a large 4-31G* basis set,[24] the rest of heavy atoms by the 3-21G basis set, and the hydrogen atoms by the STO-3G one. The second mixed basis set, called MIXED 2 (4-31G* (N1,N3):3-21G:STO-3G (H)), defined the N1 and N3 atoms (where protonation occurs) by means of the large 4-31G* basis set, whereas the rest of the heavy atoms were represented by the 3-21G basis set and the hydrogen atoms by the STO-3G one. The MIXED 2 basis set is used only to compute accurate values of the molecular electrostatic potential (MEP) minima on N1 and N3 atoms.

Molecular electrostatic potentials were calculated at the ab initio level by using the wave functions calculated from the STO-3G, 3-21G, and MIXED 2 basis sets. It should be stressed that, according to our previous calculations,[24] MEP minimum energy values obtained from MIXED 2 basis set are almost identical with those obtained from the large 6-31G** basis set.[25] Minima on N1 and N3 atoms were located within an error in the position lower than 0.01 atomic units (au). Minima for N7 and N8 were not determined, since our previous work[9] as well as several experimental studies (ref 16 and 8 and references therein) clearly

(12) Krugh, T. R. *J. Am. Chem. Soc.* **1973**, *95*, 4761.
(13) Chenon, M. Th.; Pugmire, R. J.; Grant, D. M.; Panzica, R. P.; Townseld, C. B. *J. Heterocycl. Chem.* **1973**, *10*, 431.
(14) Chenon, M. Th.; Panzica, R. P.; Smith, J. C.; Pugmire, R. J.; Grant, D. M.; Townseld, C. B. *J. Am. Chem. Soc.* **1976**, *98*, 4736.
(15) Dodin, G.; Bensande, O.; Dubois, J.-E. *J. Am. Chem. Soc.* **1980**, *102*, 3897.
(16) Cole, F. X.; Schimmol, P. R. *J. Am. Chem. Soc.* **1978**, *100*, 3957.
(17) Ceasar, G. P.; Greene, J J. *J. Med. Chem.* **1974**, *17*, 1122.
(18) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899.
(19) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J Am. Chem. Soc.* **1985**, *107*, 3902.
(20) Topiol, S. *J. Comput. Chem.* **1987**, *8*, 142.
(21) Bofill, J. M.; Castell, J.; Olivella, S.; Sole, A. *J. Org. Chem.* **1988**, *53*, 5148.
(22) Hehre, W. J.; Stewart, R. F.; Pople, J. A. *J. Am. Chem. Phys.* **1969**, *51*, 2657.
(23) Binkley, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 939.
(24) Orozco, M.; Luque, F. J. *Chem. Phys. Lett.* **1989**, *160*, 305.
(25) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213.

Table I. SCF Energies of the N8–H and N7–H Tautomers of 7-Aminopyrazolopyrimidine in Their Neutral, N1-Protonated, and N3-Protonated Forms, Calculated with the STO-3G, 3-21G, MIXED 1 (4-31G* (N7,N8):3-21G:STO-3G(H)), and MIXED 2 (4-31G* (N7,N8):3-21G:STO-3G(H)) Basis Sets[a]

compd	STO-3G	3-21G	MIXED 1	MIXED 2
neutral N7–H tautomer	−458.575 742	−461.832 516	−462.298 881	−462.300 912
neutral N8–H tautomer	−458.566 633	−461.830 194	−462.295 574	−462.296 842
N1-protonated N7–H tautomer	−459.023 932	−462.208 870	−462.661 909	
N1-protonated N8–H tautomer	−459.034 321	−462.221 261	−462.672 540	
N3-protonated N7–H tautomer	−459.031 829	−462.223 657	−462.676 065	
N3-protonated N8–H tautomer	−459.035 215	−462.231 185	−462.681 902	

[a] Energies are expressed in atomic units.

demonstrate the low basic character of the pyrazolo nitrogens. [Our previous calculations at the ab initio STO-3G levels pointed out minima on N7 (N8–H tautomer) and N8 (N7–H tautomer) of only −68.9 and −72.9 kcal/mol, respectively.]

AM1 calculations were performed with a locally modified version[26] of the MOPAC computer program.[27] Ab initio calculations were performed with a locally modified version of the HONDO-76 computer program.[28] All the calculations have been carried out on the IBM 3090 of the Centre d'Informatica de la Universitat de Barcelona.

Results

In the present paper the N7H and N8H tautomers of the aminopyrazolopyrimidine molecule are considered in the neutral, N1-protonated and N3-protonated forms (see Scheme II). The Hartree–Fock self-consistent field (SCF) energy of the six species, calculated from the STO-3G, 3-21G, and MIXED 1 basis sets, are displayed in Table I, where the SCF energy of the N7–H and N8–H tautomers of neutral aminopyrazolopyrimidine calculated from the MIXED 2 basis set are also displayed.

Results presented in Table I demonstrate that no significant change appears in the relative stability of the different species when the basis set quality is increased, except for the N3-protonated N7H tautomer, which is less stable than the N1-protonated N8H tautomer at the STO-3G level and more stable at the 3-21G and MIXED 1 levels. It should be noted that the lower energy obtained from the MIXED 2 basis set when comparing with MIXED 1 is due to the high electronic density at the N1 and N3 atoms (greater than that existing at the pyrazolo nitrogen atoms), which is better described by the MIXED 2 basis set.

The tautomerization and the protonation energies calculated by using the STO-3G, 3-21G, and MIXED 1 basis sets are displayed in Table II. Only slight differences (around 2–4 kcal/mol) appear in the tautomerization energies calculated by using the different basis sets. However, notable differences are obtained for the protonation energy.

The three methods detect the N7H as the more stable tautomer for the neutral form, the energetic differences being small (from 1.5 (3-21G) to 5.7 kcal/mol (STO-3G)). The tautomeric preference drastically changes when the aminopyrazolopyrimidine is protonated at either N1 or N3. It should be noted that the N8H–N7H energetic difference is greater (in absolute value) for the N1-protonated form (values around 7 kcal/mol) than for the N3-protonated form (values between 2.1 (STO-3G) and 4.7 kcal/mol (3-21G).

The STO-3G basis set clearly overestimates the protonation energy by around 50 kcal/mol when compared with MIXED 1 results. Although the 3-21G basis set provides results closest to the MIXED 1 basis set than the STO-3G, it also overestimates the protonation energy (but only by around 9 kcal/mol) with respect to MIXED 1, which is expected to give quite accurate values of the protonation energy. Nevertheless, all methods provide qualitatively similar information, showing that the protonation at the N3 atom leads to more stable compounds than that occurring at the N1 atom. Thus the N3-protonated N7–H tautomer is around 5–9 kcal/mol more stable than the N1 protonated N7–H tautomer. Moreover, the N3-protonated N8–H tautomer is between 0.6 (STO-3G) and 6.2 kcal/mol (3-21G) more stable than the N1-protonated N8–H tautomer.

The protonation energy gives a measure of the global enthalpy variation of the reaction but does not provide information about the energy changes accompanying the early stages of the protonation reaction, which can determine in some cases the position where the protonation occurs. Since the electrostatic is the strongest interaction at large distances, molecular electrostatic potential gives a good insight into the early stages of the protonation

Table II. N8–H—N7–H Tautomerization Energy for the N1- and N3-Protonated Forms of 7-Aminopyrazolopyrimidine and N1 and N3 Protonation Energies of the N7–H and N8–H Tautomers of Neutral 7-Aminopyrazolopyrimidine, Calculated with the STO-3G, 3-21G, MIXED 1 (4-31G* (N7,N8):3-21G:STO-3G(H)), and MIXED 2 (4-31G* (N7,N8):3-21G:STO-3G(H)) Basis Sets[a]

	STO-3G	3-21G	MIXED 1
tautomerization N8–H—N7–H energy (neutral)	5.72	1.46	2.08
tautomerization N8–H—N7–H energy (N1-protonated)	−6.52	−7.78	−6.67
tautomerization N8–H—N7–H energy (N3-protonated)	−2.12	−4.72	−3.66
N1-protonation energy (N7–H tautomer)	−281.24	−236.17	−227.80
N1-protonation energy (N8–H tautomer)	−293.48	−245.40	−236.55
N3-protonation energy (N7–H tautomer)	−286.20	−245.44	−236.69
N3-protonation energy (N8–H tautomer)	−294.04	−251.62	−242.42

[a] Energies are expressed in kcal/mol.

Table III. Energies (kcal/mol) of the Molecular Electrostatic Potential Minima on N1 and N3 for Neutral 7-Aminopyrazolopyrimidine, Calculated with the STO-3G, 3-21G, MIXED 1 (4-31G* (N7,N8):3-21G:STO-3G(H)) and MIXED 2 (4-31G* (N7,N8):3-21G:STO-3G(H)) Basis Sets

	MEP minimum on N1	MEP minimum on N3
STO-3G (N7–H tautomer)	−84.64	−91.02
STO-3G (N8–H tautomer)	−93.22	−95.22
3-21G (N7–H tautomer)	−75.92	−85.60
3-21G (N8–H tautomer)	−83.41	−90.32
MIXED 2 (N7–H tautomer)	−58.45	−66.85
MIXED 2 (N8–H tautomer)	−64.87	−71.29

(26) Olivella, S. *QCPE Bull.* **1984**, *4*, 10.
(27) Stewart, J. J. P. *QCPE Bull.* **1983**, *3*, 101.
(28) Dupuis, M.; Rys, J.; King, H. F. *QCPE Bull.* **1977**, *58*, 17.

reaction and therefore is useful to determine the most feasible sites of protonation.[29-31]

Molecular electrostatic potential minimum energies on N1 and N3 atoms are displayed in Table III. Of particular note is the poor ability of both STO-3G and 3-21G basis sets to provide quantitatively correct values of the MEP minimum energy, confirming our previous suggestions that the inclusion of polarization functions is necessary to obtain reliable MEP energy values.[24,32] Nevertheless, for this molecule, from a qualitative point of view all the methods provide similar results. Thus irrespective of the wave function employed, the N3 MEP minimum is deeper than the N1 one, the difference varying from 6.4 (STO-3G) to 9.7 kcal/mol (3-21G) for the N7–H tautomer and between 2 (STO–3G) and 6.9 kcal/mol (3-21G) for the N8–H tautomer. MEP minima on N1 and N3 for the N8–H tautomer are deeper than those of the N7 tautomer. These results agree with the protonation energy values shown in Table II and clearly demonstrate that the N3 atom is the most basic point in either N7–H or N8–H tautomeric forms of the aminopyrazolo molecule and that the less stable N8–H tautomer is more basic than the N7–H tautomer, in agreement with the suggestions of Dodin et al.[15]

Discussion

The main objective of this work has been the study of the intrinsic tautomeric and acid/base characteristics of the 7-aminopyrazolopyrimidine molecule. However, the interest of extrapolating the conclusions obtained here to the formycin molecule and other derivatives is obvious. NMR results reported by Chenon et al.[14] clearly demonstrated that the tautomerism of the 7-aminopyrazolopyrimidine derivatives is not related to the nature of the 9-substituent group (3-substituent group according to IUPAC nomenclature). This leads us to the suggestion that the conclusions obtained here about the tautomerism of the 7-aminopyrazolopyrimidine are also valid for the formycin molecule. No experimental studies on the role of the ribose moiety in the acid/base characteristics of the 7-aminopyrazolopyrimidine exist to our knowledge. Available data on the acid/base properties of adenosine and adenine[33] show that the presence of the ribose causes a small effect on the pK_a value of adenine, both adenine and adenosine being protonated at the N1 atom. Accordingly, for the formycin molecule, it has been suggested that the ribose moiety causes a slight decrease in the basicity of both N1 and N3 and that this decrease is greater for the N3 atom, especially if the ribose moiety is in the syn conformation around the glycosidic bond.[9]

Our ab initio quantum chemical calculations point out that the N7–H is the most feasible tautomer of the neutral aminopyrazalopyrimidine molecule, in excellent agreement with experimental data of formycin.[8,13-16] The calculated energy difference between the N7–H and N8–H tautomers is about 2 kcal/mol (at the MIXED 1 level), in good agreement with the value of 1 kcal/mol reported by Dodin[15] for the formycin molecule. The protonation of the molecule at either N1 or N3 atoms produces a drastic change in the tautomeric perference from the N7–H to the N8–H tautomer. It should be noted that the N8–H—N7–H energy difference is notable for the N1-protonated form but smaller for the N3-protonated form. These facts explain why Koyama et al.[11] found for the N1-protonated formycin that the N8–H tautomer was present, while McKenna et al. for the N3-protonated 3′-deoxyformycin found that the change from the N7–H to the N8–H did not occur.[7]

Experimental results[8] point out the existence of both N1 and N3 protonated forms of formycin in solution. Our theoretical calculations suggest that the N3 atom is more basic than the N1 one (in agreement with the results reported by McKenna et al.[7]) and that the difference in basicity is more notable for the N7H tautomer than for the N8H tautomer. The presence of N1-protonated form in the crystal structure reported by Koyama et al.[11] can be due to the low energy difference in the basicity of N1 and N3 for the N8–H tautomer and to the effect of the ribose moiety as discussed above.

Both N7–H and N8–H tautomers of 7-aminopyrazolopyrimidine derivatives can exist in either neutral, N1-protonated, or N3-protonated forms. Theoretical results suggest that in the *gas phase* N3 is the most basic atom of the molecule. N7–H is the most stable tautomeric form for the neutral molecule, while N8–H is the preferred tautomer for protonated molecule. It is also interesting to note that the neutral N8–H tautomer is a stronger base than the neutral N7–H tautomer. Results presented in this paper are consistent with the data existing for neutral formycin (see ref 8, 10, and 12–16). Also, references about the increase in basicity when formycin changes from N7–H to N8–H tautomeric form have been reported.[15] Finally, it should be stressed that the most stable structure found by quantum chemical calculations for the protonated 7-aminopyrazolopyrimidine molecule is different from either Koyama's[11] nor McKenna's[7] crystal structures.

Our quantum mechanical calculations have been performed within the Hartree–Fock framework, and no large extended basis set has been used due to the computational limitations derived from the size of the molecules studied. Nevertheless, since qualitatively similar results are obtained from the different basis sets, it can be suggested that the extension of the basis set and the inclusion of correlation effects would not introduce significant variations in the conclusions obtained.

Acknowledgment. We are thankful for the excellent technical help of S. Olivella, J. Bofill, and F. Illas. Likewise, we are indebted to F. J. Luque and C. Laughthon for many helpful discussions.

Registry No. IA, 13877-56-0.

(29) Scrocco, E.; Tomasi, J. *Top. Curr. Chem.* **1973**, *42*, 95.
(30) Kollman, P.; McKelvery, J.; Johansson, A.; Rothenberg, S. *J. Am. Chem. Soc.* **1975**, *97*, 955.
(31) Tomasi, J. In *Chemical Applications of Atomic and Molecular Electrostatic Potential*; Plenum Press: New York, 1981; pp 257–294.
(32) Luque, F. J.; Illas, F.; Orozco, M. *J. Comput. Chem.*, in press.
(33) Izatt, R. M.; Christensen, J. J.; Rytting, J. H. *Chem. Rev.* **1971**, *71*, 439.

A Very Convenient Synthesis of Cyclopenta[*cd*]pyrene

Nynke M. Spijker, Anne M. van den Braken-van Leersum, Johan Lugtenburg, and Jan Cornelisse*

Gorlaeus Laboratories, Leiden University, PO Box 9502, 2300 RA Leiden, The Netherlands

Received December 15, 1987

Cyclopenta[*cd*]pyrene (CPP, **5**), a constituent of the class of the polycyclic aromatic hydrocarbons, occurs in a wide variety of carbon black soots,[1-9] in cigarette smoke,[10]

(1) Falk, H. L.; Steiner, P. E. *Cancer Res.* **1952**, *12*, 30.
(2) Kotin, P.; Falk, H. L.; Thomas, M. *Arch. Ind. Hyg. Occup. Med.* **1954**, *9*, 164.

0022-3263/90/1955-0756$02.50/0