Boat and Twist-Boat Structures of 2,4,6-Tris(isopropylamino)-1,3,5-trinitrobenzene: Conformational Change through Intermolecular Hydrogen Bonding[1]

J. Jens Wolff,*,† Stephen F. Nelsen,* and Douglas R. Powell

S. M. McElvain Laboratories of Organic Chemistry, Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706

Received March 28, 1991

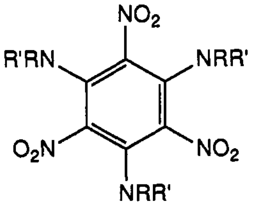
2,4,6-Tris(isopropylamino)-1,3,5-trinitrobenzene (**2a**) cocrystallizes with isopropylamine in a highly distorted boat form (**2a$_1$**) but adopts an almost equally distorted twist-boat from (**2a$_2$**) in a cocrystal with toluene. In the boat from, a quinonoid resonance pattern is found for the benzene core, whereas no such simple resonance equivalent exists for the twist-boat form. Differences in the donor–acceptor relationships between **2a$_1$** and **2a$_2$** are discussed in terms of bond lengths and are substantiated by UV–vis spectroscopy: the band at longest wavelengths in the solid-state UV–vis spectrum of **2a$_1$** is shifted by 27 ± 7 nm in comparison to that of **2a$_2$**, a difference of 5.8 ± 1.5 kcal/mol in energy. For solutions of **2a**, UV–vis spectroscopy indicates the presence of both conformers in different amounts that vary with temperature.

Introduction

It is of great interest, both from a fundamental and practical point of view, to be able to predict the solid-state arrangements of organic molecules.[2] In the absence of strong ionic interactions, solid-state structures of individual molecules and their packing patterns depend on the interplay of energetically rather subtle "steric" (van der Waals) and "polar" (di- and multipolar, hydrogen bonding) interactions. The most notable progress has been made both experimentally and theoretically for two extreme cases: "pure" van der Waals interactions, as found in the crystals of hydrocarbons,[3] and hydrogen bonding, which provides a strong directional ordering force.[4,5] The influence of a crystal field on the conformations of individual molecules has also been modeled.[6]

Comparing the packing of chemically closely related molecules has been difficult in solid-state organic chemistry. Rather minor structural changes in the individual molecules can lead to quite substantial changes in their cooperative behavior, i.e., the crystal structure. Individual contributions of atoms, functional groups or molecules are difficult to disentangle. Common methods of correlation analysis in physical organic chemistry such as Hammett correlations are no longer feasible. It is desirable, therefore, not to change the constitution of the molecule at all, but to devise compounds with great conformational flexibility that show conformational polymorphism.[7,8] Such molecules adopt different conformations in different crystal forms. If the flexible molecules cocrystallize[9] with different neutral guests ("pseudopolymorphism"), the conformations observed may be used as a probe for the influence of "crystal packing forces", which are induced by the neutral guest molecule. Two advantages are associated with this approach. Independent conformational analysis of the host molecule by theoretical and experimental techniques allows quantification of the impact of crystal packing forces on the conformation of the molecule, and different conformation isolated in crystals may be isolated and studied in detail that is not available for solution studies. This paper deals primarily with the latter aspect, and we have chosen tris(alkylamino)trinitrobenzenes for this purpose.

Siegel and co-workers[10] have shown the benzene core of 2,4,6-tris(diethylamino)-1,3,5-trinitrobenzene (**1**) to be drastically distorted toward a boat form, with the sum of absolute values of torsional angles within the ring amounting to 172°. We have demonstrated[11] that only one alkyl group on nitrogen, as in **2**, suffices to achieve rather similar distortions. X-ray studies on the potassium salts of trinitrophloroglucinol[1] and AM1 calculations[1,11] revealed that it is the electronic "push–pull" interaction in tris-



1: R = R' = Et

2: R' = H; R = *i*-Pr, Et, *neo*-Pentyl, *t*-Bu
a **b** **c** **d**

---

† New address: Organisch-Chemisches Institut der Universität Heidelberg Im Neuenheimer Feld 270, D-6900 Heidelberg F.R.G..

[1] Structures of Tris(donor)–Tris(acceptor)-Substituted Benzenes. 3. Part 2: Wolff, J. J.; Nelsen, S. F.; Powell, D. R.; Desper, J. M. *Chem. Ber.* **1991**, *124*, 1727. Part 1: ref 11.

[2] "Crystal engineering" is, for example, of crucial importance in nonlinear optics.[17] For reviews, see: Schmidt, G. M. J. *Pure Appl. Chem.* **1971**, *27*, 647. Sarma, J. A. R. P.; Desiraju, G. R. *Acc. Chem. Res.* **1986**, *19*, 222. Ramamurthy, V.; Venkatesan, K. *Chem. Rev.* **1987**, *87*, 433. For a recent report concerning nonlinear optics, see: Staab, E.; Addadi, L.; Leiserowitz, L.; Lahav, M. *Adv. Mater.* **1990**, *2*, 40.

[3] Kitaigorodskij, A. *Molecular Crystals and Molecules*; Academic Press: New York, 1973. See also: McBide, J. M.; Bertman, S. B.; Cioffi, D. Z.; Segmüller, B. E.; Weber, B. A. *Mol. Cryst. Liq. Cryst.* **1988**, *161*, 1.

[4] Leiserovitz, L.; Tuval, M. *Acta Crystallogr., Sect. B* **1978**, *34*, 1230.

[5] (a) Etter, M. C.; Reutzel, S. M. *J. Am. Chem. Soc.* **1991**, *111*, 2586. (b) Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120 and references cited therein.

[6] For a recent ab initio calculation, see: Popelier, P.; Leustra, A. T. H.; van Alsenoy, C.; Geise, H. J. *J. Am. Chem. Soc.* **1989**, *111*, 5658. Gavezotti, A. In *Organic Materials for Non-lindear Optics*; Hann, R. A., Bloor, D., Eds.; Royal Society of Chemistry: London, 1989. For earlier work, see, for example: Bianchi, R.; Gavezotti, A.; Simonetta, M. *J. Mol. Struct.* **1986**, *135*, 391. Ramdas, S.; Thomas, N. W. IN *Organic Solid State Chemistry*; Desiraju, G. R., Ed.; Elsevier: Amsterdam, 1987; pp 433–469. See also: Vinson, L. K.; Dannenberg, J. *J. Am. Chem. Soc.* **1989**, *111*, 2777.

[7] For a review, see: Bernstein, J. In *Organic Solid State Chemistry*; Desiraju, G. R., Ed.; Elsevier: Amsterdam, 1987; pp 471–518.

[8] Matthews, J. H.; Paul, I. C.; Curtin, D. Y. *J. Chem. Soc., Perkin Trans 2* **1991**, 113. Curtin, D. Y., Engelmann, J. H. *J. Org. Chem.* **1972**, *37*, 3439. Byrn, S. R.; Curtin, D. Y.; Paul, I. C. *J. Am. Chem. Soc.* **1972**, *94*, 890. Richardson, M. F.; Yang, Q.; Novotny-Bregger, E.; Dunitz, J. D. *Acta CRystallogr., Sect. B* **1990**, *46*, 653. Dunitz, J. D. *Pure Appl. Chem.* **1991**, *63*, 177.

[9] The cocrystallization approach has been used to study hydrogen bonding.[5a]

[10] Chance, J. M.; Kahr, B.; Buda, A. B.; Siegel, J. S. *J. Am. Chem. Soc.* **1989**, *111*, 5940.

[11] Wolff, J. J.; Nelsen, S. F.; Petillo, P. A.; D. R. *Chem. Ber.* **1990**, *124*, 1719.

0022-3263/91/1956-5908$02.50/0

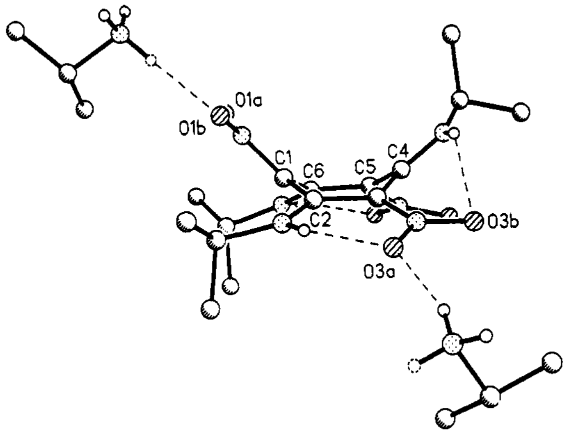


Figure 1. Ball–stick diagram for 2a·*i*-$PrNH_2$ ($2a_1$). Amino hydrogen atoms on N2, 4, and 6 have been located on the difference map. The amino hydrogen atoms of the free isopropylamine are 2-fold disordered.

(donor)trinitrobenzenes that causes the benzene core to be unusually "floppy"; steric factors then determine its actual deformation. We have also found that a boat structure is adopted for **2a**·*i*-$PrNH_2$, but that twist-boat structures are adopted for **2b–d**,[12] a difference that was attributed to the intermolecular hydrogen bonding to the guest molecule present in **2a**·*i*-$PrNH_2$. AM1 calculations suggest that there are only small energy differences between boat and twist-boat forms of **2**,[11] so that seemingly minor changes in the molecular surrounding of **2** might have a profound influence on its conformation. We report here on the conformational change of **2a** in the solid state from a boat to twist-boat form when the cocrystallizing isopropylamine is replaced with toluene.

Results and Discussion

2a, prepared from either 2,4,6-trichloro- or 2,4,6-trimethoxy-1,3,5-trinitrobenzene with excess isopropylamine in toluene,[11] crystallizes as a 1:1 complex with isopropylamine from the reaction mixture. The X-ray crystallographic analysis[11] showed its benzene ring to be highly distorted toward a boat form ($2a_1$, Figure 1 and Table I). The strong differences in bond lengths observed within the ring are best accounted for by emphasis of a nonplanar para quinonoid resonance structure: The C–C bonds at the "side" of the boat are 0.05 Å shorter than the average of the four other bonds, the C–NHR bond at the "bow" carbon is shortened by 0.05 Å relative to the bonds at the side, and the C–NO_2 bond at the "stern" carbon is likewise shortened by 0.02 Å.[13] Two intramolecular hydrogen bonds, indicated by the distances of the corresponding heavy atoms, are formed between the amino and nitro groups on the side of the boat; the third amino group has an additional weak interaction with a nitro group on the side (Table I). The free nitro and amino groups on bow and stern engage in intermolecular hydrogen bonding to the additional isopropylamine, but not to another molecule of $2a_1$. The steric bulk present seems to prevent an interaction of the latter sort, which is common for nitroanilines.[5b]

Sublimation of **2a**·*i*-$PrNH_2$ at 140 °C (0.5 Torr) removes the excess amine; crystallization from toluene then leads to a 1:1 complex with that solvent. The X-ray analysis reveals a twist-boat form for the benzene core ($2a_2$, Figures 2 and 3). The basic structural features correspond to those found for **2b–d**, which crystallize in twist boat forms. In $2a_2$, there is less bond alternation than in **2a**·*i*-$PrNH_2$ ($2a_1$), the average C–C bond is longer, and the ring is less distorted as measured by the sum of absolute values of dihedral angles[14] (Table I). $2a_2$ cannot be characterized by a single dominant resonance form, but, on the basis of the

Table I. Comparison of Structural Features for 2a • *i*-$PrNH_2$ ($2a_1$) vs 2a • $C_6H_5CH_3$

Bond Lengths (Å)

	$2a_1$	$2a_2$
C1–C2	1.471 (7)	1.449 (13)
C2–C3	1.412 (7)	1.452 (14)
C3–C4	1.482 (7)	1.452 (21)
C4–C5	1.474 (7)	1.425 (25)
C5–C6	1.411 (8)	1.445 (15)
C6–C1	1.452 (7)	1.407 (19)
C–C(ave)	1.450	1.438
range	0.071	0.045
C2–N2	1.332 (7)	1.323 (16)
C4–N4	1.281 (7)	1.329 (14)
C6–N6	0.327 (6)	1.344 (20)
C–NHR(ave)	1.310	1.332
range	0.051	0.021
C1–N1	1.366 (7)	1.385 (11)
C3–N3	1.377 (6)	1.372 (21)
C5–N5	1.393 (7)	1.389 (27)
C–NO_2(ave)	1.379	1.382
range	0.027	0.017

Nonbonded Distances (Å)

	$2a_1$		$2a_2$
H2a–O3a	1.911	H2–O3a	2.240
H4a–O3b	2.402	H4–O3b	1.619
H4a–N7c	2.073	H6–O1a	1.757
H6a–O5b	1.960	N2–O3a	2.537
N2–O3a	2.571	N4–O3b	2.583
N4–O3b	2.842	N6–O1a	2.616
N6–O5b	2.586		
N7a–O1a	3.238		
N7a–O1b	2.974		
N7b–O3a	2.907		
N7c–O3b	2.974		
N7c–N4	2.941		

Dihedral Angles (deg)

	$2a_1$	$2a_2$
C1C2C3C4	4.8 (7)	−15.6 (23)
C2C3C4C5	−41.3 (7)	−19.0 (21)
C3C4C5C6	39.5 (7)	40.5 (18)
C4C5C6C1	−1.0 (8)	−24.7 (18)
C5C6C1C2	−38.0 (7)	−11.8 (19)
C6C1C2C3	36.0 (7)	32.1 (20)
$\sum\lvert \text{dih} \angle \rvert$	161	144

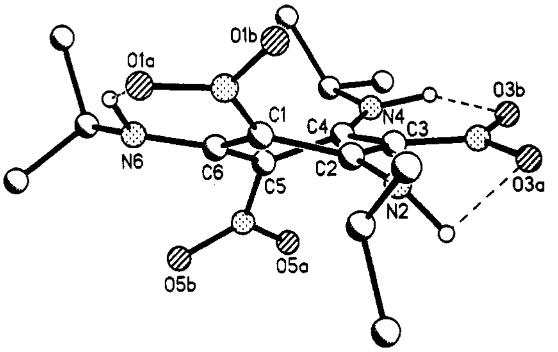


Figure 2. Ball–stick diagram for **2a**·$C_6H_5CH_3$ (**2a**). The toluene has been omitted for clarity.

---

[12] **2c** and **2d**: ref 11. **2b**: Wolff, J. J.; Nelsen, S. F.; Powell, D. R. Unpublished result.

[13] It may be argued that some of the bond length differences discussed here lie within experimental error. The general trend, however, is consistent in each case, so that our approach is justified.

[14] We have established[1,11,12] an exponential correlation between the average C–C bond lengths within the benzene core and the sums of absolute values of torsional angles, which holds also for this case.

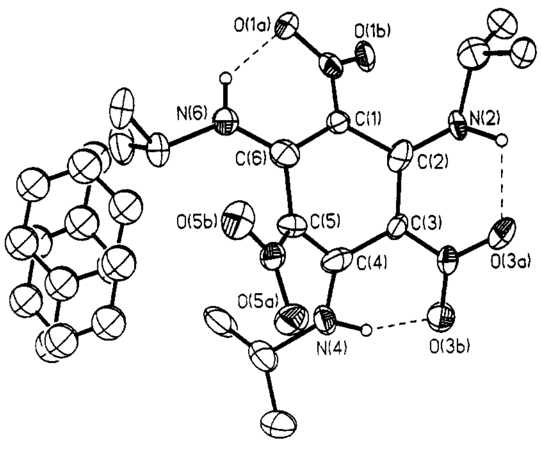


Figure 3. Thermal ellipsoid plot for $2a{\cdot}C_6H_5CH_3$ ($2a_2$).

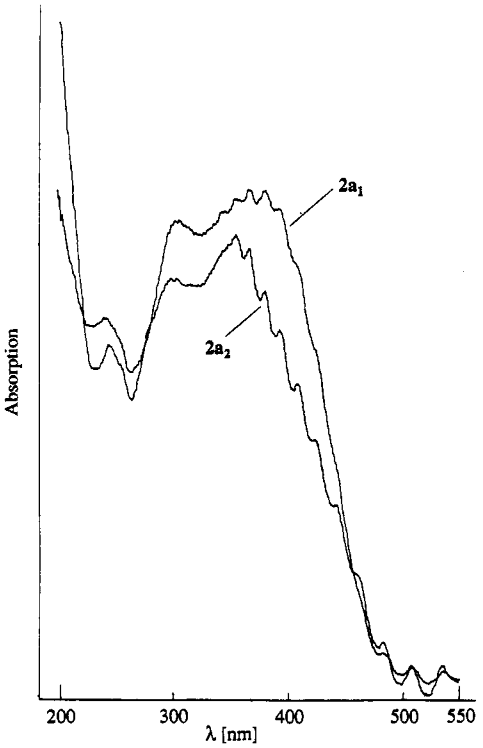


Figure 4. Solid-state UV–vis spectra of $2a_1$ and $2a_2$.

observed bond lengths, there is clearly a stronger electronic interaction between two amino groups at the "side" of the twist boat and the nitro group in their common ortho position. At least formally, a useful description arises from a dissection of the central benzene core into an allyl cation subunit (C2–C4, amino-substituted at the termini) and an allyl anion unit (C5–C1, nitro-substituted at the termini).

Judged by the consistent trend in the averaged C–C, C–NHR, and C–NO_2 bond lengths (Table I), push–pull interaction in the twist-boat $2a_2$ is weaker than in boat $2a_1$. This is a surprising result, since in $2a_2$ intermolecular hydrogen bonding that might attenuate intramolecular interactions is lacking, intramolecular hydrogen bonding is considerably stronger (relevant nonbonded distances are 7–15% shorter than in $2a_1$), and the ring deviates less from planarity.

A quantitative spectroscopic measure for the difference in push–pull interaction is provided by the UV–vis spectra of $2a_1$ and $2a_2$ in the solid state[15] (Figure 4). The absorption band at highest wavelength for the isopropylamine complex is substantially red-shifted; otherwise, the spectra are nearly superimposable. If the fine structure visible in both spectra is approximated with a smoothed curve and a conservative error limit is used, λ_{max} = 380 ± 5 nm for the amine complex and λ_{max} = 353 ± 5 nm for the toluene complex are found. In this spectral region, the difference of 27 ± 7 nm corresponds to 5.8 ± 1.5 kcal/mol. Solutions of either complexes or sublimed **2a** in dichloromethane give identical spectra (Figure 5): the band at highest wavelength (376 ± 1 nm) has a shoulder at ca. 350 nm that increases relative to the major band when the temperature is lowered. Clearly, both conformers are present in solution and their absorption bands are superimposed.

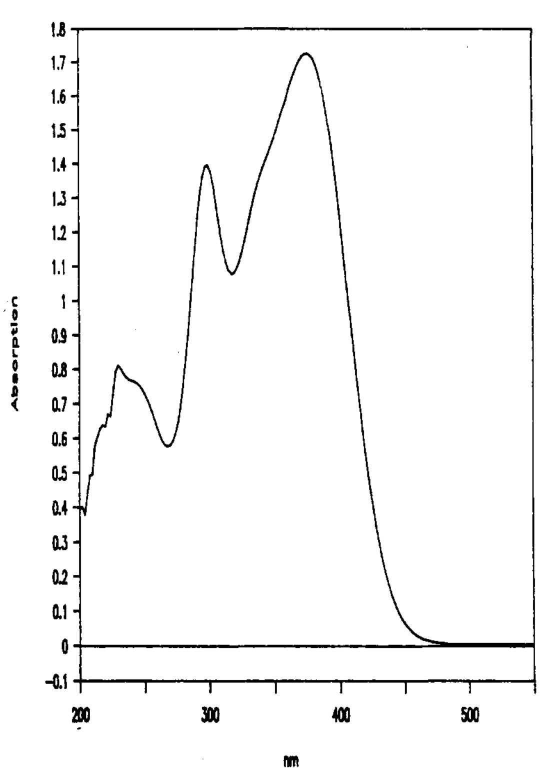


Figure 5. UV–vis spectrum of **2a** in dichloromethane (0.05 mmol/L).

Conclusion

Depending on a cocrystallizing molecule, **2** can be stabilized in either of two otherwise labile conformations, a boat and a twist-boat form that coexist in solution. Although these conformations are of similar energy, there are very substantial differences in their geometric features and in the donor–acceptor relationships between the nitro and amino groups. Nitroanilines are known to have good nonlinear optical properties that arise mainly from strong intramolecular charge transfer present in their excited states.[16] Since the donor–acceptor pattern changes profoundly on going from $2a_1$ to $2a_2$, the conformational change is expected to have a major impact on the β or $\chi^{(2)}$

---

(15) We thank Mrs. M. Baumann for help with this technique.

(16) Overviews: Prasad, P. N.; Williams, D. J. *Introduction to Nonlinear Optical Effects in Molecules and Polymers*; Wiley: New York, 1991. Chemla, D. S., Zyss, J., Eds. *Nonlinear Optical Properties of Organic Molecules and Crystals*; Academic Press: LOndon, 1987. Shen, Y. R. *The Principles of Nonlinear Optics*; Wiley: New York, 1984. Williams, D. J. *Angew. Chem.* **1984**, *96*, 637; *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 690. There has been a report on a weak second harmonic generation from 2,4,6-triamino-1,3,5-trinitrobenzene, despite of the centrosymmetric space group in which it crystallizes: Ledoux, I.; Zyss, J.; Siegel, J. S.; Brienne, J.; Lehn, J.-M. *Chem. Phys. Lett.* **1990**, *172*, 440.

J. Org. Chem. **1991**, *56*, 5911-5918 **5911**

values of those phases. Evaluations of the nonlinear optical properties of **2** are in progress and will be reported in due course.[17]

Experimental Section

The synthesis of **2a** has been described elsewhere.[11] X-ray analysis: Siemens P3f, Cu Kα, −165 (2) °C, highly oriented graphite crystal. 2θ range: 4.0–114.0°; scan speed 2.00–12.00°/min; scan range (ω) 0.80°. Background measurement: stationary crystal and stationary counter at beginning and end of scan, each for 16.7% of total scan time. A total of 1897 reflections collected, 1823 independent reflections (R_{int} = 4.02%); 1331 reflections observed ($F > 4.0\sigma(F)$); no absorption correction. Yellow prisms, 0.20 × 0.30 × 0.50 mm, $C_{15}H_{24}N_6O_6{\cdot}C_7H_8$, formula weight 476.5; monoclinic, space group *Cc*, a = 16.944 (6) Å, b = 17.189 (8) Å, c = 11.169 (4) Å, β = 129.84 (3)°, V = 2498 (2) Å^3; 25 peaks to determine cell, 2θ range of cell peaks 45.00, 49.00°; Z = 4; density (calcd) 1.267 g/cm^3; absorption coefficient 0.741 mm^{-1}, $F(000)$ 1016. Solution by direct methods,[18] full-matrix least-squares; absolute structure η = 1 (3); extinction correction χ = 0.0015 (4), where $F^* = F(1 + 0.002\chi F^2/\sin(2\theta))$?; hydrogen atoms riding model, isotropic U; weighting scheme $w^{-1} = \sigma^2(F) + 0.0006F^2$; 266 parameters refined; R (obsd data) = 6.96, R_w = 7.06%; Gof = 1.60; largest and mean Δ/σ 0.040, 0.003; largest difference peak 0.32 eÅ^{-3}, largest difference hole −0.29 eÅ^{-3}.

Acknowledgment. We thank the National Institutes of Health for partial financial support under GM.29549 and the Humboldt-Stiftung for a *Feodor Lynen* fellowship to J.J.W.

Registry No. **2a**, 132699-66-2; *i*-$PrNH_2$, 75-31-0; $C_6H_5CH_3$, 108-88-3.

Supplementary Material Available: Atomic coordinates for **2a**·$C_6H_5CH_3$ (heavy and hydrogen atoms), bond lengths, bond angles, anisotropic displacement coefficients, and stereoviews of packing diagrams for $\mathbf{2a}_1$ and $\mathbf{2a}_2$ (7 pages). Ordering information is given on any current masthead page.

---

(17) Wolff, J. J.; McMahon, R. J.; Nelsen, S. F. Manuscript in preparation.

(18) Sheldrick, G. M. SHELXTL PLUS, Version 4.2; Siemens Analytical X-ray Instruments, Inc., Madison, WI, 1990.

Conformations of the Phosphorus-Containing Rings of Nucleoside Cyclic 3′,5′-Phosphoramidates. The Question of the Chair to Twist Free Energy Change for cAMP

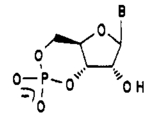
Alan E. Sopchik, Jozsef Beres, Jeno Tomasz, and Wesley G. Bentrude*

Department of Chemistry, University of Utah, Salt Lake City, Utah 84112

Received June 4, 1991

A series of nucleoside cyclic 3′,5′-phosphoramidates has been studied by ^1H NMR spectroscopy. For *cis*-**9**–**20** a chair–twist equilibrium has been characterized for the six-membered 1,3,2-dioxaphosphorinane (phosphoramidate) ring. The chair–twist equilibrium constant was estimated on the basis of the proton–phosphorus coupling constants for the 5′a and 5′b protons and found to vary with the nature of the amino group on phosphorus, the solvent, and to a lesser degree, the 2′-substituent (H or OH), and the heterocyclic base (purine or pyrimidine). The replacement of a pyrimidine base (uracil) with a purine base (adenine) shifts the equilibrium toward the chair conformation by only 0.1–0.3 kcal/mol. The presence of a 2′-OH also favors the chair form to a small extent (0.2–0.4 kcal/mol). The observed equilibrium constant for the *N*,*N*-dimethyl phosphoramidate derived from thymidine is used to estimate an intrinsic resistance of the six-membered ring to chair to twist interconversion ($\Delta G^\circ(C \rightarrow T)$) in three solvents of only 0.5–0.8 kcal/mol. Correction of this value by 0.5 ± 0.2 kcal/mol (change of base and 2′-substituent) gives an estimated $\Delta G^\circ(C \rightarrow T)$ for cAMP of 0.8–1.5 kcal/mol. Similarly corrected, the value of $\Delta G^\circ(C \rightarrow T)$ for cAMP, based on the previously studied trans phenyl cyclic 3′,5′-phosphate derived from thymidine, becomes 2.5–2.9 kcal/mol. The potential for chair–twist conversion on binding of cAMP to an enzyme is pointed out, although no experimental evidence regarding this question exists. *trans*-**9**–**20** all are shown to exist in the chair conformation. ^1H NMR reveals no evidence for conformational change in the sugar rings of these molecules on chair to twist conversion. The relative destabilization order for an axial amino substituent in the series **9**–**20** was found to be Me_2N > piperidinyl > $PhCH_2NH$ > PhNH.

Both adenosine cyclic 3′,5′-monophosphate, cAMP (**1**), and guanosine cyclic 3′,5′-monophosphate, cGMP (**2**), play central roles in the regulation of cell metabolism.[1] cAMP binds to the regulatory subunits of protein kinases I and II to free the catalytic subunit that is responsible for the phosphorylation leading to activation of certain key metabolic enzymes.[2] The enzymatic, hydrolytic ring-opening conversion of cAMP to adenosine 5′-monophosphate (5′-AMP) is accomplished by specific isozymic phosphodiesterases.[3] A detailed understanding of the binding of cAMP to the active site is critical to a full understanding of the interaction of cAMP with protein kinases (PK's) or phosphodiesterase (PDE's).



1 B = Adenine
2 B = Guanine

---

(1) See, for example the review series: *Adv. Cyclic Nucleotide Res.* **1971–1983**, *1–15*. *Adv. Cyclic Nucleotide Res. Protein Phosphorylation Res.* **1983–1987**, *16–20*. *Adv. Second Messenger Phosphoprotein Res.* **1988–1990**, *21–24*.

(2) Taylor, S. S.; Buechler, J. A.; Yonemoto, W. *Ann. Rev. Biochem.* **1990**, *59*, 971.

(3) Beavo, J. A. *Adv. Second Messenger Phosphoprotein Res.* **1988**, *22*, 1.

0022-3263/91/1956-5911$02.50/0