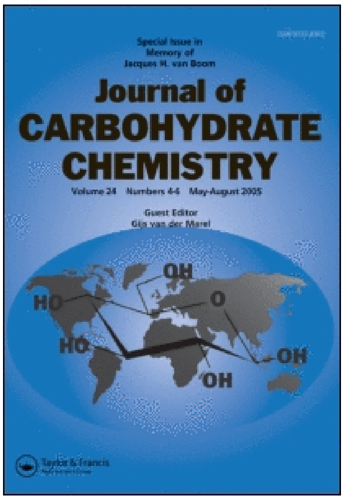

Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Crystal Structure of 1,3,4,6-Tetra-*O*-Acetyl-2-deoxy-2-fluoro-β-*D*-Galactopyranoside

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To cite this Article Srikrishnan, T. and An, S. H.(1988) 'Crystal Structure of 1,3,4,6-Tetra-*O*-Acetyl-2-deoxy-2-fluoro-β-*D*-Galactopyranoside', Journal of Carbohydrate Chemistry, 7: 3, 571 — 581
To link to this Article: DOI: 10.1080/07328308808057551
URL: http://dx.doi.org/10.1080/07328308808057551

J. CARBOHYDRATE CHEMISTRY, 7(3), 571-581 (1988)

CRYSTAL STRUCTURE OF 1,3,4,6-TETRA-O-ACETYL-2-DEOXY-2-FLUORO-β-D-GALACTOPYRANOSIDE

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Received February 8, 1988 - Final Form April 18, 1988

ABSTRACT

1,3,4,6-Tetra-O-acetyl-2-deoxy-2-fluoro-β-D-galactopyranoside is a key intermediate in the synthesis of phenyl-2-fluoro-2-deoxy-α-D-galactopyranoside which is used in the studies of the inhibitory activities of α-2-L-fucosyl transferase. Crystals of the title compound ($C_{14}H_{19}O_9F$) are triclinic, space group P1, with cell dimensions a=7.679(1), b=9.933(1), c=11.458(2)Å, α=89.31(1), β=72.83(1), γ=86.49(1)°, V=833.5Å^3, Z=2 (two independent molecules in the unit cell), F.W. 351.3, D_{obs} = 1.39 g/c.c, D_{calc} = 1.401 g/c.c, CAD-4 diffractometer data (3533 reflections, 2483 >3σ) and final R = 0.048. The sugars of both the independent molecules have chair conformations with C(3) and O(1) deviating by 0.64 and -0.66Å in one molecule and C(2) and C(5) deviating by 0.70 and -0.69Å in the other molecule from the best plane involving the other four atoms of the pyranose ring. The conformation across C(5)-C(6) is gauche-trans in both molecules. The acetyl groups take up the preferred trans conformation across the C-O bond.

INTRODUCTION

1,3,4,6-Tetra-O-acetyl-2-deoxy-2-fluoro- β -D-galactopyranoside was synthesized with a slight modification of the procedure of Korytnyk and his coworkers.[1] 3,4,6-Tri-O-acetyl-D-galactal was treated with XeF_2 in the presence of BF_3-etherate to give a racemic mixture of 3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-D-galactopyranosyl fluoride. The unseparated racemic mixture was hydrolyzed with methanolic hydrogen chloride, followed by acetylation, to give 1,3,4,6-tetra-O-acetyl-2-deoxy-2-fluoro-β-D-galactopyranoside as a major product. X-ray crystallographic investigation of the title compound was undertaken to confirm the characterization of this intermediate as well as to study the conformation of the acetyl groups in the solid state and correlate the patterns of C-O bond lengths at the acetal centers of galactopyranosides with strongly electronegative oxygen substituents adjacent to the ring oxygen.

RESULTS AND DISCUSSION

The final atomic positional and thermal parameters for both the molecules in the unit cell are given in Table 1. The anisotropic thermal parameters and lists of observed and calculated structure factors are given as supplementary material. Table 2 lists the $B_{eq} = 4/3 \Sigma_i \Sigma_j B_{ij} (\alpha_i \cdot \alpha_j)$ for the non-hydrogen atoms and isotropic thermal parameters, B_{iso} for the hydrogen atoms. ORTEP[2] drawings for both the molecules A and B (together with the atom numbering followed in this paper) are shown in Figs. 1(a) and (b). The bond lengths and angles involving the non-hydrogen atoms are shown in the schematic diagrams Figs. 2(a) and (b). The average C-C and C-O bond lengths for the pyranoside ring are 1.515(7) and 1.419(6) Å, respectively. Both of the values agree well with the values reported for other pyranosides.[3-5] The two adjacent endocyclic C-O bond lengths C(1')-O(5') and C(5')-O(5') are unequal [1.407(5) and 1.442(7) Å in molecule A and 1.396(8) and 1.434(6) Å in molecule B, respectively]. The bond angles in the two molecules generally agree with each other and also with most values reported in the literature for β-D-pyranosides.[5,6] The bond angle at O(5') is 111.7° in molecule A and 111.5° in molecule B and is similar to the mean value of 111.1° observed for β-D-pyranosides.[6] The exocyclic bond angles O(5')-C(5')-C(6') are 107.3 and 107.2° in molecules A and B, respectively, and agree very well with the mean value of 107.5° found in β-D-pyranosides.[6]

Both of the independent molecules have a chair conformation. C(3) and O(5) deviate by 0.64 and -0.66 Å from the best plane in molecule A and C(2) and C(5) deviate by 0.70 and -0.69 Å in molecule B. The Cremer-Pople puckering parameters[4] Q, Θ and ϕ are 0.57(1), 5.3(7) and 342(7)° in molecule A and 0.60(1), 2.7(7)° and 316(14)° in molecule B, respectively. The conformation across C(5')-C(6') is gauche-trans with the torsion angles O(5')-C(5')-C(6')-O(6') and C(4')-C(5')-C(6')-O(6') having values of -71.8 and 166.2° in molecule A and -74.9 and 165.1° in molecule B, respectively (see Table 2 for all torsion angles in the molecules).

The trend towards longer exocyclic bonds at the acetal center in compounds with strongly electronegative aglycones, is also exhibited in this compound, C(3')-O(3'), C(4')-O(4') and C(6')-O(6') being much larger than C(1')-O(1'). Similar bond lengths patterns have been found in several peracetylated α-hexopyranosides including α-pentaacetates of altrose,[7] gulose[8] and idose.[9] The acetyl groups take up the preferred trans conformation across C-O bonds. The torsion angles involving the acetyl groups namely C(1')-O(1')-CA(1')-CM(1'), C(3')-O(3')-CA(3')-CM(3'), C(4')-O(4')-CA(4')-CM(4') and C(6')-O(6')-CA(4')-CM(6') have values of -179.1, +164.8, -171.5, and 178.3° in molecule A and -175.3, 174.6, -176.7, and 178.7° in molecule B, respectively. The average C-O bond distance is 1.347(7) Å, the C=O distance is 1.193(7) Å and the C-C distance is 1.489(9) Å. Table 3 gives the C-H...X interactions. The crystal structure is stabilized by a number of C-H...O interactions and some C-H...F interactions.

CONCLUSIONS

The conformations of the two independent molecules, though very similar, have some marked differences in the relative orientations of the acetyl groups at C(3') and C(4') of the pyranose

Table 1. Final Fractional Positional Parameters and Temperature Factors for all Atoms in the Molecule and their Estimated Standard Deviations in Parentheses.[a]

Atom	X	Y	Z	$B(\AA^2)$
Molecule A				
C(1')	0.1948(7)	0.6002(5)	0.2598(4)	3.0(1)
C(2')	0.1820(7)	0.5698(5)	0.1351(5)	3.1(1)
C(3')	0.2257(7)	0.6926(5)	0.0558(4)	3.1(1)
C(4')	0.4096(8)	0.7436(5)	0.0561(4)	3.0(1)
C(5')	0.4176(7)	0.7592(5)	0.1853(4)	3.0(1)
O(5')	0.373(-)	0.636(-)	0.252(-)	3.15(8)[b]
O(1')	0.1683(6)	0.4802(4)	0.3289(3)	3.77(9)
CA(1')	0.1057(9)	0.4919(7)	0.4524(5)	4.3(1)
OA(1')	0.0651(9)	0.6000(5)	0.5013(4)	6.7(2)
CM(1')	0.087(1)	0.3604(8)	0.5128(6)	5.9(2)
F(2')	0.0018(5)	0.5387(4)	0.1453(3)	4.55(8)
O(3')	0.2418(5)	0.6578(4)	-0.0688(3)	3.65(8)
CA(3')	0.1332(9)	0.7527(7)	-0.1258(5)	4.5(1)
OA(3')	0.0013(9)	0.7944(6)	-0.0728(5)	8.7(2)
CM(3')	0.205(1)	0.7009(8)	-0.2608(6)	5.7(2)
O(4')	0.5529(5)	0.6486(4)	-0.0081(3)	3.41(8)
CA(4')	0.6452(9)	0.6784(7)	-0.1264(5)	4.5(1)
OA(4')	0.6239(8)	0.7816(5)	-0.1722(4)	6.4(1)
CM(4')	0.768(1)	0.5590(8)	-0.1833(7)	6.6(2)
C(6')	0.6018(8)	0.7931(6)	0.1922(5)	3.6(1)
O(6')	0.5761(5)	0.8368(4)	0.3167(3)	4.29(9)
CA(6')	0.7241(8)	0.8643(6)	0.3484(5)	3.9(1)
OA(6')	0.8754(6)	0.8493(5)	0.2797(4)	5.7(1)
CM(6')	0.680(1)	0.9118(9)	0.4764(6)	6.5(2)

Table 1 cont'd...

Molecule B				
C(1')	0.4864(8)	0.2804(6)	-0.3069(5)	3.4(1)
C(2')	0.3521(8)	0.3131(6)	-0.1814(5)	3.4(1)
C(3')	0.3390(8)	0.1888(5)	-0.1017(4)	3.3(1)
C(4')	0.5291(8)	0.1397(5)	-0.0966(5)	3.3(1)
C(5')	0.6543(7)	0.1185(5)	-0.2270(5)	3.1(1)
O(5')	0.6572(5)	0.2421(4)	-0.2933(3)	3.42(8)
O(1')	0.5090(6)	0.4046(4)	-0.3724(3)	4.02(8)
CA(1')	0.582(1)	0.3932(7)	-0.4947(5)	4.8(2)
OA(1')	0.614(1)	0.2892(5)	-0.5473(4)	7.7(2)
CM(1')	0.613(1)	0.5288(8)	-0.5508(6)	6.3(2)
F(2')	0.1787(5)	0.3438(4)	-0.1974(3)	4.81(3)
O(3')	0.2246(5)	0.2304(4)	0.0186(3)	3.52(8)
CA(3')	0.1520(9)	0.1307(6)	0.0923(6)	4.7(2)
OA(3')	0.1764(8)	0.0155(5)	0.0600(5)	7.6(2)
CM(3')	0.050(1)	0.1795(8)	0.2190(6)	6.1(2)
O(4')	0.6017(6)	0.2406(4)	-0.0387(3)	3.72(8)
CA(4')	0.598(1)	0.2208(7)	0.0799(6)	5.0(2)
OA(4')	0.536(1)	0.1213(6)	0.1350(4)	8.0(2)
CM(4')	0.668(1)	0.3369(8)	0.1262(6)	7.6(2)
C(6')	0.8495(8)	0.0786(6)	-0.2307(5)	3.8(1)
O(6')	0.9333(5)	0.0285(4)	-0.3537(3)	4.29(9)
CA(6')	1.1128(8)	0.0162(6)	-0.3928(5)	3.8(1)
OA(6')	1.2090(6)	0.0462(5)	-0.3349(4)	5.7(1)
CM(6')	1.179(1)	-0.0403(8)	-0.5218(6)	5.6(2)

[a] Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as: (4/3)*[A2*B(1,1)+B2*B(2,2)+C2*B(3,3)+ AB(COS GAMMA)*B(1,2)+AC(COS BETA)*B(1,3)BC(COS ALPHA)*B(2,3)].

[b] This atom was kept fixed for origin definition.

Table 2. Some Important Torsion Angles in the Molecule.

Angle	Molecule A	Molecule B
O(5')-C(1')-C(2')-C(3')	-59.9(6)°	-59.8(7)°
C(1')-C(2')-C(3')-C(4')	53.5(7)	55.3(7)
C(2')-C(3')-C(4')-C(5')	-50.7(7)	-54.4(7)
C(3')-C(4')-C(5')-O(5')	52.9(7)	57.3(7)
C(4')-C(5')-O(5')-C(1')	-61.0(5)	-64.5(6)
C(5')-O(5')-C(1')-C(2')	64.5(6)	65.3(7)
C(2')-C(1')-O(1')-CA(1')	-155.4(7)	-162.9(8)
O(5')-C(1')-O(1')-CA(1')	86.8(6)	81.2(7)
C(1')-O(1')-CA(1')-CM(1')	-179.1(9)	-175.3(9)
C(1')-O(1')-CA(1')-OA(1')	3.8(9)	5.4(9)
C(2')-C(3')-O(3')-CA(3')	122.5(8)	161.1(8)
C(4')-C(3')-O(3')-CA(3')	-117.4(8)	-80.1(8)
C(3')-O(3')-CA(3')-OA(3')	-2.8(9)	-1.7(9)
C(3')-O(3')-CA(3')-CM(3')	164.8(8)	174.6(9)
C(3')-C(4')-O(4')-CA(4')	100.1(6)	102.3(7)
C(5')-C(4')-O(4')-CA(4')	-138.9(7)	-139.1(7)
C(4')-O(4')-CA(4')-OA(4')	7.3(9)	0.2(9)
C(4')-O(4')-CA(4')-CM(4')	-171.5(8)	-176.7(9)
C(4')-C(5')-C(6')-O(6')	166.2(7)	165.1(7)
O(5')-C(5')-C(6')-O(6')	-71.8(7)	-74.9(7)
C(5')-C(6')-O(6')-CA(6')	175.6(8)	164.2(7)
C(6')-O(6')-CA(6')-OA(6')	-2.8(8)	-1.6(9)
C(6')-O(6')-CA(6')-CM(6')	178.3(9)	178.7(9)

ring [the torsion angles C(3')-O(3')-CA(3')-CM(3') and C(4')-O(4')-CA(4')-CM(4') at these two carbon atoms are 164.8 and -171.7° in molecule A, and 174.6 and -176.7° in molecule B, respectively]. The pyranosides have the preferred ${}^5C_2$ chair conformations, gauche-trans across C(5')-C(6') and a preferred trans conformation for all the acetyl groups.[10]

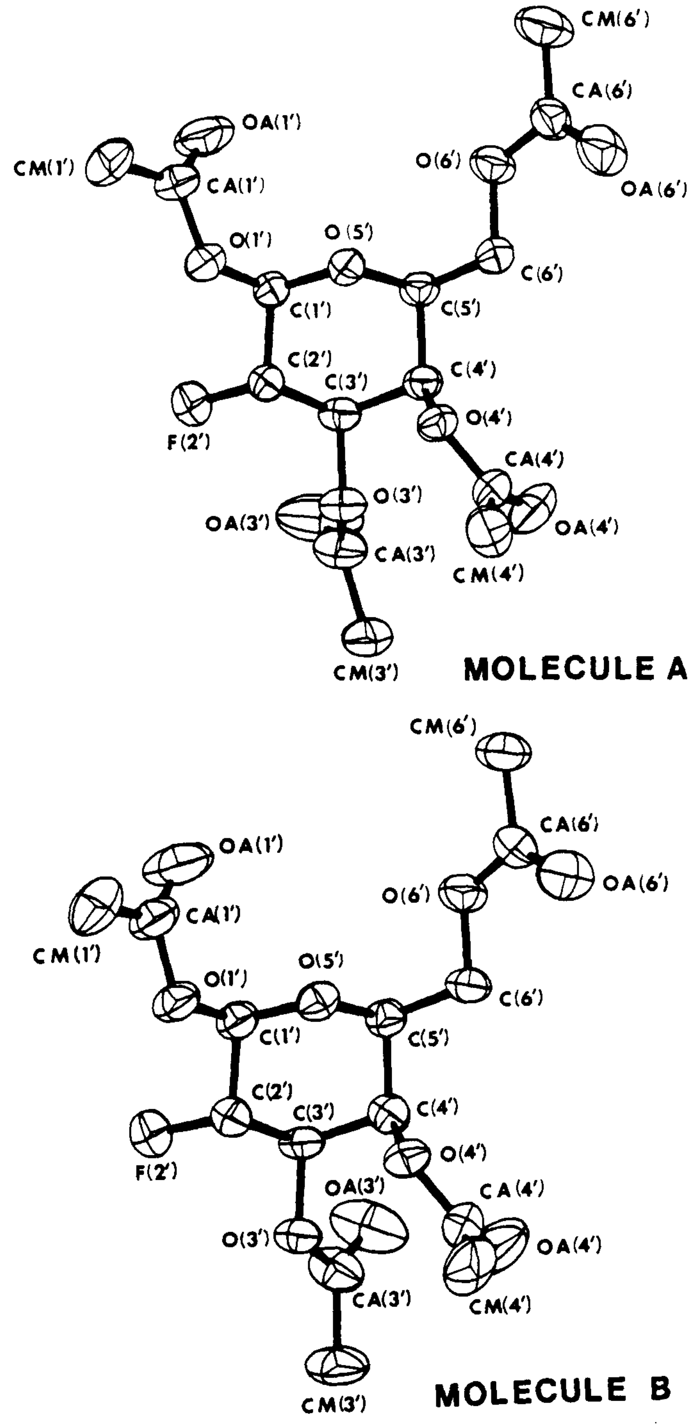
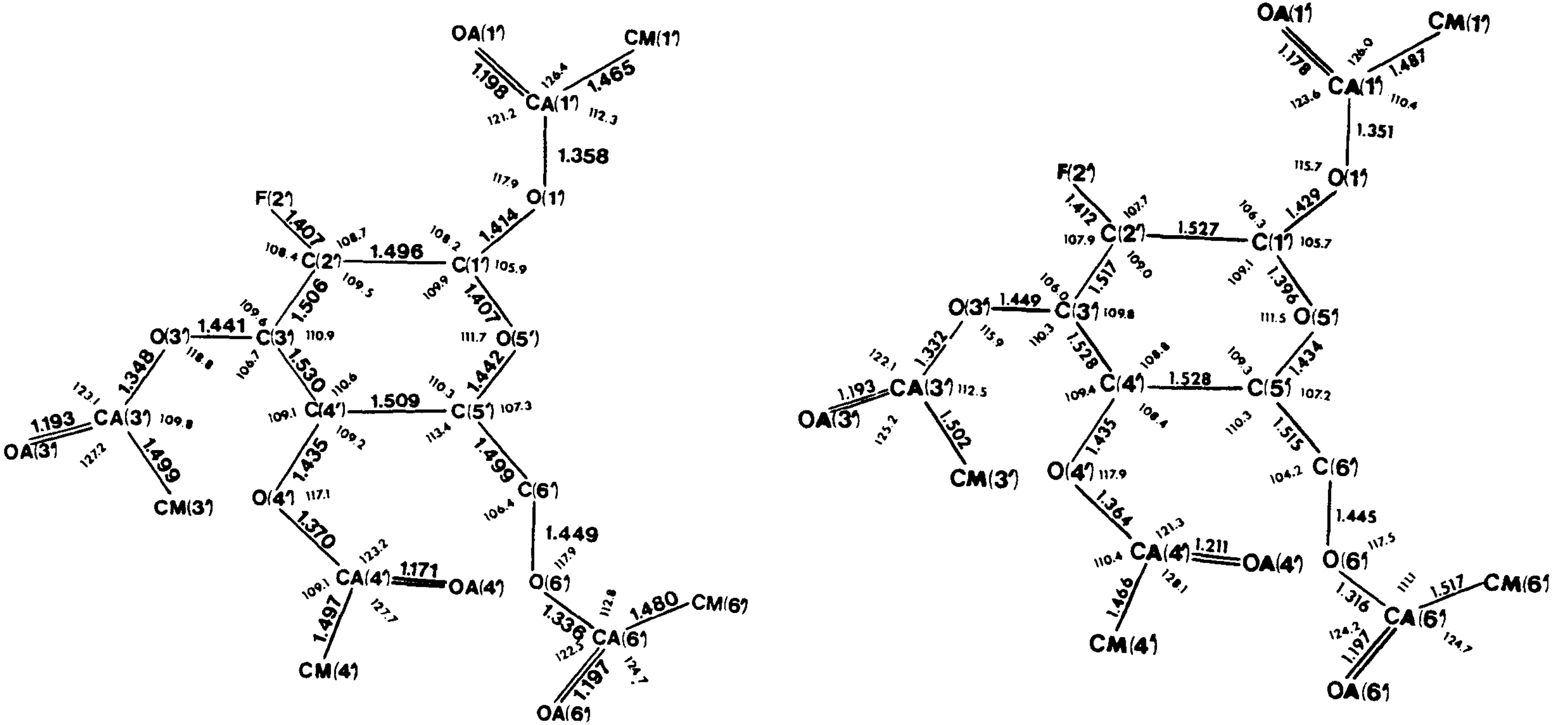


FIG. 1. An ORTEP plot of molecules A and B showing atom numbering and labels.



MOLECULE A

MOLECULE B

FIG. 2. Bond lengths (in Å) and bond angles (in degrees) for molecules A and B.

Table 3. Hydrogen Bond Distances (in Å) and Angle (°): C–H...X Interactions.

Donor D	Hydrogen H	Acceptor A	Distances in Å D–H	H...A	D...A	Angle D–H...A	Data Set
C(1')A	HC(1')A	OA(6')A	0.99	2.43	3.337	153°	(1+x,y,z)
C(2')A	HC(2')A	O(3')B	1.05	2.69	3.601	145°	(x,y,z)
C(3')A	HC(3')A	OA(6')A	1.09	2.49	3.428	144°	(1+x,y,z)
CM(1')A	H3M(1')A	F(2')B	0.79	2.87	3.591	152°	(1+x,y,z)
CA(3')B	H1M(3')B	F(2')A	0.87	2.87	3.678	162°	(1+x,y,z)
CA(4')B	H1M(4')B	O(4')A	1.18	2.61	3.617	143°	(x,y,z)
CA(4')B	H2M(4')B	O(5')A	1.02	2.88	3.658	133°	(x,y,z)

EXPERIMENTAL

Crystals of the compound were obtained by slow evaporation of an aqueous methanol solution. A crystal of dimensions 0.25 x 0.25 x 0.1 mm (μCuKα = 10.4 cm^{-1}) was chosen for data collection on an Enraf-Nonius CAD-4 diffractometer using Ni filtered CuKα radiation (λ= 1.5418 Å). The unit cell dimensions were obtained using 25 reflections with θ in the range from 10 to 30°. Data was collected using the $\omega/2\theta$ scan. Scan widths were calculated using (0.8 + 0.14 tan θ) and aperture widths were calculated using (3.0 + 1.2 tan θ). The intensities of three reflections were monitored after every hour of exposure, and the loss of intensity was less than 5%. The orientation matrix was checked after measurement of 100 reflections. A total of 3533 reflections were measured ($2\theta_{max}$ = 154°), out of which 2483 had intensities $>3\sigma(I)$. Three reflections with $\chi \sim 90°$ were chosen, and their intensities were measured for all values of ϕ from 0 to 360° in steps of 10°. The resultant transmission curve was used to correct for absorption effects. The average transmission factor was 0.92. The density of the crystal was measured by flotation in bromoform and benzene. Lorentz and polarization corrections were applied to the intensities.

Structure Determination and Refinement: The structure was solved by the application of multi-solution techniques[11] using 326 largest E values ($E \geqslant 1.5$). An E-map calculated for the set with the highest combined figure of merit of 2.49 and a residual value of 0.22 revealed almost all the nonhydrogen atoms, except for four hydroxyl oxygens which were found from subsequent difference Fourier synthesis. The R factor at the end of the isotropic refinement was 0.152 and after the refinement with anisotropic temperature factors was 0.065. The locations of hydrogen atoms were obtained from difference electron density maps. All hydrogens except fourteen which belonged to the terminal methyl groups of the acetyl linkages were found from the difference maps. The final R factor using full matrix least squares with anisotropic temperature factors for non-hydrogens and isotropic temperature factors for the hydrogen atoms was 0.048 for the observed 2483 reflections ($I>3\sigma$). The weighted R factor was 0.060 and the goodness of fit was 1.74. The quantity that was minimized in the full-matrix refinement was $w(|Fo|-(1/k)|Fc|)^2$ where the weight $w = 4(|Fo|^2/\sigma^2(|Fo|^2)$ and $\sigma^2(|Fo|^2) = [\sigma^2(I)+p^2I^2]/LP$ where p is an "ignorance factor" to down weight intense reflections ($p = 0.05$), $\sigma(I)$ is the standard deviation in intensity I based on counting statistics and k is the scale factor. All the calculations were carried out on the PDP 11/34 computer using the "structure determination package" programs of ENRAF-NONIUS.[12] Scattering factors for oxygen, nitrogen and carbon atoms are from the International Tables for X-ray Crystallography[13] and for the hydrogen atoms from Stewart, Davidson and Simpson.[14] Supplementary materials can be obtained as noted.[15]

ACKNOWLEDGEMENTS

Our thanks are due to Dr. Parthasarathy for the use of the crystallographic facilities, to Dr. K. L. Matta for suggesting this project and for his interest in the investigation, and to Mrs. Judith Mann for excellent technical assistance. This work was supported by grants NIH GM24864 and GM31425 and the New York State Department of Health.

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