Short Communication

X-Ray Analysis of Ca^{2+} Antagonists: 3,5-Bis-(methoxycarbonyl)-2,6-dimethyl-4-(2-aminophenyl)-1,4-dihydropyridine Hydrate

Rune Fossheim

Department of Chemistry, University of Oslo, P.O. Box 1033, Blindern, 0315 Oslo 3, Norway

Fossheim, Rune, 1986. X-Ray Analysis of Ca^{2+} Antagonists: 3,5-Bis(methoxycarbonyl)-2,6-dimethyl-4-(2-aminophenyl)-1,4-dihydropyridine Hydrate. – Acta Chem. Scand. B 40: 776–778.

The structures of several Ca^{2+} antagonists of the 1,4-dihydropyridine type were determined in order to investigate relationships between conformational parameters and pharmacological activity related to their smooth muscle relaxant properties.[1-4] Unlike previously studied derivatives, intramolecular hydrogen bonding involving one or both carbonyl groups should be possible in the title compound. The molecular structure was determined in order to investigate possible effects of hydrogen bonding on molecular conformation.

The crystals of $(C_{17}H_{20}N_2O_4)H_2O$ are triclinic, space group $P\bar{1}$ (No. 2), $Z = 2$, with cell dimensions $a = 7.622(2)$, $b = 10.157(2)$, $c = 11.371(2)$ Å, $\alpha = 86.40(1)$, $\beta = 89.81(2)$ and $\gamma = 69.03(2)°$. Data were collected on a Nicolet P3/F four-circle diffractometer at ca. −140 °C using MoK_α radiation and the $\theta/2\theta$ scanning mode. A total of 4144 observed reflections were recorded in the 2θ range 2.5–65.0° (crystal size 0.50 · 0.25 · 0.10 mm). Correction for absorption effects was not deemed necessary.

The structure was solved by direct methods and refined by least-squares techniques. All hydrogen atoms were located in a difference Fourier map. Non-hydrogen atoms were refined anisotropically; hydrogen atoms were refined isotropically, giving a final R value of 4.7 % [R(w) = 4.5 %] for 4144 reflections. The computer programs used are described by Groth.[5] Final fractional coordinates are given in Table 1. A schematic drawing of the molecule is given in Fig. 1. Selected torsion angles and bond angles may be found in Table 2.

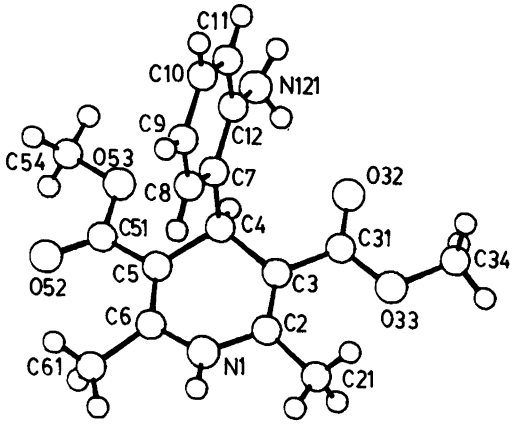

Fig. 1. A schematic drawing of the molecule showing the adopted atomic labeling scheme.

The sum of the bond angles around the amino N atom (331°) is very close to the value in sp^3 hybridized N atoms (328.4°). Both hydrogen atoms are located on the same side of the phenyl ring plane. In the crystal structure of aniline the nitrogen atom is less pyramidal,[6] the sum of the angles being 338° and 346° for the two independent aniline molecules in the crystal.

The hydrogen bond accepting and donating amino group and the cocrystallized water molecule make the hydrogen bonding pattern more

complex than in other crystal structures in this series. An illustration of the hydrogen bonding pattern is given in Fig. 2. The water molecule is involved in hydrogen bonding to three neighbouring dihydropyridine molecules. It is the acceptor in a hydrogen bond to the dihydropyridine ring nitrogen and the donor in the hydrogen bonds to O52 and the amino group. An intramolecular hydrogen bond is formed between O32 and the amino group; O32 is also involved in a weaker hydrogen bond to the amino group of a neighbouring molecule.

The hydrogen bonding pattern does not impose large conformational differences between this compound and previously studied *ortho* phenyl-substituted derivatives. In particular, the ester groups adopt the conformation most often observed: the carbonyl groups being twisted in opposite directions. The preference for forming strong intermolecular hydrogen bonds may be decisive for the conformation adopted in the crystal lattice. It is possible that intramolecular hydrogen bonding favours the conformation with both carbonyl groups antiperiplanar with respect to the ring double bonds in solution. This conformation has so far not been observed in the solid state.

Acknowledgement. I thank Dr. D. J. Triggle for supplying the crystals.

Table 1. Fractional atomic coordinates. Estimated standard deviations in parenthesis.

Atom	*x*	*y*	*z*
O1	.1090(2)	.1819(1)	.1812(1)
O32	.2339(2)	.7449(1)	.5068(1)
O33	.2908(1)	.5227(1)	.5775(1)
O52	.2374(2)	.6981(1)	−.0500(1)
O53	.2445(1)	.8462(1)	.0862(1)
N1	.2103(2)	.4163(1)	.2370(1)
N121	.0349(2)	.9948(1)	.3529(1)
C2	.2202(2)	.4493(1)	.3525(1)
C3	.2159(2)	.5807(1)	.3735(1)
C4	.1702(2)	.6979(1)	.2747(1)
C5	.2145(2)	.6344(1)	.1549(1)
C6	.2245(2)	.5007(1)	.1405(1)
C7	−.0365(2)	.7964(1)	.2785(1)
C8	−.1745(2)	.7469(2)	.2409(1)
C9	−.3646(2)	.8268(2)	.2435(1)
C10	−.4210(2)	.9610(2)	.2852(1)
C11	−.2878(2)	1.0127(2)	.3231(1)
C12	−.0953(2)	.9328(1)	.3199(1)
C21	.2400(2)	.3276(2)	.4404(1)
C31	.2464(2)	.6243(1)	.4895(1)
C34	.3073(2)	.5682(2)	.6937(1)
C51	.2326(2)	.7247(1)	.0537(1)
C54	.2733(3)	.9382(2)	−.0089(1)
C61	.2561(2)	.4265(2)	.0272(1)
H1	.005(3)	.217(2)	.146(2)
H2	.095(3)	.113(2)	.231(2)
H11	.195(3)	.333(2)	.223(2)
H41	.251(2)	.753(2)	.288(1)
H81	−.133(2)	.654(2)	.215(1)
H91	−.459(2)	.793(2)	.219(1)
H101	−.547(3)	1.016(2)	.288(2)
H111	−.323(2)	1.105(2)	.350(2)
H122	.133(3)	.931(2)	.392(2)
H123	−.021(3)	1.067(2)	.395(2)
H211	.375(3)	.284(2)	.470(2)
H212	.158(2)	.360(2)	.507(2)
H213	.205(3)	.256(2)	.403(2)
H341	.393(3)	.620(2)	.696(2)
H342	.181(3)	.629(2)	.721(2)
H343	.358(2)	.478(2)	.744(2)
H541	.286(3)	1.021(2)	.029(2)
H542	.377(3)	.887(2)	−.052(2)
H543	.164(3)	.971(2)	−.064(2)
H611	.163(3)	.480(2)	−.032(2)
H612	.375(3)	.421(2)	−.005(2)
H613	.256(3)	.333(2)	.037(2)

Table 2. Selected torsion angles and bond angles. Estimated standard deviations in parenthesis.

Angle	(°)
C6 – N1 – C2 – C3	10.1(2)
N1 – C2 – C3 – C4	9.6(2)
C2 – C3 – C4 – C5	−23.8(2)
C3 – C4 – C5 – C6	21.7(2)
C2 – N1 – C6 – C5	−12.2(2)
C4 – C5 – C6 – N1	−5.5(2)
C21– C2 – C3 – C31	5.4(2)
C51– C5 – C6 – C61	0.9(2)
C2 – C3 – C31– O32	−176.8(1)
C4 – C5 – C51– O52	−167.5(1)
C3 – C31– O33– C34	−175.6(1)
C5 – C51– O53– C54	176.7(1)
C3 – C4 – C7 – C8	−73.9(1)
C3 – C4 – C7 – C12	104.8(1)
C7 – C12–N121–H122	−40.4(13)
C11– C12–N121–H123	20.0(13)
C12–N121–H122	110.5(12)
C12–N121–H123	110.0(12)
H122–N121–H123	110.9(16)

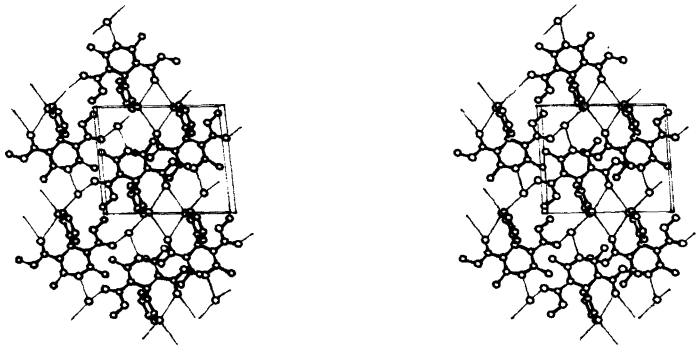

Fig. 2. The molecular packing arrangement as seen down the *a* axis. Hydrogen atoms are omitted.

References

1. Triggle, A. M., Shefter, E. and Triggle, D. J. *J. Med. Chem. 23* (1980) 1442.
2. Fossheim, R., Svarteng, K., Mostad, A., Rømming, C., Shefter, E. and Triggle, D. J. *J. Med. Chem. 25* (1982) 126.
3. Fossheim, R. *Acta Chem. Scand. B 39* (1985) 785.
4. Fossheim, R. *J. Med. Chem. 29* (1986) 305.
5. Groth, P. *Acta Chem. Scand. 27* (1973) 1837.
6. Fukoyo, M., Hirotsu, K. and Higuchi, T. *Acta Crystallogr. B 39* (1982) 640.

Received May 5, 1986.