MOLECULAR PROPERTIES OF LOCAL ANESTHETICS: THE CRYSTAL STRUCTURE OF PROCAINE HYDROCHLORIDE

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The crystal structure of procaine hydrochloride has been determined from three-dimensional diffractometer data. Structural similarities with acetylcholine and other molecules active in the cholinergic system suggests a common membrane receptor.

INTRODUCTION

Many compounds of diverse nature act as local anesthetics. Several of them, including procaine, are chemically similar to natural compounds active in nerve impulse transmission. We have undertaken the X-ray diffraction investigation of the crystal structure of procaine hydrochloride The structure of this molecule has several features which can be compared with molecules of the cholinergic system and other related molecules.

EXPERIMENTAL

Crystals of procaine hydrochloride suitable for X-ray analysis were obtained by slow evaporation of an ethanol-ethyl acetate solution. The crystals are orthorhombic (space group Pbca) with cell dimensions a = 8.280, b = 25.023, c = 14.157Å. Three-dimensional intensity data were collected on a Phillips Pailred diffractometer employing equi-inclination geometry. All data were collected using silicon monochromatized molybdenum Kα radiation. The fixed counter moving crystal method was used employing a 2° scan range and a 1° per minute scan. Background was measured on each side of the scan for two minutes. All reflections for which the statistical counting error exceeded 50% were rejected (Ladell, 1965). A total of 883 reflections were used in the analysis.

The positional parameters of the chlorine atom were obtained from a

three-dimensional Patterson synthesis. All remaining non-hydrogen atoms were located in the structure using the method of atomic superposition. All hydrogen atom positional parameters except for H(15) of the C(13) methyl group were located in the three-dimensional Fourier difference synthesis. The structure was refined by three-dimensional full-matrix least squares. All atoms were included in the refinement. Positional parameters and anisotropic temperature factors were refined for the non-hydrogen atoms

TABLE 1

POSITIONAL PARAMETERS

	x	y	z
CL(1)	0.0787	0.2097	0.1172
C(1)	0.1175	0.5211	0.0951
C(2)	0.1326	0.5757	0.1004
C(3)	0.0348	0.6049	0.1641
C(4)	-0.0802	0.5776	0.2129
C(5)	-0.0965	0.5236	0.2069
C(6)	0.0053	0.4941	0.1469
C(7)	-0.0118	0.4357	0.1454
C(8)	0.1010	0.3543	0.0887
C(9)	0.2256	0.3352	0.0194
C(10)	0.4355	0.3109	0.1371
C(11)	0.6110	0.2993	0.1487
C(12)	0.4598	0.3985	0.0530
C(13)	0.4258	0.4261	-0.0378
O(1)	0.1063	0.4117	0.0937
O(2)	-0.1155	0.4089	0.1836
N(1)	0.0538	0.6604	0.1708
N(2)	0.3996	0.3410	0.0491
H(1)	-0.0089	0.6697	0.2181
H(2)	0.1600	0.6700	0.1200
H(3)	0.1859	0.5006	0.0481
H(4)	0.1865	0.5897	0.0656
H(5)	-0.1618	0.5944	0.2506
H(6)	-0.1670	0.5077	0.2318
H(7)	0.0135	0.3380	0.0634
H(8)	0.1357	0.3437	0.1555
H(9)	0.2226	0.3013	0.0125
H(10)	0.2278	0.3532	-0.0464
H(11)	0.3990	0.4183	0.1162
H(12)	0.5369	0.3946	0.0825
H(13)	0.4717	0.4082	-0.0855
H(14)	0.4986	0.4539	-0.0376
H(15)	0.3400	0.4600	-0.0400
H(16)	0.3937	0.3348	0.1905
H(17)	0.3853	0.2817	0.1403
H(18)	0.6660	0.2770	0.1028
H(19)	0.6103	0.2717	0.1987
H(20)	0.6670	0.3255	0.1710
H(21)	0.4788	0.3246	-0.0068

while only the positional parameters of the hydrogen atoms were refined. Isotropic temperature factors of 6.0 were assigned to the hydrogen atoms. The final positional parameters of all atoms are shown in table 1. The final R index was 0.065.

RESULTS AND DISCUSSION

The measured bond distances and angles of procaine hydrochloride are shown in figure 1. The estimated standard deviations of the bond distances are all approximately ± 0.01Å. All bond distances and angles are essentially normal and agree with similar dimensions observed in a variety of related compounds (Sutton, 1958).

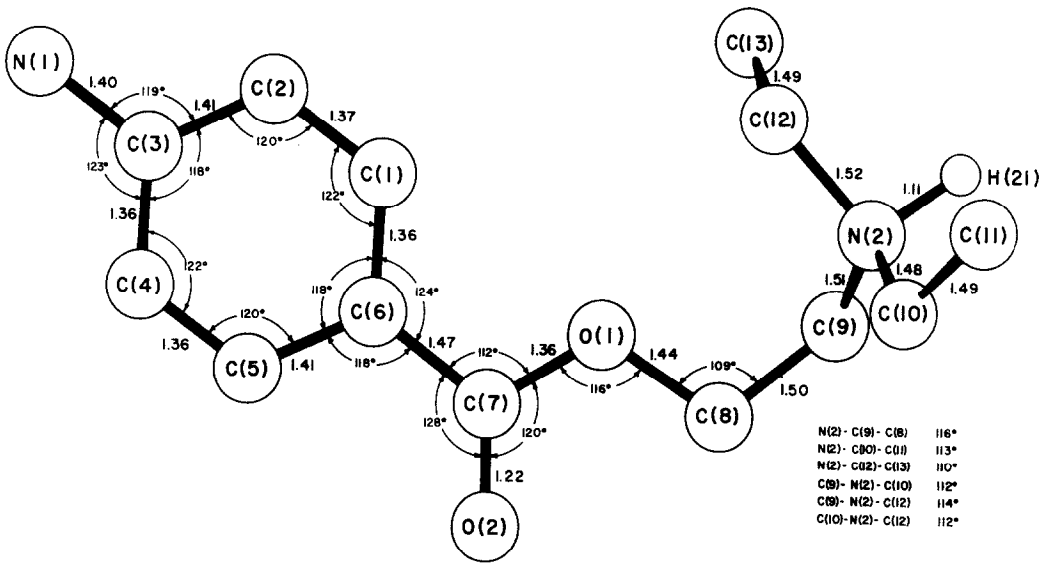

Figure 1: Molecular dimensions of procaine hydrochloride

The major portion of the molecule, extending through atom C(8), is planar. Atom C(9) is nearly in this plane; the C(7)-O(1)-C(8)-C(9) torsion angle being 172.8°. As seen in figure 1, atom N(2) is rotated out of the plane such that the torsion angle O(1)-C(8)-C(9)-N(2) is 70.4°. The environment about the N(2) atom is essentially tetrahedral.

It is fairly well agreed upon that local anesthetic action occurs on nerve membranes and blocks conduction by interfering with the cross membrane movement of sodium and potassium ions. Because of the structural similarity between procaine and acetylcholine, it is tempting to postulate that local anesthetics compete with natural nerve transmission effectors at specific receptor sites. Thus, a comparison of the structures of molecules active in cholinergic systems with those of local anesthetics should be useful in describing the geometry of membrane receptor sites. The structure of acetylcholine bromide (Canepa, Pauling and Sörum, 1966) is very similar to that of procaine hydrochloride. Related bond distances and angles are all equal within experimental error. The only major difference between the two molecules is that the C-O-C-C torsion angle is about 80° in acetylcholine compared to 172.8° in procaine. Both molecules have the nitrogen atom gauche to the ether oxygen. Kier (1967), using molecular orbital calculations on acetylcholine, predicts the most stable conformation to be a gauche N^{+}-C-C-O system and a trans C-O-C-C system. Culvenor and Ham (1966), on the basis of NMR data, claim that the predominant solution conformer of acetylcholine is that predicted by Kier and observed in crystalline procaine hydrochloride. It has also been pointed out by Mathieson (1965) that the trans C-O-C-C conformation is normally found in primary esters. In spite of the conformational difference between procaine and acetylcholine, the relative position of the ether oxygen with respect to the quaternary ammonium group is quite similar in the two compounds and in a variety of related substances as shown in table 2. The average N(2)···O(1) distance in these compounds is 3.17Å and the average C(12)···O(1) distance is 3.00Å. Thus the proximity of the ammonium nitrogen atom to the ether oxygen atom and the orientation of the ammonium substituents, relative to the ether oxygen, appear to be important features necessary for effective effector-receptor interaction.

The nature of the anesthetic ability of procaine-like molecules is

Table 2. Comparison of selected interatomic distances found in compounds related to procaine hydrochloride

Compound	N(2)···O(1)	C(12)···O(1)
Procaine hydrochloride	3.07	3.00
Acetylcholine bromide[a]	3.29	3.02
Choline chloride[b]	3.26	3.07
Muscarine iodide[c]	3.07	2.87
Glycerylphosphorylcholin[d]	3.14	3.03
L-(+)-cis-2-5-Methyl-4-(R)-trimethylammonium-methyl-1-3-dioxolan iodide[e]	3.18	-
Van der Waal's contact[f]	2.9	3.4

a. Canepa, Pauling and Sörum (1966); b, Senko and Templeton (1960); c. Jellinek (1957); d. Abrahamsson and Pascher (1966); e. Pauling and Petcher (1969); f. Pauling (1960).

less obvious. The presence of an aromatic ring system appears to be important. Sax and Pletcher (1969) suggest that the formation of a hydrogen-bonded complex between the drug and a membrane acceptor group is an active feature of local anesthetics. However in both procaine hydrochloride and in the complex, procaine bis-p-nitro phenyl phosphate, only the para amino group and not the carbonyl group participates in hydrogen bonding. Yet replacing the amino group with an ethoxy group, which cannot hydrogen bond in the same manner, increases anesthetic ability several fold (Galinsky, Gearien, Perkins and Susina, 1963). Much additional work on the structural properties of local anesthetics is needed before a clear picture of the nerve blocking mechanism can be drawn.

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