Crystal Structure of 1-[2-(Phenylcarbamoyloxy)ethyl]piperidinium Chloride

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The title compound $C_{14}H_{21}ClN_2O_2$ possesses a local anesthetic and antiarrhythmic activity and consists of a phenylcarbamate moiety and an ethylpiperidine skeleton in which the N atom is protonated. The piperidinium and the phenylcarbamate groups are in a *gauche* conformation for both molecules in the asymmetric unit. The carbamate group in both molecules is approximately coplanar with the phenyl ring, but there is no indication for any significant conjugation between the two groups. The molecules associate in pairs due to hydrogen bonding with the chloride anions with both NH groups of the cation acting as H-bond donors.

The title compound (*Ia*) belongs to the phenylcarbamate class of local anesthetics which are esters of phenylcarbamic acid with primary or secondary aminoalcohols. Previous studies have indicated that the common structural features of these compounds, an ammonium group and a phenylcarbamate function (namely the carbonyl O atom and a π-excessive phenyl ring), directly participate in interaction with the anesthetic receptor [1, 2]. Consequently, as a part of our ongoing study aimed at exploring the stereostructural requirements for interaction at the anesthetic receptor, the present crystal structure determination was undertaken. Another point of interest in the present structure was the hydrogen-bonding pattern of the protonated cations with the chloride anions.

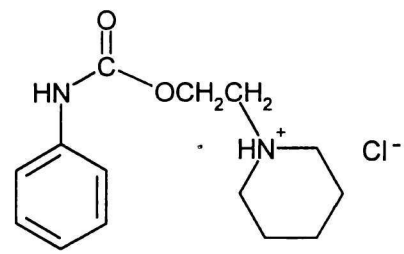
The results obtained here are compared with those obtained previously for heptacaine hydrochloride [3], a closely related phenylcarbamate derivative which differs from *Ia* in having a heptyloxy substituent at the position 2 of the phenyl ring (*Ib*).

EXPERIMENTAL

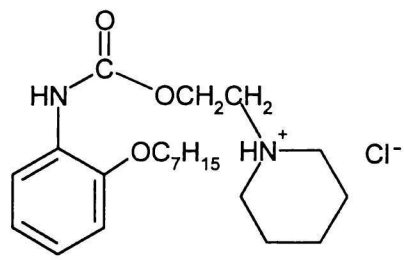
1-[2-(Phenylcarbamoyloxy)ethyl]piperidinium chloride was prepared as described in Ref. [4]. Monocrystals were separated from its chloroform solution by diffusion of benzene vapours. The plate-like crystal had approximate dimensions 0.55 mm × 0.60 mm × 0.12 mm. Its density was measured by a flotation method in the mixture consisting of tetrachloromethane and benzene.

X-Ray Structure Analysis

Crystal data: $C_{14}H_{21}ClN_2O_2$, m.p. = 211 °C, M_r = 284.79, monoclinic, a = 2.5188(19) nm, b = 1.0695(7) nm, c = 1.1462(7) nm, β = 102.97(6)°, V = 3.008(4) nm^3, Z = 8, Dm = 1.28(2) g cm^{-3}, Dx = 1.26 g cm^{-3}, space group $P2_1/c$ (No. 14), Mo$K\alpha$ radiation, λ = 0.071069 nm, μ = 2.54 cm^{-1}, $F(000)$ = 1216, without absorption correction.



Ia



Ib

The lattice parameters were refined on a four-circle diffractometer Syntex $P2_1$, applying the least-squares method from angles of twenty selected reflections ($10.0 < 2\Theta < 20.5$). 3078 independent reflections were scanned by a Θ—2Θ scan technique ($2\Theta_{max} = 50°$); 1816 ($I > 1.96\,\sigma(I)$) were observed; *hkl* index in the range of 0/23, −9/11, −13/12; after scanning every 98 reflections integral intensity was remeasured for two standard reflections −1, 1, −7 and −4, 1, −1; the reflections intensities were corrected for the Lorentz and polarization factor.

The structure was solved by means of the program SHELXS-86 [5], using molecule scattering factors for the calculation of E values. Refinement on F^2 for all reflections and 344 crystal structure parameters was performed by the program SHELXL-93 [6]. Positional and anisotropic temperature parameters for nonhydrogen atoms were refined. Hydrogen atoms were inserted in the calculated positions and all H-atoms were refined with U_{iso} set to $1.2\,U_{eq}$ of the parent atom. The final $R(F) = \sum ||Fo| - |Fc|| / \sum |Fo| = 0.069$ for 1816 reflections ($|Fo| > 4\sigma(Fo)$), and $R = 0.125$ for 3078 reflections, goodness of fit $S = 1.038$, $wR(F^2) = 0.165$ for the observed reflections, where $wR(F^2) = [\sum w|\Delta F^2|^2 / \sum w|Fo^2|^2]^{1/2}$. In the last refining cycle the weighting parameters $w = 1.0/[\sigma^2(Fo^2) + (0.0865P)^2 + 2.0431P]$, where $P = (Fo^2 + 2Fc^2)/3$, were applied; refinement least-square shift $(\Delta/\sigma)_{max} = 0.001$ in the last cycle. The maximum residual electron density was $\rho(e^-)_{max} = 348$ nm^{-3} in proximity of the Cl(1A) atom, and minimum residual electron density was $\rho(e^-)_{min} = -326$ nm^{-3}. The final atom parameters are listed in Table 1.

Table 1. Fractional Atomic Coordinates and Equivalent Isotropic Displacement Parameters with e.s.d.'s in Parentheses $U_{eq} = 1/3 \sum_i \sum_j U_{ij} a_i^* a_j^* a_i a_j$

Atom	$x \cdot 10^4$	$y \cdot 10^4$	$z \cdot 10^4$	$U_{eq} \cdot 10^3/(10^{-2}$ nm)
Cl(1A)	5505(1)	4529(2)	−2298(1)	64(1)
O(1A)	3792(2)	973(5)	1103(4)	79(1)
O(2A)	4266(2)	2512(4)	495(4)	65(1)
N(1A)	3704(2)	2997(5)	1602(4)	59(1)
N(2A)	5366(2)	2751(5)	−327(4)	53(1)
C(1A)	3315(3)	2947(8)	2303(6)	62(2)
C(2A)	3166(3)	4054(9)	2706(6)	78(2)
C(3A)	2794(3)	4105(11)	3425(8)	110(3)
C(4A)	2587(4)	2990(14)	3737(9)	123(4)
C(5A)	2722(4)	1919(12)	3345(9)	113(3)
C(6A)	3090(3)	1864(9)	2605(7)	94(3)
C(7A)	3906(3)	2051(8)	1080(6)	63(2)
C(8A)	4510(3)	1605(6)	−140(5)	63(2)
C(9A)	4799(3)	2296(6)	−910(5)	64(2)
C(10A)	5398(2)	3473(6)	782(4)	52(2)
C(11A)	5940(3)	4095(8)	1180(6)	82(2)
C(12A)	6384(3)	3157(11)	1314(8)	121(4)
C(13A)	6333(4)	2332(9)	195(9)	105(3)
C(14A)	5785(3)	1794(7)	−163(6)	78(2)
Cl(1B)	−548(1)	5423(2)	−2810(1)	71(1)
O(1B)	1170(2)	9138(5)	2135(4)	77(1)
O(2B)	714(2)	7512(4)	1164(4)	67(1)
N(1B)	1284(2)	7137(6)	2833(5)	66(2)
N(2B)	−401(2)	7181(5)	−701(4)	51(1)
C(1B)	1687(3)	7300(8)	3918(6)	66(2)
C(2B)	1810(3)	6265(9)	4617(7)	85(2)
C(3B)	2180(4)	6395(15)	5722(10)	135(5)
C(4B)	2414(4)	7520(16)	6046(10)	133(5)
C(5B)	2293(4)	8523(12)	5371(10)	120(4)
C(6B)	1923(3)	8434(10)	4267(7)	99(3)
C(7B)	1077(3)	8043(8)	2058(6)	61(2)
C(8B)	447(3)	8397(7)	265(5)	69(2)
C(9B)	156(3)	7645(7)	−765(5)	73(2)
C(10B)	−406(3)	6477(6)	409(5)	57(2)
C(11B)	−946(3)	5834(7)	298(6)	75(2)
C(12B)	−1391(3)	6766(10)	66(9)	109(3)
C(13B)	−1381(3)	7548(9)	−1033(8)	100(3)
C(14B)	−838(3)	8139(7)	−924(6)	85(2)

RESULTS AND DISCUSSION

There are two molecules (A and B) in the asymmetric part of the unit cell; they are identical so that only one is shown in Fig. 1. Equivalent bond lengths and angles for the two molecules agree within 4σ (Table 2). Somewhat larger differences are observed for torsion angles which might be accounted for by different crystal environment for the two independent molecules. As noted above, from the pharmacological point of view the most important structural feature of the phenylcarbamate type local anesthetics is a three-dimensional relationship between the common functional groups, *i.e.* the N^+—H bond (acting as an H-bond donor) of a protonated amine, phenyl ring, and a negatively charged heteroatom (usually car-

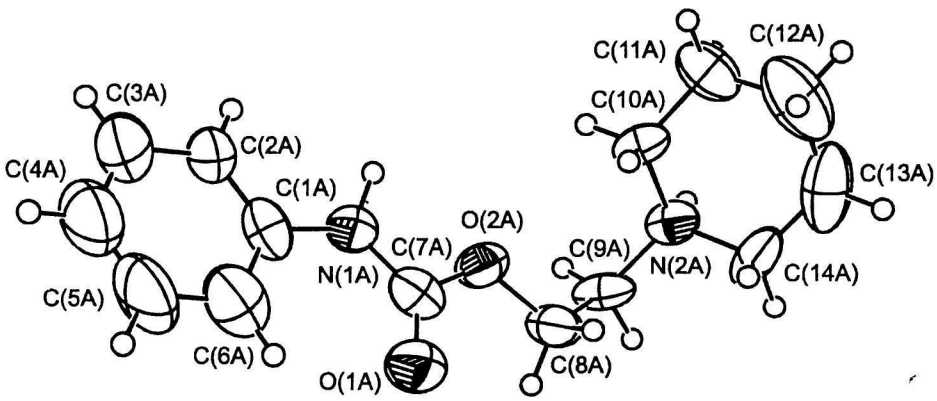


Fig. 1. A view of the title molecule (molecule A) showing the labelling of the non-H atoms. Thermal ellipsoids are shown at 50 % probability levels; H atoms are drawn as small circles of arbitrary radius.

Table 2. Selected Bond Lengths/(10^{-1} nm), Bond and Torsion Angles/° with e.s.d.'s in Parentheses

O(1A)—C(7A)	1.191(8)	O(1B)—C(7B)	1.193(8)
O(2A)—C(7A)	1.336(8)	O(2B)—C(7B)	1.337(8)
O(2A)—C(8A)	1.433(7)	O(2B)—C(8B)	1.449(7)
N(1A)—C(7A)	1.333(8)	N(1B)—C(7B)	1.338(9)
N(1A)—C(1A)	1.399(8)	N(1B)—C(1B)	1.429(8)
N(2A)—C(14A)	1.450(8)	N(2B)—C(10B)	1.481(7)
N(2A)—C(10A)	1.474(6)	N(2B)—C(14B)	1.483(8)
N(2A)—C(9A)	1.515(7)	N(2B)—C(9B)	1.506(7)
C(8A)—C(9A)	1.464(8)	C(8B)—C(9B)	1.480(8)
C(10A)—C(11A)	1.494(8)	C(10B)—C(11B)	1.503(8)
C(11A)—C(12A)	1.485(11)	C(11B)—C(12B)	1.480(10)
C(12A)—C(13A)	1.538(12)	C(12B)—C(13B)	1.517(11)
C(13A)—C(14A)	1.467(10)	C(13B)—C(14B)	1.485(10)
C(7A)—O(2A)—C(8A)	115.0(6)	C(7B)—N(1B)—H(1B)	117.1(4)
C(7A)—N(1A)—C(1A)	128.0(6)	C(1B)—N(1B)—H(1B)	117.1(4)
C(14A)—N(2A)—C(10A)	111.1(5)	C(10B)—N(2B)—C(14B)	110.6(5)
C(14A)—N(2A)—C(9A)	114.6(5)	C(10B)—N(2B)—C(9B)	113.4(5)
C(10A)—N(2A)—C(9A)	114.3(4)	C(14B)—N(2B)—C(9B)	115.3(6)
O(1A)—C(7A)—N(1A)	127.3(7)	O(1B)—C(7B)—O(2B)	124.2(7)
O(1A)—C(7A)—O(2A)	124.2(8)	O(1B)—C(7B)—N(1B)	128.3(7)
N(1A)—C(7A)—O(2A)	108.4(7)	O(2B)—C(7B)—N(1B)	107.4(7)
N(2A)—C(10A)—C(11A)	111.4(5)	O(2B)—C(8B)—C(9B)	106.2(6)
N(2A)—C(14A)—C(13A)	111.7(7)	C(8B)—C(9B)—N(2B)	116.1(5)
C(7B)—O(2B)—C(8B)	113.3(5)	N(2B)—C(10B)—C(11B)	110.0(5)
C(7B)—N(1B)—C(1B)	125.8(7)	N(2B)—C(14B)—C(13B)	110.7(7)
N(1A)—C(1A)—C(2A)—C(3A)	−178.6(6)	O(2A)—C(8A)—C(9A)—N(2A)	83.3(7)
N(1A)—C(1A)—C(6A)—C(5A)	177.5(7)	N(1B)—C(1B)—C(2B)—C(3B)	−176.4(6)
C(1A)—N(1A)—C(7A)—O(1A)	0.5(11)	N(1B)—C(1B)—C(6B)—C(5B)	176.7(7)
C(1A)—N(1A)—C(7A)—O(2A)	179.8(5)	C(8B)—O(2B)—C(7B)—O(1B)	1.5(9)
C(8A)—O(2A)—C(7A)—O(1A)	0.7(9)	C(1B)—N(1B)—C(7B)—O(1B)	−2.9(11)
C(8A)—O(2A)—C(7A)—N(1A)	−178.6(5)	C(1B)—N(1B)—C(7B)—O(2B)	179.9(5)
C(7A)—O(2A)—C(8A)—C(9A)	168.7(5)	O(2B)—C(8B)—C(9B)—N(2B)	84.3(7)

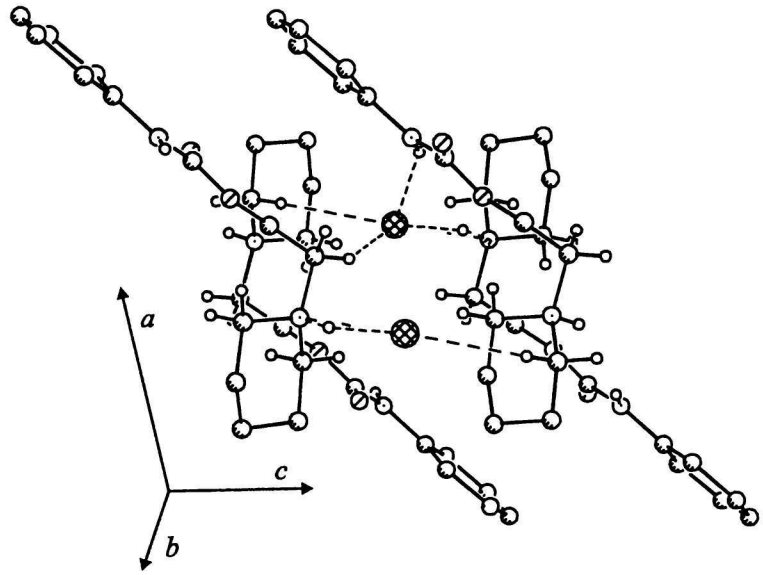


Fig. 2. Crystal packing in the *c* direction of the title molecule. Some H atoms are omitted for clarity.

bonyl oxygen as an H-bond acceptor) appropriately positioned relative to the phenyl ring. The relative disposition of these groups is determined by conformations at the rotatable bonds of the ethylammonium chain and bonding characteristics of the phenylcarbamate moiety. The arrangement of the phenylcarbamate and the piperidinium groups around the C(8)—C(9) bond is *gauche* (torsion angles 83.3(6)° and 84.3(7)° for molecules A and B, respectively). Similar conformation has also been observed in heptacaine hydrochloride (−83.6(9)°) as well as in other structures containing the O—C—C—N^+ fragment irrespective of the substitution pattern at the carbon atoms [7, 8]. Although the *gauche* conformation brings the N(2) atom close to O(2), there is no indication for H-bond formation between these atoms (as given below, the $N(2)^+$—H moiety of both molecules is involved in the H-bond interaction with a chloride anion). As in heptacaine hydrochloride, the piperidinium ring adopts a chair conformation and is rotated around the C(9)—N(2) bond in such a manner that the $N(2)^+$—H bond is *trans* to C(8)—C(9) (torsion angles C(8)—C(9)—N(2)—C(10) and C(8)—C(9)—N(2)—C(14) are −52.2(7)° and 77.6(7)° in molecule A and −53.9(8)° and 75.0(7)° in molecule B). As to the phenylcarbamate pharmacophore, the bond length and angles within the carbamate moiety are affected by conjugation. The lengths of the C(sp^2)—O and O—C(sp^3) bonds, C(7)—O(2) (1.336(8) × 10^{-1} nm and 1.337(8) × 10^{-1} nm in molecules A and B, respectively) and O(2)—C(8) (1.433(7) × 10^{-1} nm in A and 1.449(7) × 10^{-1} nm in B) are equal within the limits of experimental error to the average values of 1.447 × 10^{-1} nm and 1.340 × 10^{-1} nm found for the corresponding bonds in the carboxylic ester groups in various compounds [9].

Similarly, the N(1)—C(7) bond distances of 1.333 (8) × 10^{-1} nm (molecule A) and 1.338(9) × 10^{-1} nm (molecule B) correspond to the range (1.32—1.34) × 10^{-1} nm typically observed for the N—C=O bond in amides. On the other hand, although the C(1)—N(1) bond lengths observed in the two independent molecules differ by more than 3σ (Table 2), both cluster around the value of 1.425 × 10^{-1} nm found for a pure C(sp^2)—N single bond [10, 11].

All these facts indicate that a lone pair of electrons on the carbamate N atom is delocalized through conjugation with the ester group rather than with the phenyl ring; however, some degree of conjugation with the phenyl ring cannot be excluded [12].

Due to conjugation, the carbamate group (atoms N(1), C(7), O(1), O(2)) is planar within experimental error (χ^2 = 3.84 for both molecules) and makes an angle of 2.9(3)° (molecule A) and 5.4(3)° (molecule B) with the plane of the phenyl ring [13]. Thus, although the C(1)—N(1) bond length differs in the two molecules by 3σ, the carbamate group in both molecules lies approximately in the phenyl ring plane. These results are consistent with a previous finding [14] that the phenyl ring—carbamate group dihedral angle (φ) and the C_{arom}—N bond length are completely uncorrelated: while φ varies in a broad range of 0°—70°, C_{arom}—N distance is randomly distributed in a narrow range (1.40—1.43) × 10^{-1} nm. This is also in accordance with the literature data on various *N*-phenylcarbamates (see *e.g.* [15]) which suggest that the π-electron-accepting and -donating effects of the carbamate group are negligible. Examination of the unit-cell packing reveals that both of the two potential H-bond donors of the cations are involved in hydrogen-bonding interactions with two different Cl^- ions related by a centre of symmetry, thus leading to

the formation of centrosymmetric dimers. The details of the geometry of these H-bonds are:

N(2A)—H···Cl(1A): H···Cl 2.14 × 10^{-1} nm, N···Cl 3.032(5) × 10^{-1} nm, N—H···Cl 169°; N(1A)—H···Cl(1A) $(1-x, 1-y, -z)$; H···Cl 2.54 × 10^{-1} nm, N···Cl 3.301(6) × 10^{-1} nm, N—H···Cl 148°; N(2B)—H···Cl(1B): H···Cl 2.13 × 10^{-1} nm, N···Cl 3.020(5) × 10^{-1} nm, N—H···Cl 167°; N(1B)—H···Cl(1B) $(-x, 1-y, -z)$; H···Cl 2.51 × 10^{-1} nm, N···Cl 3.304(6) × 10^{-1} nm, N—H···Cl 153°. Two such dimers (centred at 1/2, 1/2, 0 and 1/2, 0, 1/2) made of the A cations and two dimers (at 0, 1/2, 0 and 0, 0, 1/2) composed of the B cations occur in the unit cell. The dimers (composed of both A and B molecules) are packed in a parallel manner along the *c* direction by ionic forces acting between the Cl^- ions and the C(9), C(10), and C(14) methylene groups, thus satisfying the coordination demands of the chloride anions (Fig. 2). The dimers made of the A cations are rotated by *ca.* 90°around the *b* axis relative to those composed of the B cations so that the packing of the A and B dimers is realized *via* the T-shaped "edge-to-face" interactions [16].

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