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*Acta Cryst.* (1999). C**55**, 441-443

# Absolute configuration of 2-(1,4-benzodioxan-2-yl)imidazolinium bromide

Serge Brunel,[a] Jean Louis Maurel,[a] Jean Paul Ribet,[a] Laure Monconduit,[b] Monique Tillard[b] and Claude Belin[b]

[a]*Centre de Recherche Pierre Fabre, Département de Chimie Analytique, 17 Avenue Jean Moulin, 81106 Castres CEDEX, France, and* [b]*Laboratoire des Agrégats Moléculaires et Matériaux Inorganiques, ESA 5072 CC15, Université de Montpellier II, Sciences et Techniques du Languedoc, 2 Place Eugène Bataillon, 34095 Montpellier CEDEX 5, France. E-mail: cbelin@univ-montp2.fr*

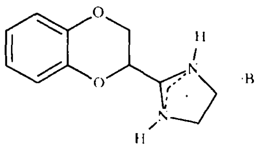
(*Received 26 May 1998; accepted 12 October 1998*)

## Abstract

The title compound, $C_{11}H_{13}N_2O_2^+\cdot Br^-$, crystallizes in the $P2_12_12_1$ space group. The absolute configuration of the therapeutically active molecule idazoxan [2-(1,4-benzodioxan-2-yl)imidazoline] could be resolved in this hydrobromide salt. The asymmetric C atom of the benzodioxanyl group is bonded to an H atom and to a C atom of the imidazolinium ring. (+)-Idazoxan has the *S* configuration. Packing of molecules in the crystal is stabilized by weak N—H···Br [N···Br = 3.226 (5) and 3.217 (5) Å] hydrogen bonding.

## Comment

Idazoxan [(±)-2-(1,4-benzodioxan-2-yl)imidazoline (CAS registry number 79944-58-4)] is a potent and highly selective $\alpha$-2-adrenoreceptor antagonist. The potential of this new chemical entity is currently under clinical evaluation. Idazoxan has one asymmetric C atom on the benzodioxanyl ring (C10) and therefore exhibits two enantiomers. However, idazoxan undergoes facile exchange of hydrogen (H10) at 308 K in phosphate buffer maintained at pH 7.4. It is therefore possible that some racemization of the enantiomers of idazoxan occurs during pharmacological testing. To confirm this hypothesis, we have prepared and determined the configuration of the title compound, (I), a highly crystalline enantiomer salt.



(I)

The *S* configuration of the molecule of (I) is shown in Fig. 1. Benzodioxan is attached, through the asymmetric C10 atom, to the imidazole cycle, which is protonated at one N atom. The sums of the angles around the N atoms are nearly 360° and atoms H12 and H15 refined close [0.16 (7) and 0.01 (6) Å, respectively] to the imidazole mean plane. The bonding scheme (scheme 2) has been determined by extended Hückel molecular orbital calculations. Analysis at the N12—C11—N15 edges shows that $\sigma$ bonding results from $sp^2$ hybridized orbitals. Combination of the $p_z$ (out of the imidazole plane) orbitals, represented in the second scheme, leads to a delocalized $\pi$ bond involving atoms N12, C11 and N15 and a non-bonding pair delocalized over N12 and N15. Bonding overlap populations of 1.04, 1.02, 0.67 and 0.65 for C11—N12, C11—N15, C13—N12 and C14—N15, respectively (1.290, 1.294, 1.442 and 1.478 Å, respectively) are consistent with bond orders of 1.5 and 1.0. Noteworthy is the discrepancy with corresponding bond orders of 1.9 and 1.0, obtained from the empirical Pauling formula, $d_1 - d_n = 0.6\log(n)$ (Pauling, 1947, 1949). Atoms H12 and H15, attached to N12 and N15, are involved in weak hydrogen

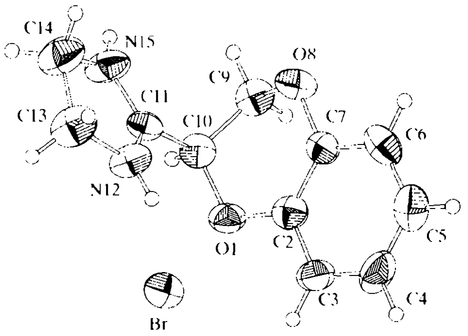


Fig. 1. Molecular structure of the title compound, showing 50% probability displacement ellipsoids for non-H atoms. H atoms are shown as spheres of an arbitrary radius.

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bonding with the $Br^-$ anion. The N···Br distances of 3.226 (5) and 3.217 (5) Å are smaller than the sum of the van der Waals radii of the elements (3.40 Å) and comparable with those found in other hydrogen-bonded systems, for example 3.30 Å in 11-aminoundecanoic acid·HBr·$H_2O$ (Sim, 1955) or 3.17 and 3.26 Å in ethyl dihydrobenzofuranyl imidazolinium bromide (Belin *et al.*, 1995). Geometric hydrogen-bond details are given in Table 3.

Scheme 2

## Experimental

(+)-Idazoxan was obtained by the crystallization in water of the salt of racemic idazoxan with (+)-tartaric acid. The resulting (+)-idazoxan/(+)-tartaric acid salt (99.8 enantiomeric excess; 2.02 g, 5.18 mmol) was added to an aqueous $NaHCO_3$ solution and stirred for a few minutes. The resulting mixture was rapidly extracted with ethyl acetate, and the organic layer was washed with water and brine and then dried over $Na_2SO_4$. Gaseous hydrobromic acid was bubbled through the solution prior to evaporation. The white residue was stirred in diethyl ether, filtered off and then recrystallized in acetonitrile to give white crystals of (I) (yield 0.84 g). This procedure yields a high level of enantiomeric purity (> 99.4%); this was checked by chiral chromatography using an Ultron ES-OVM column (Rockland Technologies). The optical rotation of compound (I) was $\alpha_D$ = + 61.86° ($c$ = 0.43 in water at 298 K).

*Crystal data*

$C_{11}H_{13}N_2O_2^+\cdot Br^-$
$M_r = 285.14$
Orthorhombic
$P2_12_12_1$
$a = 8.817(2)$ Å
$b = 9.872(2)$ Å
$c = 13.672(3)$ Å
$V = 1190.0(4)$ Å$^3$
$Z = 4$
$D_x = 1.592$ Mg m$^{-3}$
$D_m$ not measured

Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å
Cell parameters from 25 reflections
$\theta = 10.2$–$22.3°$
$\mu = 3.442$ mm$^{-1}$
$T = 295(2)$ K
Flat rod
0.40 × 0.30 × 0.25 mm
Colourless

*Data collection*

Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: numerical (*SHELX*76; Sheldrick, 1976)
$T_{min} = 0.31$, $T_{max} = 0.42$
2716 measured reflections
2333 independent reflections

1576 reflections with $I > 2\sigma(I)$
$R_{int} = 0.021$
$\theta_{max} = 25.97°$
$h = -10 \rightarrow 10$
$k = -12 \rightarrow 12$
$l = -16 \rightarrow 16$
3 standard reflections every 100 reflections intensity decay: <2%

*Refinement*

Refinement on $F^2$
$R[F^2 > 2\sigma(F^2)] = 0.036$
$wR(F^2) = 0.089$
$S = 0.959$
2333 reflections
153 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0386P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$

$\Delta\rho_{max} = 0.32$ e Å$^{-3}$
$\Delta\rho_{min} = -0.40$ e Å$^{-3}$
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute structure: Flack (1983)
Flack parameter = −0.02 (2)

Table 1. *Selected bond lengths (Å)*

| | | | |
|---|---|---|---|
| O1—C2 | 1.393 (6) | O8—C9 | 1.429 (7) |
| O1—C10 | 1.428 (5) | C9—C10 | 1.484 (7) |
| C2—C7 | 1.374 (7) | C10—C11 | 1.506 (7) |
| C2—C3 | 1.379 (7) | C11—N12 | 1.290 (6) |
| C3—C4 | 1.382 (7) | C11—N15 | 1.294 (7) |
| C4—C5 | 1.387 (8) | N12—C13 | 1.442 (7) |
| C5—C6 | 1.377 (8) | C13—C14 | 1.520 (8) |
| C6—C7 | 1.373 (7) | C14—N15 | 1.478 (8) |
| C7—O8 | 1.387 (6) | | |

Table 2. *Contact distances (Å)*

| | | | |
|---|---|---|---|
| Br···N15$^i$ | 3.217 (5) | C9···C10 | 1.484 (7) |
| Br···N12 | 3.226 (5) | N12···C13 | 1.442 (7) |

Table 3. *Hydrogen-bonding geometry (Å, °)*

| *D*—H···*A* | *D*—H | H···*A* | *D*···*A* | *D*—H···*A* |
|---|---|---|---|---|
| N12—H12···Br | 0.84 (6) | 2.52 (5) | 3.226 (5) | 142 (5) |
| N15—H15···Br$^{ii}$ | 0.79 (6) | 2.46 (7) | 3.217 (5) | 161 (6) |

Symmetry codes: (i) $\frac{1}{2} - x, 2 - y, \frac{1}{2} + z$; (ii) $\frac{1}{2} - x, 2 - y, z - \frac{1}{2}$.

H atoms attached to C were treated as riding, following the *SHELXL*97 (Sheldrick, 1997) *HFIX/AFIX* instructions; they were given an isotropic displacement parameter equal to 1.2 times the $U_{eq}$ of the parent C atom. H atoms attached to N were positioned from a difference Fourier map, and both their positions and their isotropic displacement parameters were refined.

Data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989). Cell refinement: *CAD*-4 *Software*. Data reduction: local program. Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1985). Program(s) used to refine structure: *SHELXL*97. Molecular graphics: *ORTEP*II (Johnson, 1976).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FR1149). Services for accessing these data are described at the back of the journal.

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*Acta Cryst.* (1999). C55, 443–445

# A 2,2′-azobenzene-substituted calix[4]-arene-crown-6†

PIERRE THUÉRY,[a] MARTINE NIERLICH,[a] MOHAMED SAADIOUI,[b] ZOUHAIR ASFARI[b] AND JACQUES VICENS[b]

[a]*CEA Saclay, SCM, CNRS URA 331, Bâtiment 125, 91191 Gif-sur-Yvette, France, and* [b]*ECPM, Laboratoire de Chimie des Interactions Moléculaires Spécifiques, CNRS URA 405, 1 rue Blaise Pascal, 67008 Strasbourg, France. E-mail: thuery@drecam.cea.fr*

(*Received 2 July 1998; accepted 26 October 1998*)

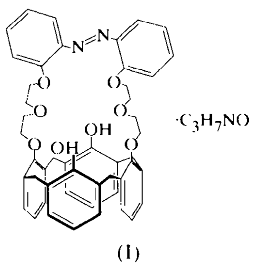
## Abstract

The calix[4]arene macrocycle, 25,27-dihydroxy-26,28-(*O*,*O*′-azobenzene)calix[4]arene-crown-6 [which crystallizes as an *N*,*N*-dimethylformamide solvate ($C_{48}H_{46}N_2O_8{\cdot}C_3H_7NO$)], in the cone conformation, has two opposite phenolic rings bridged by an -(O—$CH_2$—$CH_2$)$_2$O—$C_6H_4$—N=N—$C_6H_4$—(O—$CH_2$—$CH_2$)$_2$O– unit. The two other phenolic O atoms are unsubstituted. The azobenzene geometry is the more stable *trans* one. This structure is compared to other previously reported structures, involving differently bonded azobenzene moieties.

## Comment

In the course of our investigation of calixcrown compounds, *i.e.* molecules resulting from the fusion of a calix[4]arene platform and one or two crown ether loops (which may contain some substituents), we have been interested in compounds comprising a photoisomerizable azobenzene unit. Calixcrowns with simple ether bridges containing six O atoms have proven to be efficient selective complexants for caesium ions and we have used X-ray crystallography to gain some insight into this property which may be of interest for caesium recovery during nuclear-fuel reprocessing (Thuéry, Nierlich *et al.*, 1997, and references therein). The long-term goal of this study of azobenzene-containing calixcrowns is to reach a photocontrol of ion complexation.

We have already reported the structures of ligands with an azobenzene-containing chain of variable length (four to eight O atoms) bridging two opposite phenolic groups of the calixarene unit, with or without additional substituents (ether chains or ether bridge) on the other two phenolic O atoms (Saadioui *et al.*, 1997; Thuéry, Lance *et al.*, 1997). This work led us to put in evidence the effect of crown length and calixarene conformation (cone or 1,3-alternate) on the geometry (*cis* or *trans*) of the azobenzene group. Recently, we have also reported the existence of conformational polymorphism and a phase transition in one of those compounds, resulting from the high flexibility of the bridges (Thuéry *et al.*, 1999). In the compounds investigated up to now, the azobenzene moiety was bonded in a 4,4′ fashion, *i.e.* the N atom and the ether O atom were in *para* positions on the aromatic rings. We report herein the first structure of a compound in which the azobenzene is bonded in a 2,2′ fashion (N and O in *ortho* positions), (I).



(I)

The asymmetric unit is composed of two calixcrown and two *N*,*N*-dimethylformamide molecules. One of the molecules is represented in Fig. 1. The two calixcrown molecules are different as to the bridge conformation, with no evidence of disorder. Since there is no substituent on the phenolic O atoms, O7 and O8, the calixarene adopts the cone conformation, as already observed in other members of the series (Thuéry, Lance *et al.*, 1997). As in the previous cases, the two phenolic rings bearing the bridge are more 'vertical' than the two other ones with respect to the plane defined by the four methylene C atoms [defined within ±0.084 (2) and ±0.187 (3) Å for molecules *A* and *B*, respectively]: the corresponding dihedral angles are 71.03 (8), 65.58 (8) (molecule *A*), 73.02 (10) and 77.37 (9)° (molecule *B*) for the rings bonded to the bridge, and 50.49 (9), 44.41 (12) (molecule *A*), 45.36 (11) and 42.53 (14)° (molecule *B*) for the other rings. Those values compare well with those previously found. Some O···O distances are compatible with the existence of hydrogen bonds that could stabilize the cone conformation: O1*A*···O7*A* 2.752 (3), O6*A*···O8*A* 2.643 (4), O1*B*···O7*B* 2.743 (4) and O6*B*···O8*B* 2.796 (4) Å. This is confirmed by the location of the phenolic H atoms on the Fourier-difference map.

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† IUPAC name: 3,6,9,24,27,30-hexaoxa-16,17-diaza-octacyclo-[30.15.7.1,$^{38,42}$.1$^{49,53}$.0$^{2,44}$.0$^{10,15}$.0$^{18,23}$.0$^{31,36}$]hexapentaconta-1,10,-12,14,16,18,20,22,31,33,35,38,40,42(55),44,46,49(56),50,52-nonadecene-55,56-diol–*N*,*N*-dimethylformamide (1/1).

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