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Synthesis of R-(−)-2-ethyl-*N*-benzyl (benzo-monoaza-15-crown-5) and the Crystal Structure of Its Sodium Perchlorate Complex

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Abstract

A new complex of a chiral monoaza-crown ether, [R-(−)-2-ethyl-*N*-benzyl-4,7,10,13-tetraoxa-8,9-benzo-1-azacyclopentadec-8-ene·$NaClO_4$], has been prepared and studied by x-ray diffraction. The compound crystallizes in space group $P2_1$ with cell dimensions a = 8.721(1), b = 16.318(2), c = 8.905(1) Å, β = 100.80(1)°. The sodium cation is heptacoordinated and located significantly out of the best plane of the macrocycle ring. The donor atoms of the macrocycle are in the half-chair arrangement.

Introduction

Host–guest chemistry has played a major role in understanding processes of biological significance [1–11]. Crown ethers are particularly useful compounds in such studies [4, 10]. The catalytic and recognition properties of these compounds are similar to natural compounds like enzymes [12]. Chiral crown ethers posses a special interest in this manner because of their ability to discriminate between molecules, e.g., enantiomers, so they have also successfully been used as chiral catalysts or chiral templates in many asymmetric reactions, e.g., Michael addition [13], reduction [14], and hydrogen cyanide addition [15]. Studies on the structural elucidation of host–guest compounds is another concern of research in chemistry because of their role in the understanding of non-covalent interactions in biological processes.

Herein we report the synthesis and characterisation of a new complex of chiral monoaza-15-crown-5 containing one aromatic benzene ring. The solid state structure of the complex is determined by x-ray diffraction in order to obtain the bonding and ligand behaviour in more detail.

Experimental

Apparatus and chemicals

All chemicals were reagent grade unless otherwise specified. Melting points were determined with a Gallenkamp Model apparatus with open capillaries. Infrared spectra were recorded on a Midac-FTIR Model 1700 Spectrophotometer. Elemental analyses were obtained with a Carlo-Erba Model 1108 apparatus. Optical rotations were recorded using a Atago DR Model 21949 polarimeter. ^{1}H-(400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker DPX-400 High Performance Digital FT-NMR spectrometer. Refraction indexes were measured using a Atago Abbe refractometer.

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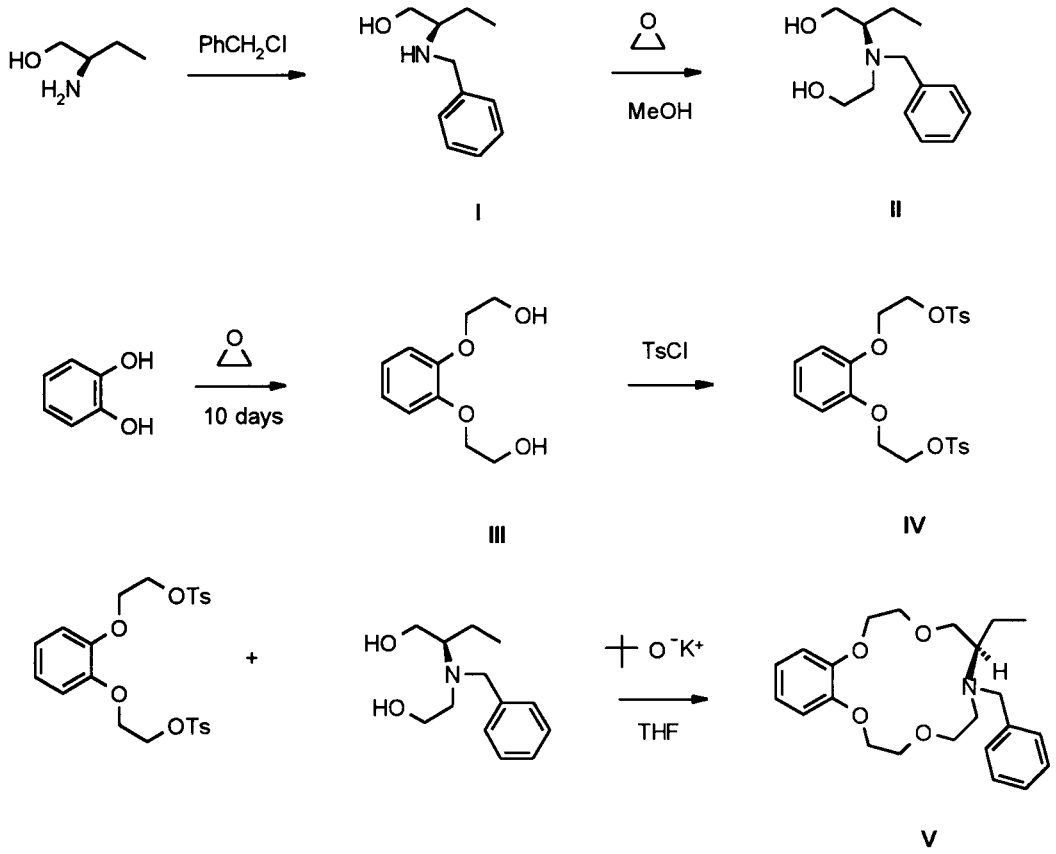
Synthesis

R-(−)-N-benzyl-2-amino-1-butanol (I)

R-(−)-2-amino-1-butanol (71.2 g, 0.8 mol), benzyl chloride (25.3 g, 0.2 mol) and Na_2CO_3 (20 g, 0.18 mol) were placed in a 250 mL two-necked round bottomed flask equipped with an addition Dean Stark apparatus. The mixture was stirred at 100 °C for 8 h under dry N_2. Then the mixture was cooled and $CHCl_3$ (100 mL) was added to the mixture and refluxed for 1 h. The $CHCl_3$ layer was separated from the solid phase. The remaining solid was re-extracted with $CHCl_3$ (3 × 25 mL). The combined $CHCl_3$ layers were dried (Na_2SO_4) and evaporated. The product was distilled at reduced pressure to give 33 g (94%), $[\alpha]_D^{20} = -25.63$ (c = 0.08, EtOH). b.p. 98–100 °C/0.1 mmHg, m.p. 71–72 °C. M.w. 179 g/mol (Found: C, 73.67; H, 9.63; N, 7.74; $C_{11}H_{17}NO$ requires C, 73.70; H, 9.56; N, 7.80); IR (KBr): 3287, 3076, 2931, 2836, 1467, 1361, 1068 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.98 (3H, t, J = 7.48 Hz), 1.48–1.63 (2H, m), 2.64–2.68 (1H, m), 3.38–3.85 (2H, ddd), 3.75–3.85 (2H, dd), 7.29–7.39 (5H, m) ; ^{13}C NMR ($CDCl_3$) δ 10.73, 24.64, 51.48, 60.21, 63.05, 127.45, 128.86, 140.83



Scheme 1.

R-(−)-N-benzyl-4-hydroxymethyl-3-azahexzane-1-ol (II)

A solution of 47 g (260 mmol) of (**I**) in 100 mL of methanol was cooled to −20 °C in a 250 mL flask. 11.52 g (260 mmol) of ethylene oxide in 50 mL of methanol was added to the solution dropwise at the same temperature. After addition the mixture was stirred for 12 h at −20 °C and then for 24 h at +4 °C. The mixture was kept for one day at room temperature. Methanol was evaporated *in vacuo*. The product was purified by distillation under reduced pressure at 155 °C/0.1 mmHg to give 56 g (94%) of (**II**).η_i^{20} = 1.524 $[\alpha]_D^{20}$ = −14.89 (c = 0.08, EtOH).m.w. = 223 g/mol (Found: C, 66.76; H, 9.04; N, 6.08, $C_{13}H_{21}NO_2$ requires C, 66.90; H, 9.07; N, 6.00); IR (neat film): 3368, 3085, 3061, 3026, 2957, 2876, 1602, 1494, 1453, 1372, 1155, 1054, 729, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7.47 Hz), 1.22–1.29 (^1H, m), 1.60–1.67 (1H, m), 2.59–2.64 (1H, dt), 2.71–2.85 (2H, m), 3.41 (2H, t, J = 10.28 Hz), 3.45–3.56 (2H, ddd), 3.62–3.84 (4H, dd), 7.22–7.37 (5H, m); ^{13}C NMR ($CDCl_3$) δ 12.23, 19.72, 51.87, 55.32, 60.52, 61.90, 63.41, 127.41, 128.76, 129.16, 140.52.

1,2-Bis-(2-hydroxy ethoxy) benzene (III)

This compound was prepared according to the procedure recorded in the literature [20–21] from catechol (11.0 g, 100 mmol), diethylamine hydrochloride (as catalyst) and ethylene oxide (9.8 mL, 200 mmol) to give 18.8 g, 95%; mp 81–83 °C.

1,2-Bis-(2-p-tolylsulphonyl ethoxy) benzene (IV)

This compound was prepared according to the procedure recorded in the literature [20–21] from 1,2-bis-(2-hydroxy ethoxy) benzene (26.73 g 135 mmol), pyridine (110 mL) at −10 °C and *p*-toluene sulphonyl chloride (51.43, 270 mmol) to give 65.48 g, 96%; mp 95–95.5 °C.

R-(−)-2-ethyl-N-benzyl-4,7,10,13-tetraoxa-8,9-benzo-1-azacyclopentadec-8-ane (V)

Tertiary butanol (74.2 g, 1 mol) and metallic potassium (6.825 g, 175 mmol) were added simultaneously to a solution of dry THF (500 mL) in a four-necked flask. The mixture was stirred at 80 °C. 1,2-bis-(2-*p*-tolylsulphonylethoxy) benzene (17.71 g, 35 mmol) in THF (100 mL) and R-(−)-*N*-Benzyl-4-hydroxymethyl-3-azahexzane-1-ol (7.80 g, 35 mmol) in THF (100 mL) was added dropwise to the mixture in 2 hours. After addition the mixture was stirred and refluxed for 24 hours under dry N_2. Then the mixture was cooled to room temperature, filtered and the solvent was evaporated. The residue was dissolved in chloroform and washed with water, dried (Na_2SO_4) and evaporated. The residual oil was purified by flash column chromatography on silica ((triethylamine-ethylacetate-petroleum ether (40–60), 3:17:80 and 3:30:67 respectively). $[\alpha]_D^{20}$ = −4.38 (c = 0.04 EtOH) M.w: 385 g/mol (Found: C, 71.74; H,7.98; N,3.68; $C_{23}H_{31}NO_4$ requires C, 71.68; H, 8.05; N, 3.63); IR (neat film): 3080, 3041, 2972, 2876, 1602, 1506, 1452, 1245, 1201, 1123, 1050, 934, 752, 702, cm^{-1}; 1H NMR ($CDCl_3$) δ

Table 1. Crystal data and details of the structure determination for R-(−)-2-ethyl-*N*-benzyl (monobenzo-monoaza-15-crown-5) $NaClO_4$

Crystal data:	
Formula	$C_{23}H_{31}Cl\ N\ Na\ O_8$
Formula weight	507.93
Crystal system	Monoclinic
Space group	$P2_1$ (No. 4)
a, Å	8.721(1)
b, Å	16.318(2)
c, Å	8.905(1)
β, deg	100.80(1)
V, Å^3	1244.8(3)
Z	2
D_c, g cm^{-3}	1.36
$F(000)$	536
μ, cm^{-1}	19.4
Crystal size, mm	0.48 × 0.30 × 0.51
Data Collection:	
Temperature (K)	295
Radiation, λ	CuK_α, λ = 1.54184 Å
Range of relative transm. factors, %	43.8–59.4
Range of *hkl*	−10: 10; −2: 11; −6: 10
Scan type	$\omega/2\theta$
Number of collected reflections	1484 total, 1400 unique
Standard reflections	3 measured every 120 min.
R_{int}	1.7%
Structure refinement:	
No. of reflections in refinement	1400
No. of refined parameters	312
Linear agreement factor $R = \Sigma\|\Delta F\|/\Sigma\|F_0\|$	0.042
Weighted agreement factor $wR = [\Sigma w\|\Delta F\|^2/\Sigma w\|F_0\|^2]^{1/2}$	0.1363
Goodness of fit	1.11
Max. Shift/Error	0.01
Final $\Delta\rho_{max}$, $\Delta\rho_{min}$, e Å^{-3}	0.25, −0.25

0.87 (3H, t, J = 7.38 Hz), 1.37–1.50 (2H, m), 2.70–2.75 (2H, p), 2.97—3.00 (1H, m), 3.49–4.09 (14H, m), 6.79–7.27 (9H, m); ^{13}C NMR ($CDCl_3$) δ 12.33, 22.13, 30.12, 50.88, 56.16, 62.50, 69.50, 69.87, 69.98, 71.89, 73.47, 114.04, 121.64, 126.93, 128.45, 128.92, 141.80, 149.57.

*$NaClO_4$ complex of (***V***)*

A solution of 3.8 g (11 mmol) of host (**V**) in 20 mL of ethyl acetate was added to 1.58 g (11 mmol) $NaClO_4.H_2O$ dissolved in 10 mL of ethyl acetate. The mixture was stirred for 1 h. and kept for 24 h at room temperature. The product was filtered and recrystallized from methanol. m.p. 152–154 °C; $[\alpha]_D^{20} = -2.22$ (c = 0.04 EtOH). M.w: 507.5 g/mol (Found: C, 54.64; H, 6.21; N,2.72; $C_{23}H_{31}NO_4$. $NaClO_4$ requires C, 54.38; H, 6.10; N, 2.75) ; IR (KBr): 3061, 3024, 2968, 2876, 1593, 1503, 1455, 1250, 1199, 1117, 1028, 928, 748, 702, 623 cm^{-1}; 1H NMR ($CDCl_3$) δ 0.94 (3H, t, J = 7.32 Hz), δ1.63 (1H, bs), (1.56 (1H, bs), (2.86–4.31 (17H, m), (6.75–7.31 (9H, m) ;^{13}C NMR ($CDCl_3$) δ12.51, 18.23, 66.79, 68.30, 68.67, 70.75, 113.02, 122.45, 127.55, 128.77, 129.36, 147.13

X- ray crystallography

X-ray crystallographic measurements were carried out using an Enraf-Nonius CAD4 diffractometer with graphite monochromatised CuK_α radiation [$\lambda(CuK_\alpha)$ = 1.54184 Å] and $\omega/2\theta$ scan mode to 2θ = 148.7° at 295 K. The crystal used for data collection was colourless, transparent and prismatic shaped. The cell constants and the orientation matrices for data collection were obtained from a least-squares refinement using the setting angles of 25 carefully centred reflections in the range $22.8° < 2° < 43.0°$. The data were treated and corrected for Lorentz-polarisation effects and for absorption using empirical psi-scans.

The structure was solved by direct methods using the SHELX97 program package and refined on F^2 [16]. The non-H atoms were refined with anisotropic displacement parameters. Hydrogen atoms, except that of chiral carbon C1 (detected in the difference Fourier) were introduced at calculated positions in their described geometries and during refinement were allowed to ride on the attached carbon atom with fixed isotropic thermal parameters (1.2 Ueq of the parent carbon atoms). Crystal data, a summary of intensity

data collection and structure refinement are given in Table 1 while selected geometric parameters and the important torsion angles are listed in Tables 2 and 3, respectively.

Results and discussion

X-ray crystal structure studies

The molecular structure conformation and the numbering scheme of the title compound is shown in Figure 1. The structure predicted from chemical and spectral analysis is confirmed by X-ray analysis of the single crystal. The 15-membered ring is severely strained and deviates from the expected conformation of 15-crown-5 type molecules. This is established by the torsion angles listed in Table 3. This strain is expected because of the presence of the aromatic benzene ring in the macrocyclic ring and also the benzyl and ethyl groups bonded to the N(1) and C(1) atoms of the ring. Perhaps, in order to form a complex involving all the donor atoms of the ring the conformation of the macrocycle might be changed. Some of the D–C–C–D (D=oxygen or nitrogen donor atom) torsion angles have values which are more typical of complexes. For example, the torsion angles O(4)–C(13)–C(14)–N(1) and O(1)–C(3)–C(4)–O(2) are −64.8(8) and −54.8(7)°, respectively.

The donor atoms of the macrocycle are in the half-chair arrangement, and the metal ion resides significantly out of the best plane. The macrocycle oxygen atoms are on average 0.004(5) Å alternately above and below the oxygen mean plane. The sodium ion is situated 0.560(3) Å above the mean plane while the deviation of the nitrogen atom from the plane is −0.857(6) Å. These values are comparable with those found in the structure of *R-(−)-2-ethyl-−benzyl(monoaza-15-crown-5)* [17].

The Na ion is bound to all heteroatoms of the macrocycle. The coordination shell of the sodium is completed by two oxygen atoms of the perchlorate anion and thus the sodium cation is heptacoordinated. The perchlorate anion is asymmetrically bound with Na–O(5), O(6) contacts of 2.510(8) and 2.698(10) Å, respectively. The Na–Oeth (etheric) distances, (Table 2), are in the range 2.318(5)–2.461(6) Å, while the distance for Na–N(1) is 2.610(6) Å. It has been shown that the metal center is shifted to one side of the macrocyclic cavity. The effective ionic radius for heptacoordinated Na^+ is 1.12 Å [18], and the macrocycle's mean cavity radius R, which is determined from the structural data as defined by Mathieu *et al.* [19] is 0.967 Å. Thus there is not enough space to accommodate a Na^+ in the three dimensional cavity.

As shown in Figure 1, the perchlorate anion is located over the best plane of the macrocycle in an apical position while the phenyl ring C(16)–C(20) is lying beneath the plane. The dihedral angles between the planes of the four ring oxygen atoms and the phenyl rings are 55.8(2)° [C(16)–C(20)] and 25.0(2)° [C(5)–C(10)] respectively. The angle between the phenyl rings is 63.8(3)°. The ethyl group bonded to the chiral carbon atom is oriented outwards from the

Table 2. Selected interatomic distances (Å) and bond angles (°) for R-(−)-2-ethyl-*N*-benzyl (monobenzo-monoaza-15-crown-5) $NaClO_4$

Cl–O(5)	1.367(5)	O(3)–C10)	1.383(8)
CO(6)	1.42(1)	O(3)–C(11)	1.433(7)
Cl–O(7)	1.360(7)	O(4)–C(12)	1.426(9)
Cl–O(8)	1.453(9)	O(4)–C(13)	1.41(1)
Na–O(1)	2.318(5)	N(1)–C(1)	1.494(8)
Na–O(2)	2.461(6)	N(1)–C(14)	1.49(1)
Na–O(3)	2.392(6)	N(1)–C(15)	1.474(9)
Na–O(4)	2.322(4)	C(1)–C(2)	1.50(1)
Na–O(5)	2.510(8)	C(1)–C(22)	1.55(1)
Na–N(1)	2.610(6)	C(3)–C(4)	1.49(1)
Na–O(6)	2.698(10)	C(5)–C(10)	1.407(9)
O(1)–C(2)	1.426(9)	C(11)–C(12)	1.47(1)
O(1)–C(3)	1.41(1)	C(13)–C(14)	1.52(1)
O(2)–C(4)	1.430(6)	C(15)–C(16)	1.51(1)
O(2)–C(5)	1.379(8)	C(22)–C(23)	1.52(1)
O(1)–Na–O(2)	67.6(2)	O(4)–C(12)–C(11)	108.3(6)
O(1)–Na–N(1)	70.8(2)	O(4)–C(13)–C(14)	108.7(5)
O(2)–Na–O(3)	63.1(2)	N(1)–C(14)–C(13)	111.4(7)
O(2)–Na–O(5)	130.8(2)	N(1)–C(15)–C(16)	114.5(6)
O(3)–Na–O(4)	69.5(2)	Na–O(1)–C(2)	116.6(4)
O(3)–Na–O(5)	123.5(3)	Na–O(2)–C(4)	110.4(4)
C(1)–N(1)–C(14)	111.7(6)	Na–O(2)–C(5)	110.3(4)
C(1)–N(1)–C(15)	113.0(6)	Na–O(3)–C(10)	112.8(3)
N(1)–C(1)–C(2)	109.7(7)	Na–O(3)–C(11)	111.5(5)
N(1)–C(1)–C(22)	114.4(6)	Na–O(4)–C(12)	115.6(5)
O(1)–C(2)–C(1)	108.8(6)	Na–O(4)–C(13)	116.4(4)
O(1)–C(3)–C(4)	108.1(6)	Cl–O(5)–Na	103.4(4)
O(2)–C(4)–C(3)	107.3(5)	Na–N(1)–C(1)	92.4(4)
O(2)–C(5)–C(10)	114.4(6)	Na–N(1)–C(14)	92.0(4)
O(3)–C(11)–C(12)	107.0(6)	Na–N(1)–C(15)	132.8(5)

Table 3. Torsion angles about the monobenzo-monoaza-15-crown-5 ligand (°)

C(3)–O(1)–C(2)–C(1)	−167.5 (6)
C(2)–O(1)–C(3)–C(4)	−176.7 (5)
O(1)–C(3)–C(4)–O(2)	−54.8 (7)
C(5)–O(2)–C(4)–(C(3)	179.1 (6)
C(4)–O(2)–C(5)–C(10)	−165.8 (7)
O(2)–(C(5)–C(10)–O(3)	1.2 (1)
C(11)–O(3)–C(10)–(C(5)	170.9 (7)
C(10)–O(3)–C(11)–C(12)	177.4 (6)
O(3)–(C(11)–C(12)–O(4)	58.5 (9)
C(13)–O(4)–C(12)–(C(11)	178.5 (6)
C(12)–O(4)–C(13)–C14)	159.3 (7)
O(4)–(C(13)–C(14)–N(1)	−64.8 (8)
C(1)–N(1)–C(14)–(C(13)	158.6 (6)
C(14)–N(1)–C(1)–C(2)	−160.1 (6)
N(1)–(C(1)–C(2)–O(1)	63.7 (8)
C(1)–N(1)–C(15)–C(16)	−138.7 (7)
N(1)–C(1)–C(22)–C(23)	−158.5 (8)

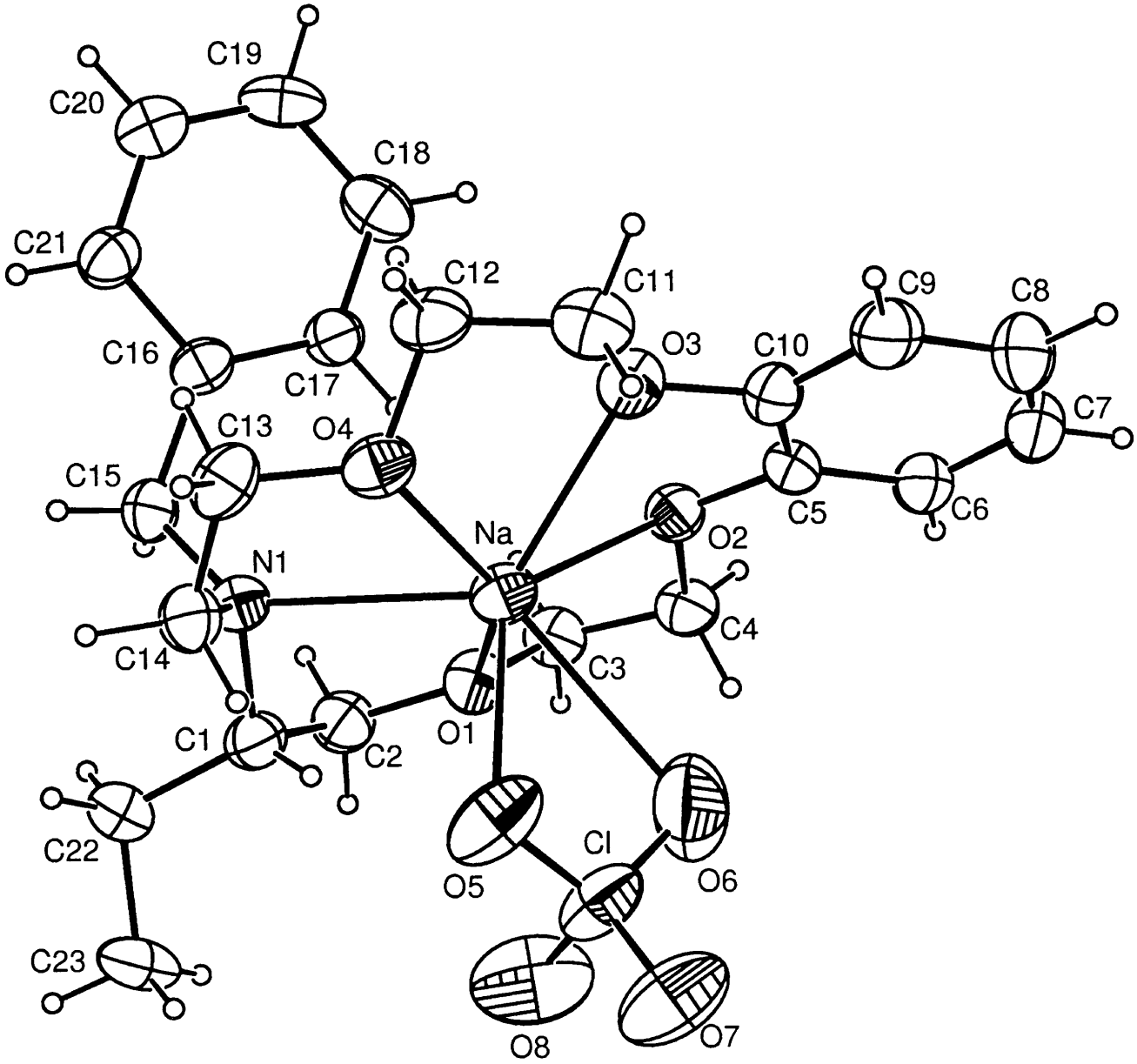


Figure 1. Drawing of the title compound with 35% probability displacement ellipsoids and the numbering scheme.

macrocycle by the torsion angle of C(2)–C(1)–C(22)–C(23) (76.0(1)°).

Comparison of this study with our previous one [17] revealed that benzene substitution on the crown ether diminishes the donor properties of oxygen. As a result, it was shown from X-ray data that the bond distance of sodium with the aromatic ether is smaller than the aliphatic ether bond. So sodium used two oxygens of perchlorate hence it is heptacoordinated.

Molecular recognition of protonated chiral amines with these chiral macrocycles is under investigation.

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