Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 2721–2726

TETRAHEDRON:
ASYMMETRY

Spontaneous resolution of chiral cobalt(III) complexes

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Received 25 September 2001; accepted 25 October 2001

Abstract—Two novel methods for inducing partial spontaneous resolution of conglomerates by crystallisation were proposed. The first one, termed 'internal entrainment', involves using a single crystal as the seed from a primary racemic mixture in its resolution by entrainment. The second method involves crystallisation under deficiency of a conglomerator, which causes homochiral packing of the crystals. Both methods were applied to Co(III) complexes with the effect of resolution up to 83% e.e. © 2001 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Analysis of the classical experiment of Louis Pasteur[1] results in two very important conclusions.[2] The phenomenon of homochiral crystallisation, discovered by him, is essentially a case of spontaneous resolution at the level of monocrystals. Complete crystallisation of his salt ($NaNH_4$·tartrate·$4H_2O$) led to a racemic mixture, whereas each single crystal was optically active and, consequently, could be used as the seed in the resolution of the primary racemic salt by entrainment. This essential modification of the Gernez method[3,4] was named 'resolution by internal entrainment',[2] so long as classical entrainment includes using as the seed an external enantiomeric crystal.[4] Both (±)-tartaric acid itself and its diammonium salt form racemic crystals, therefore the Na^+ ion can be regarded as a conglomerator that brings about homochiral packing of the Pasteur salt. Obviously, if the conglomerator is deficient, the crystallisation is the path to predetermined spontaneous resolution on preparative scale, as has been confirmed by several examples.[2]

In this work we have demonstrated these two new methods as applied to preparative spontaneous resolutions of chiral Co(III) complexes. The latter were studied intensely[5] and are of great historical interest:[6] the proof of their chirality by classical methods became a triumph of Werner's coordination theory.[7]

2. Results and discussion

Resolution of racemates using achiral reagents seems to be impossible. However, it is possible when a compound crystallises as a conglomerate. Then, the internal entrainment procedure or crystallisation under deficiency of conglomerator can be used. It is quite obvious that under the deficiency of conglomerator **C** spontaneous resolution would be predetermined as follows.

The characteristic time of nucleation is rather long, and the first appearing seed initiates rapid crystallisation. As the crystallisation proceeds, the concentration of **C** decreases and, correspondingly, the probability of nucleation of the opposite antipode diminishes as well (Scheme 1).

A rigorous approach to this method requires two principal cases to be considered. The first case is a situation when compound (**D**,**L**) does not form homochiral crystals, but with conglomerator **C** crystallises as a conglomerate **DC**,**LC** (single conglomerate method). The second situation is the case when a system of two racemic conglomerates with the same **D**,**L** part is present. In this case different solubility conditioned by different conglomerators C_1 and C_2 leads to resolution (double conglomerate method).

$$\text{cryst}\,(LC)_n \xleftarrow[{[C]\to 0}]{} nL + nD + nC \xrightarrow[{[C]\to 0}]{} (DC)_n\,\text{cryst}$$

Scheme 1. Crystallisation of a 1:1 mixture **D** and **L** enantiomers at deficiency (1/2 mol equiv.) of conglomerator **C**.

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PII: S0957-4166(01)00480-3

There are extensive data on the properties of enantiomers and racemates of octahedral Co(III) complexes and, in particular, on their solubility[9] and chiroptical features.[10] Many of these complexes display high optical rotatory power, which is important for working with minute crystals and selecting them for the internal entrainment procedure when it is necessary to obtain crystals of a fixed sign. Therefore, two such complexes, the known conglomerates **1a**,**b**[4,8,9] and **2a**,**b**[9,12] (Scheme 2), were selected as objects for our investigation.

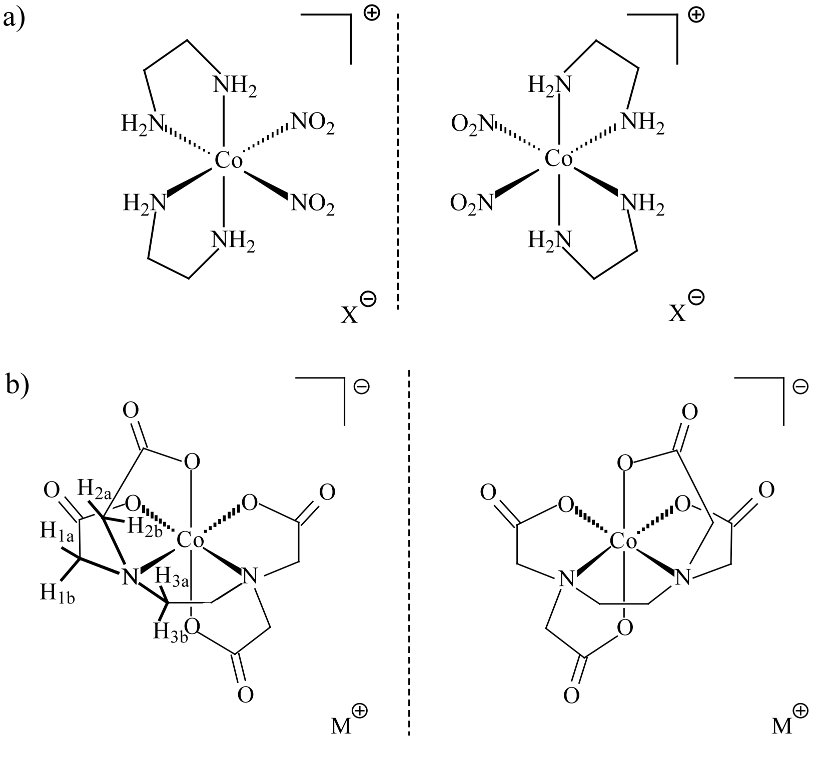
Using the above new methods we performed efficient resolution of these complexes without any external chiral reagent. We have shown that random individual crystals of racemic compounds **1a**,**b** and **2a**,**b** can be used directly for resolution of the corresponding racemates by internal entrainment. This procedure consists of selecting a single crystal from racemic crystalline material and applying it as the seed in the crystallisation of a saturated solution (Procedure A).

In the case of complexes **1a**,**b** the source of chirality is the cation $[Co(NO_2)_2(en)_2]^+$. Earlier it was found that if the counter-ion (X) is NO_2^-, the complex crystallises as racemic crystals, and when X is Cl^- or Br^- the complex is conglomerate.[8] Therefore, Cl^- or Br^- are responsible for the homochiral packing of crystals, i.e. conglomerators. To obtain resolution we made use of the different solubility of **1a** and **1b** (double conglomerate method, Procedure B) in water (at 20°C **1a** is 3.6 times more soluble than **1b**).[9]

Crystallisation of (±)-**1a** from an aqueous solution containing 0.5 molar equiv. of NaBr led to optically active bromide **1b** (Table 1, entries 1–5). Crystallisation of the 1:1 mixture of complexes **1a**,**b** from H_2O also led to enantiomerically enriched bromide **1b** (Table 1, entries 6–8). Crystals of the opposite enantiomer of **1b** were obtained from the mother liquors after the addition of NaBr up to 0.5 molar equiv. with regard to the complex cation by repeated crystallisation (Table 1, entries 4 and 5).

Optical activity of individual crystals of **2a**,**b** from their synthetic samples was observed earlier.[12] Moreover, the solubility of **2a** in water (at 20°C) is 1.9 times higher than that of **2b**.[9] Therefore, in a similar manner, crystallisation of (±)-**2a** from an aqueous solution containing 0.5 equiv. of NH_4Cl led to the optically active portion of crystals of **2b** (Table 1, entries 9–16). By reducing the amount of NH_4Cl to 0.25 molar equiv. we increased the enantiomeric excess in the crystalline material (Table 1, entry 15). Subsequent crystallisation of the mother liquor afforded crystals of the opposite enantiomer (Table 1, entry 16).

The enantiomeric purity of all specimens obtained in our experiments did not exceed 83%. We did not succeed in preparing enantiomerically pure crystals; apparently, the effect of twinning takes place here.[13] This phenomenon is probably the cause of reduced enantiomeric purity of the crystalline material obtained from stirred crystallisations.[14]



Scheme 2. View of (a) the Λ-(−)$_{589}$- and Δ-(+)$_{589}$ isomers of **1a** (X = Cl) and **b** (X = Br); (b) the Λ-(−)$_{546}$- and Δ-(+)$_{546}$ isomers of **2a**·$2H_2O$ (M = K) and **b**·$2H_2O$ (M = NH_4).

Table 1. Resolution of (±)-**1a**,**b** and (±)-**2a**,**b** by single crystallisation from aqueous solutions at deficiency of conglomerator (Br^- or NH_4^+, respectively) (double conglomerate method) and isolation of the opposite enantiomer[e]

Entry[a]	Weight (mg) of **1a**	Weight (mg) of NaBr	Molar ratio **D**,**L**:**C**	Precipitated crystals (mg) of **1b**	Chemical yield (%)	$[\alpha]^{23}_{589}$ [b]	E.e. (%)[c]
1	62.1	10.4	2:1	21.5	61.0	−5.5	12.5
2	117.4	19.7	2:1	10.8	16.0	+20.7	47.0
3[d]	117.4	19.7	2:1	11.5	17.1	−16.7	38.0
4[e]	117.4	19.7	2:1	8.2	12.2	−18.0	41.0
5[e]	117.4	19.7	2:1	18.2	27.1	+10.8	25.0
	Weight (mg) of **1a**	Weight (mg) of **1b**		Precipitated crystals (mg) of **1b**			
6	68.7	78.7	2:1	13.4	17.0	−14.1	32.0
7	68.7	78.7	2:1	16.0	20.0	+20.7	47.0
8	68.7	78.7	2:1	12.2	15.5	−24.6	56.0
	Weight (mg) of **2a**	Weight (mg) of NH_4Cl		Precipitated crystals (mg) of **2b**		$[\alpha]^{25}_{546}$ [f]	
9	1052.4	67.0	2:1	71.7	14.3	+150.0	9.9
10	1052.4	67.0	2:1	128.9	26.0	−248.0	16.4
11[d]	526.2	33.5	2:1	53.2	21.0	+300.0	20.0
12	526.2	33.5	2:1	50.1	20.0	−520.0	34.4
13	526.2	33.5	2:1	46.1	18.4	+585.7	38.8
14	526.2	33.5	2:1	44.0	17.6	+625.0	41.4
15	526.2	16.7	4:1	75.0	60.0	−1250.9	83.0
16[e]	231.4	7.3	4:1	21.3	38.9	+419.4	28.0

[a] **1a** was obtained by simple single crystallisation in 21% yield with 5% e.e.; **1b** was obtained by single crystallisation of **1a** with 1 mol of NaBr in 23% yield and 6.6% e.e.; **2a** was obtained by simple single crystallisation in 19% yield with 3.8% e.e.; **2b** was obtained by single crystallisation of **2a** with 1 mol of NH_4Cl in 19.8% yield and 2.7% e.e.; **1b** was obtained by crystallisation of **1a** with 1/2 mol of NaBr in 77–94% yield and 0.8–2.7% e.e.

[b] (*c* 1, H_2O).

[c] In all cases for **1b** (nos. 1–8) e.e. values were determined by comparison with $[\alpha]_D = -44$ of resolved compound;[11] for **2b** (nos. 9–16) e.e. values were determined by comparison with $[\alpha]^{25}_{546} = +1510$ (*c* 0.02, H_2O).[12]

[d] Mother liquors: no. 3 $[\alpha]^{23}_{589} = +15$ (*c* 1, H_2O); no. 11 $[\alpha]^{25}_{546} = -36$ (*c* 0.02, H_2O).

[e] In experiments no. 4, 5 and 16 crystallisations of mother liquors were performed and crystals of the opposite enantiomers were obtained with 36% e.e. (weight 11.0 mg), 65.4% e.e. (weight 12.3 mg) and 19.9% e.e. (weight 25.0 mg), respectively.

[f] (*c* 0.02, H_2O).

NMR spectral analysis of the complexes proved to be quite informative. In the ^1H and ^{13}C NMR spectra of **1a**,**b** a dual non-equivalence of protons and carbons of the ligands is observed. This fact corresponds to C_2 symmetry of the molecules and, therefore, is a test for isomerism and chirality of complexes. A strong shift to the lower field of the two HN signals is caused by the H···O contacts between NH_2 and NO_2 groups. These kinds of hydrogen bonds can account for the slow proton–deuterium exchange of HN protons of **1a** in D_2O. Signals of deuterated **1a** in ^{13}C NMR spectrum are shifted to lower field relative to the non-deuterated complex. Isotope effect is 0.13 ppm.

The ^1H NMR spectrum of **2a** consists of two AB systems of the N–CH_2–C(O)O fragments and one AA‘BB‘ system belonging to the N–$(CH_2)_2$–N fragment (Fig. 1). Due to the asymmetric environment, the protons in each CH_2 group (Scheme 2) are magnetically non-equivalent. Correspondingly, five signals were observed in the ^{13}C {^1H} NMR spectrum of **2a**: three CH_2 and two CO_2.

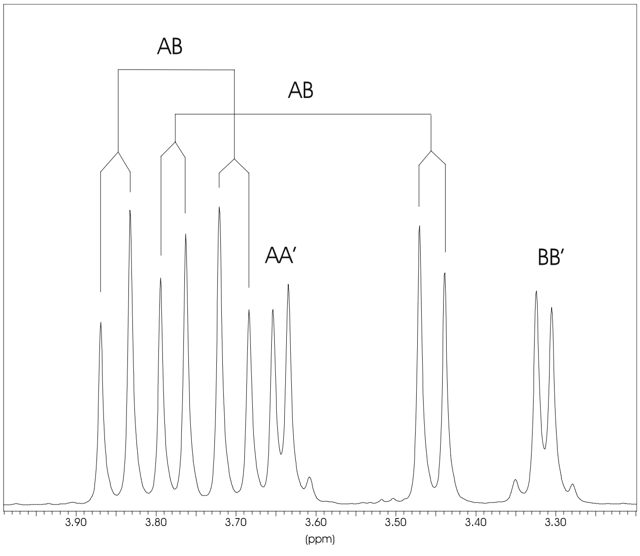


Figure 1. 500 MHz ^1H NMR spectrum of **2a** in acetone-d_6.

The assignment of carbon signals to the appropriate proton signals was made by two-dimensional HSQC and HMBC correlations. Carbon signals of e- and a-N–$\underline{\mathrm{CH}_2}$–$\mathrm{CO}_2$ groups appropriated on the basis of juxtaposition of all dihedral angles of carbons with protons and multiplicity of signals. From the X-ray data,[12] the values of φ_{CNCH} for carbon atoms of e-N–$\underline{\mathrm{CH}_2}$–$\mathrm{CO}_2$ fragments are 4, 34, 86 and 121°, whereas for carbons of a-N–$\underline{\mathrm{CH}_2}$–$\mathrm{CO}_2$ φ_{CNCH} were found to be 39, 41, 160 and 161°. Thus, for the e-N–$\underline{\mathrm{CH}_2}$–$\mathrm{CO}_2$ group it is possible to observe no more than two coupling constants $^3J_{\mathrm{CH}}$ and for the carbon of a-N–$\underline{\mathrm{CH}_2}$–$\mathrm{CO}_2$ two additional triplet splittings of the main triplet led to the transformation of each of its components into seven-line multiplets, the ratio of the coupling constants being $^3J_{1\ \mathrm{CH}} = 1/2\ ^3J_{2\ \mathrm{CH}}$.

3. Conclusion

Proposed methods for the resolution of racemates for which it is possible to find a conglomerator are very efficient and do not require the use of any external chiral reagent. The discussed principles are very common and can be applied to a great number of compounds. One can only wonder why over a period of 150 years after the famous experiments of Pasteur nobody has taken full advantage of such uniquely simple methods.

4. Experimental

Optical activities were determined by polarimetry and CD methods (polarimeter Polamat A and CD spectropolarimeter Jasco-500A, with DP-500N data processor). ^{1}H and ^{13}C NMR spectra were recorded using Bruker DPX-500, Bruker WM-400 and Bruker AC-200 spectrometers. Optical rotations were measured for aqueous solutions at 23–25°C in 1 dm tube, the observed α_λ varied from 0.03 to 0.360.

4.1. Synthesis and NMR spectra of 1a,b and 2a,b

Compounds **1a**,**b**, orange crystals, prepared by the known method[7c] via *trans*-**3a** and *cis*-**3b**-[Co(en)$_2$Cl$_2$]Cl complexes, have identical spectra: ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.3–2.4 (4H, m, 2CH$_2$N), 2.50–2.58 (4H, m, 2CH$_2$N), 4.07 (2H, br s, H$_2$N), 4.62 (2H, br s, H$_2$N), 5.28 (2H, br s, H$_2$N), 5.59 (2H, br s, H$_2$N); ^{13}C {^{1}H} NMR (200 MHz, D$_2$O+CD$_3$OD): δ 44.4 (s, CH$_2$N), 46.1 (s, CH$_2$N); ^{13}C NMR (400 MHz, H$_2$O+CD$_3$OH): δ 44.53 (t, $^1J = 144$ Hz, CH$_2$N), 46.25 (t, $^1J = 144$ Hz, CH$_2$N).

Compound **3a**, green crystals, had in ^{13}C {^{1}H} NMR only one signal because of *trans*-structure, ^{13}C {^{1}H} NMR (200 MHz, CD$_3$OH): δ 45.78s; ^{13}C {^{1}H} NMR (200 MHz, D$_2$O+CD$_3$OD): δ 45.79s.

Compound **3b**, violet crystals, ^{13}C {^{1}H} NMR (200 MHz, CD$_3$OD+D$_2$O): δ 44.4 (s, CH$_2$N), 46.1s (CH$_2$N); ^{13}C {^{1}H} NMR (200 MHz, CD$_3$OH+H$_2$O): δ 44.64 (s, CH$_2$N), 46.79 (s, CH$_2$N).

Compounds **2a**,**b**, violet crystals prepared by the known method[12] have identical spectra: ^{1}H NMR (500 MHz, acetone-d_6): δ 3.32 and 3.64 (4H, m, N(CH$_2$)$_2$N, AA′BB′ spectrum), 3.45 and 3.77 (4H, d, $\Delta\nu = 160.0$ Hz, $^2J_{\mathrm{AB}} = -15.4$ Hz, 2e-CH$_2$N, AB spectrum), 3.70 and 3.84 (4H, d, $\Delta\nu = 70.0$ Hz, $^2J = -18.8$ Hz, 2a-CH$_2$N, AB spectrum); ^{13}C NMR (500 MHz, acetone-d_6): δ 63.85 (tm, $^1J_{\mathrm{CH}} = 145.3$ Hz, N(CH$_2$)$_2$N), 65.64 (ddd, $^1J_{\mathrm{CH}} = 142.7$, $^1J_{\mathrm{CH}} = 148.4$, $^3J_{\mathrm{CH}} = 4.8$, e-NCH$_2$CO$_2$) and 65.85 (tm, $^1J_{\mathrm{CH}} = 143.5$, a-NCH$_2CO_2$), 182.02 (dd, $^2J_{\mathrm{CH}} = 6.1$, $^2J_{\mathrm{CH}} = 3.0$, e-NCH$_2$CO$_2$) and 183.62 (dd, $^2J_{\mathrm{CH}} = 5.9$, $^2J_{\mathrm{CH}} = 4.5$, a-NCH$_2$CO$_2$).

4.2. Single-crystal investigations

4.2.1. Enantiomeric purity of single crystals. There were no difficulties in preparing well-formed single crystals of **1b** and **2b**. By slow evaporation of their near-saturated aqueous solutions we obtained crystals up to 1.6 cm in length and weight of 421 mg. Their solutions were analysed by polarimetry (c 1 for **1b** and c 0.02 for **2b**, H$_2$O). The optical purity of single crystals of **1b** changed from 23 to 59%. The same situation was observed for **2b** (optical purity 60–84%). It means that there is no strong enantioselectivity during crystal growth, i.e. all crystals are not enantiomerically pure, but are made up of unequal quantities of two enantiomers. The limit of e.e. in the single crystal determines the enantiomeric purity that one can obtain in experiments of resolution via crystallisation.

4.2.2. Crystallographic data for 1b. Earlier the crystal of the (+)-**1b** was studied by X-ray diffraction analysis (space group $P2_1$).[15] Relaying on these data one cannot conclude about properties of the crystal (±)-**1b**. Therefore, a repeat X-ray diffraction study of a random crystal **1b** was carried out, and the same non-centrosymmetrical space group was confirmed (Fig. 2).

Crystal of $\mathrm{C_4H_{16}Co_1N_6O_4\ Br^-}$ is monoclinic, space group $P2_1$, $a = 6.5310(6)$, $b = 11.0682(9)$, $c = 8.2822(7)$ Å, $\beta = 107.191(2)°$, $V = 571.94(9)$ Å^3, $Z = 2$, $M = 351.07$, $d_{\mathrm{calc}} = 2.039$ g/cm^3, μ(Mo Kα) = 50.05 cm^{-1}, $F(000) = 352$. Intensities of 6539 reflections were measured with a Smart 1000 CCD diffractometer at 110 K (λ(Mo Kα) = 0.71072 Å, ω-scans with 0.3° step in ω and 10 s per frame exposure, $2\theta < 60°$), and 3194 independent reflections ($R_{\mathrm{int}} = 0.0180$) were used in further refinement. The absorption correction was carried out semi-empirically from equivalents using the Sadabs program. The structure was solved by direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. Hydrogen atoms were located from the Fourier synthesis and refined in the isotropic approximation.

The absolute configuration as well as racemic twinning was evaluated by refinement of Flack parameter,[16] which was equal in the case of $\Lambda(\delta\lambda)$-$(-)_{589}$ configuration to 0.332(8). Thus, according to the said refinement the e.e. of the single crystal investigated was 33.6% that is in the e.e. range of the polarimetry analysis.

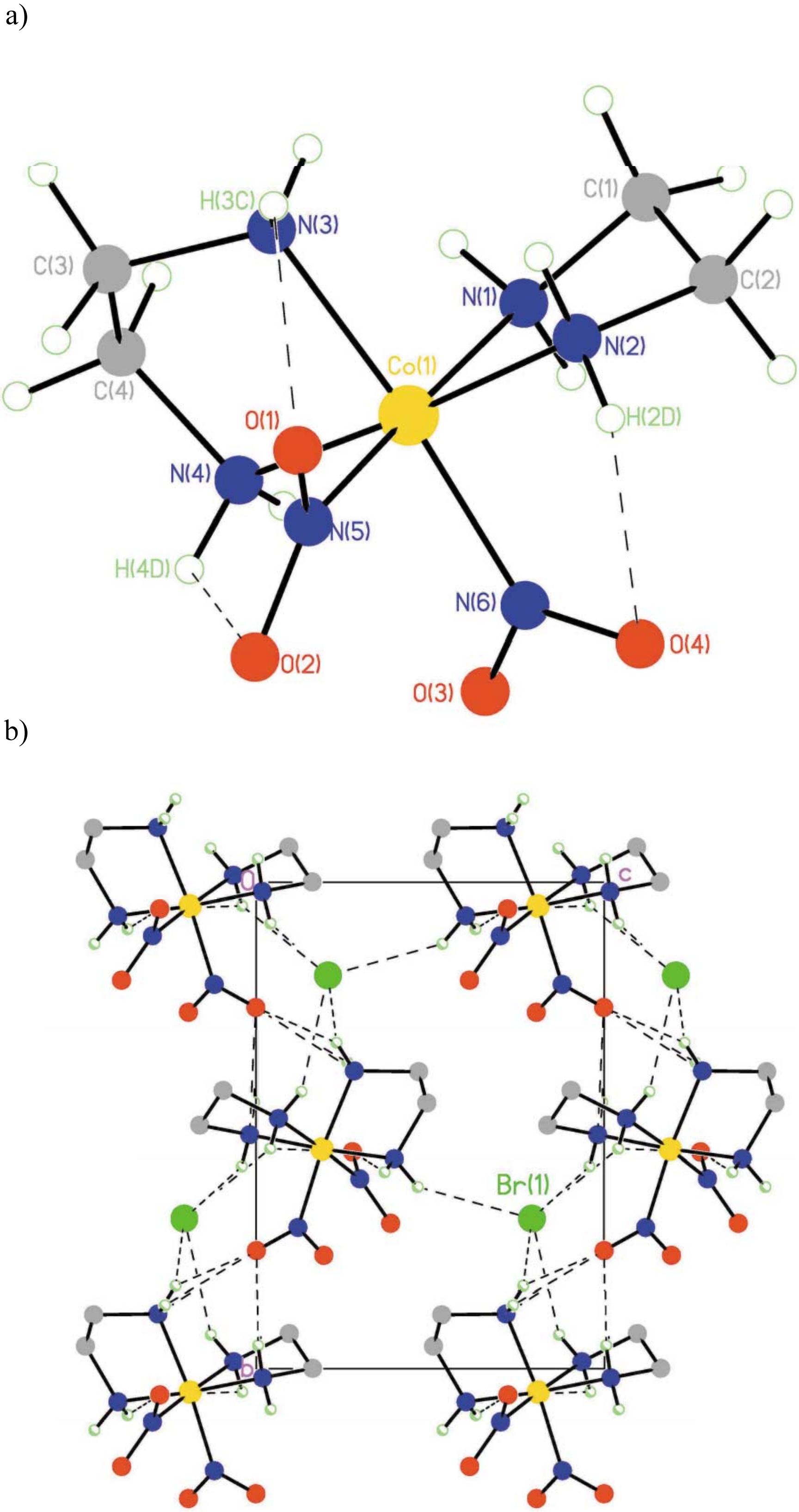


Figure 2. (a) The general view of the cation in **1b**. Selected bond lengths (Å): H(3C)···O(1) 2.44, H(2D)···O(4) 2.37, H(4D)···O(2) 2.41; (b) the [101] projection of the crystal structure **1b**, illustrating the N–H···Br and N–H···O hydrogen bonds network.

The refinement converged to $wR_2=0.0737$ and GOF= 1.045 for all independent reflections ($R_1=0.0279$ was calculated against F for 3101 observed reflections with $I>2\sigma(I)$). The number of the refined parameters was 146. All calculations were performed using SHELXTL PLUS 5.0 on IBM PC AT.

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary no. CCDC 171214. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ UK (Fax: (int.) +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk).

4.3. Examples of internal entrainment procedure (Procedure A)

From a racemic crystalline mixture of **1a** (213.4 mg) a single crystal (19.4 mg) was picked up and cut into two pieces (11.2 and 8.2 mg). The sign of optical rotation of the first piece was determined ($[\alpha]_{589}^{23}=-35.6$, ($c$ 1, H_2O)). This solution was diluted to 2.7 mL and all crystalline material was dissolved in it to the exclusion of the second piece of crystal, which was added as the seed. After 3 days of self-evaporation the deposit was separated, dried, weighed, and examined (86.3 mg, $[\alpha]_{589}^{23}=-18$ (c 1, H_2O), e.e. 36%). The same procedure for **2b**: weight of primary racemic mixture is 1.01 g, weight of monocrystal is 6.4 mg, two parts are 0.8 mg ($[\alpha]_{546}^{25}=+1268.4$, ($c$ 0.02, H_2O)) and 5.6 mg as the seed. Optical purity of crystals (340 mg) thus obtained after 2 days of crystallisation was 64.5% ($[\alpha]_{546}^{25}=+974$, (c 0.02, H_2O)).

4.4. Typical resolution procedure at deficiency of conglomerator (Procedure B)

Compound **1a** (469.6 mg, 1.53 mmol), NaBr (78.8 mg, 0.765 mmol) or compound **2a** (4.21 g, 10 mmol), NH_4Cl (0.27 g, 5 mmol) were dissolved in water (20 and 8 mL, respectively). After checking the solutions for absence of optical activity, they were divided into four equal portions to evaporate at 20–25°C. After 1–4 days of exposure the deposited solids were separated, dried, weighed and examined for optical activity. Crystals of the opposite enantiomers were obtained from the mother liquors by further self-evaporation, separated and examined. In some cases the conglomerator was added in the necessary molar ratio (racemic compound: conglomerator) to the mother liquor before performing a second crystallisation procedure.

Acknowledgements

We are grateful to Dr. Yu. A. Strelenko (N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences) for measurement of NMR spectra. This work was supported by the Russian Academy of Sciences and Russian Foundation for Basic Research (RFBR) (grant No. 00-03-32738) and INTAS (grant No. 99-00157).

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