N-Nitrosopiperidines with chirality solely due to hindered rotation about the N–N bond: enantioselective inclusion complexation with optically active hosts

Teresa Olszewska,[a] Maria J. Milewska,[a] Maria Gdaniec[b] and Tadeusz Połoński*[a]

[a] *Department of Chemistry, Technical University, 80-952 Gdańsk, Poland. E-mail: tadpol@chem.pg.gda.pl*
[b] *Faculty of Chemistry, A. Mickiewicz University, 60-780 Poznań, Poland*

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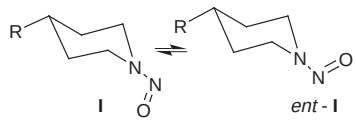
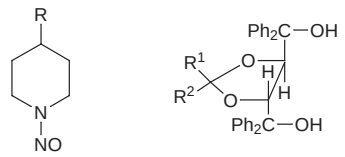
An efficient optical resolution of 4-substituted *N*-nitrosopiperidines achieved by enclathration with chiral diols was evidenced by X-ray crystallography and circular dichroism spectra in solution.

Hindered rotation about the partial double bond between the two adjacent nitrogen atoms in *N*-nitrosamines results in many unusual stereochemical and spectroscopic consequences.[1] In the absence of any improper symmetry axis the molecules of *N*-nitrosopiperidines, derived from symmetric amines, are chiral and may exist in two enantiomeric forms. Interconversion between the enantiomers occurs by rotation about the N–N bond (Scheme 1). The corresponding energy barrier is large enough (23–25 kcal mol^{-1})[2] to permit potential isolation of stereoisomers at ambient temperature.



Scheme 1

The compounds **1**–**4**, owing their chirality solely to restricted rotation of the NO group, would be useful and extremely simple models for studying the chiroptical spectra of the nitrosamino



1 R = H
2 R = Me
3 R = Ph
4 R = CH_2Ph

5a $R^1 = R^2$ = Me
5b R^1–R^2 = $(CH_2)_4$

chromophore. The optical activity of nitrosamines has been the subject of numerous investigations and much speculation in recent years.[3] However, the resolution of racemic compounds devoid of additional functional groups usually poses a serious problem.[4] A method, which has received increasing attention in the last two decades, is the inclusion crystallization of racemates with optically active hosts.[5] This seems to be a promising approach also for our purpose. Recently, we have found that cholic acid crystal matrices show strong chiral recognition ability with the nitrosamines **1** and **2**, making it possible to detect their CD spectra in the solid state.[6] Unfortunately, this technique is restricted to rather small molecules and cholic acid did not form inclusion complexes with **3** and **4**.

Here we present a simple and general procedure for optical resolution of nitrosamines that also makes possible their isolation from the host matrices. We were particularly interested in obtaining easily crystallizing compounds, which stored in the solid state could retain their optical activity for very long periods. The nitrosamines **3** and **4** were among candidates that should satisfy these conditions. With use of (*R*,*R*)-(−)-**5a** and (*R*,*R*)-(−)-**5b** (TADDOLs), easily accessible from (+)-tartaric acid,[7] as the chiral hosts we were able to prepare optically active **3** and **4** in the crystal form and record their CD spectra in solution. The 1:1 complexes of **3** and **4** with **5a** were obtained by cocrystallization of equimolar amounts of the corresponding nitrosamine and the host diol from toluene–hexane. In the case of the diol **5b** and nitrosamine **4**, after choosing the proper component proportion, two types of inclusion compound can be prepared, with mp 109 and 131 °C (guest–host ratio of 1:1 and 1:2, respectively).

Usually separation of the optically active guest from the chiral diol can be accomplished chromatographically or by fractional distillation.[5,8] Obviously neither of these techniques can be used for unstable or rapidly racemising compounds. Taking advantage of the reported strong affinity of **5a**,**b** with secondary amines,[9] we succeeded in liberating of the enclathrated nitrosamines by a competitive complexation of the host diols with piperazine. This was possible because this amine forms a very stable and almost insoluble (in nonpolar solvents) 2:1 complex with **5b**. Therefore after addition of piperazine to a suspension of **4**·2(**5b**) in Et_2O at *ca*. 0 °C, followed by filtration of the precipitated piperazine complex and evaporation of the solvent, the optically active nitrosamine (−)-**4** was isolated; mp 62–63 °C, $[\alpha]_D^{21}$ −67.2 (*c* 1.25, C_6H_6). Compound

Table1 Circular dichroism (CD) data

Compound	Solvent[a]	λ/nm ([Θ])[b]
(−)-**3**	CD	376 (−510)
3·**5a**	T	373 (−2170)
3·**5b**	T	373 (−2080)
(−)-**4**	CD	373 (−1200)
4·5a	T	372 (1230)
4·**5b**	T	372 (−1880)
4·2(**5b**)	T	371 (−1550)

[a] CD = cyclohexane–dioxane (9:1), T = toluene. [b] Molecular ellipticity in deg cm^2 dmol^{-1}, measured immediately after dissolution of the sample.

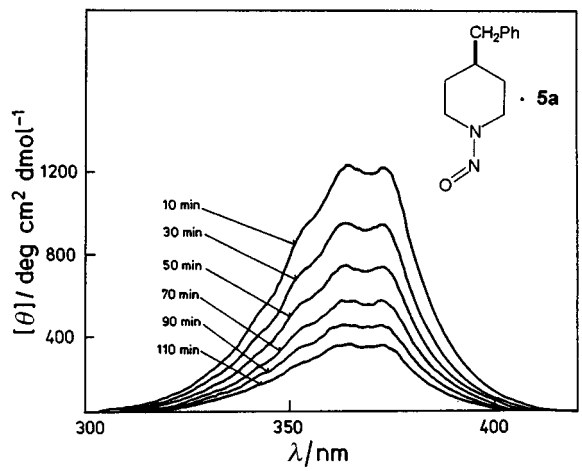


Fig. 1 Decay of the CD signal of **4**·**5a** in toluene at 22 °C.

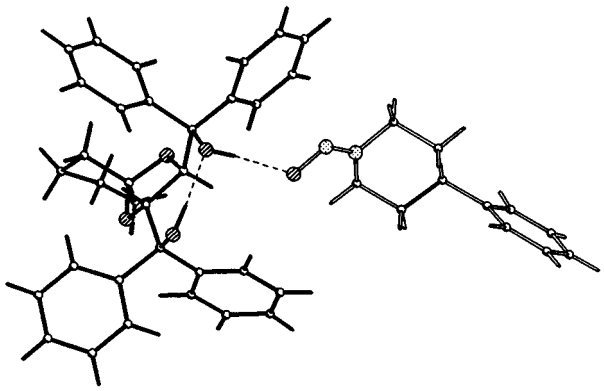


Fig. 2 Molecular structure of the complex **3**·**5b**. Broken lines represent the hydrogen bonds.

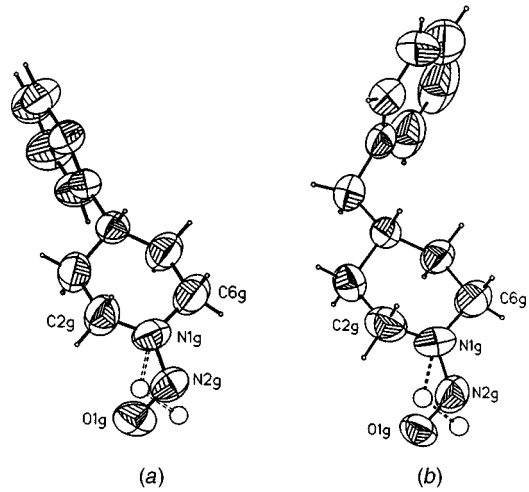


Fig. 3 ORTEP drawings of the guest nitrosamines (*a*) **3** and (*b*) **4** showing their absolute configurations.

(−)-**3** was prepared similarly; mp 66–67 °C, $[\alpha]_D^{21}$ −50.2 (*c* 1, C_6H_6).

The optical activity of the isolated nitrosamines is manifested by their chiroptical spectra in solution. Since the nitrosamine n–π* band does not interfere with the absorption of the phenyl chromophore in **5a**,**b**, the shape of the CD spectra of the complexed and free nitrosamines are essentially the same (Table 1). The CD curves observed in toluene solution show moderately strong Cotton effects corresponding to the nitrosamine n–π* electronic transition near 370 nm, which gradually decrease at room temperature (Fig. 1) due to a rapid racemization of (−)-**3** and (−)-**4**. A comparison of the CD sign of **4**·**5b** with that of **4**·2(**5b**) revealed the same configuration of the guest molecules included in both clathrates. In contrast, the opposite sign and slightly lower CD magnitude of **4**·**5a** to those shown by **4**·**5b** and **4**·2(**5b**) indicates a preferential complexation of the (+)-**4** enantiomer by the host **5a**.

The first order kinetics of the racemization process can be monitored by simple polarimetric measurements and we observed the racemisation half-life $t_{1/2}$ at 22 °C for **3** and **4** of 50 and 45 min, respectively. The calculated activation energy $\Delta G^{\ddagger}$ values of 22.0 and 21.9 kcal mol^{-1} for **3** and **4**, respectively, are comparable to the N–N rotation barrier heights obtained for *N*-nitrosopiperidines *via* NMR measurements.[2]

The X-ray crystallographic analysis of the clathrates **3**·**5b** (Fig. 2) and **4**·2(**5b**) revealed that one enantiomer of the guest nitrosamine was preferentially included in the crystals.† The absolute configurations of the guest molecules can be easily elucidated from the crystal structures of the clathrates and we found that in the case of the complexes **3**·**5b** and **4**·2(**5b**) the *S* configuration is preferred by (−)-**3** and (−)-**4** nitrosamine molecules (Fig. 3). However, a small degree of contamination of the inclusion crystals with the second nitrosamine enantiomer results in disorder of the N–NO group over two positions. A significant excess of the *S* enantiomer was determined from the refinement of the occupancy factors of two NO group positions although the exact enantiomeric ratio could not be determined due to a high correlation between the occupancy factors and dispalacement parameters of the N–NO group *via* the least-squares method. The X-ray structures of the clathrates showed that the piperidine ring in **3** and **4** assumes a chair conformation with the substituent at C-4 occupying the equatorial position. The nitroso oxygen is hydrogen bonded to one of the hydroxy groups of the host diol.

Notes and references

† Diffraction data were obtained on a Kuma KM-4 diffractometer with graphite monochromated Cu-Kα radiation (λ = 1.54178 Å). The structures were solved by direct methods with the program SHELXS-86 (ref. 10). Full-matrix least-squares refinement was carried out with SHELXL-93 (ref. 11). The *N*-nitroso groups in the guest molecules are disordered over two positions. Restraints were imposed on 1-2 and 1-3 distances and the planarity of the *N*-nitrosamino group during structure refinement. The minor components were refined with isotropic displacement parameters. *Crystal data* for **4**·2(**5b**): $2C_{33}H_{27}O_4{\cdot}C_{12}H_{16}N_2O$, M = 1189.44, monoclinic, space group $C2$, a = 35.720(7), b = 8.605(2), c = 23.661(5) Å, β = 117.94(3)°, V = 6425(2) Å^3, Z = 4, D_c = 1.230 g cm^{-3}, μ = 0.632 mm^{-1}, T = 293 K, crystal size 0.4 × 0.4 × 0.05 mm, θ_{max} = 60°, 4792 reflections measured, 4710 unique (R_{int} = 0.029) R_1 = 0.042, wR_2 = 0.107 for 3929 reflections with $I > 2\sigma(I)$ (R_1 = 0.062, wR_2 = 0.114 for all 4710 independent reflections). For **3**·**5b**: $C_{33}H_{27}O_4{\cdot}C_{11}H_{14}N_2O$, M = 682.83, monoclinic, space group $P2_1$, a = 11.292(2), b = 9.536(2), c = 17.654(4) Å, β = 97.04(2)°, V = 1886.7(7) Å^3, Z = 2, D_c = 1.202 g cm^{-3}, μ = 0.620 mm^1, T = 293 K, crystal size 0.5 × 0.15 × 0.03 mm, θ_{max} = 66°, 3511 reflections measured, 3418 unique (R_{int} = 0.024), R_1 = 0.0418, wR_2 = 0.1108 for 2633 reflections with $I > 2\sigma(I)$ (R_1 = 0.0696, wR_2 = 0.1271 for all 3418 independent reflections). CCDC 182/1275. See: http://www.rsc.org/suppdata/cc/1999/1385/ for crystallographic data in .cif format.

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