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Synthesis and resolution of naphthyl-Tröger's base

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Abstract

A naphthyl analogue of Tröger's base {8*H*,16*H*-7,15-methanodinaphtho[2,1-*b*][2′,1′-*f*][1,5]-diazocine (NTB)} was prepared and successfully resolved using (−)- and (+)-di-*p*-toluoyl-tartaric acid. Enantiomers obtained show extremely high specific rotations related to (i) the rigid [1,5]-diazocine skeleton with molecular asymmetry and (ii) the presence of condensed aromatic rings, similar to helicenes.

1. Introduction

2,8-Dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*, *f*][1,5]-diazocine **1** (TB) was first prepared as a condensation product of formaldehyde and *p*-toluidine by Tröger in 1887.[1] The structure was later elucidated by Spielman.[2] Prelog recognized that TB is asymmetric due to the pyramidal nitrogens.[3] Several Tröger's base type compounds of substituted or condensed aromatic rings have been reported,[4] for instance, 8*H*,16*H*-7,15-methanodinaphtho[2,1-*b*][2′,1′-*f*][1,5]-diazocine (NTB) was first mentioned by Farrar.[5] As condensation products of formaldehyde with 2-naphthylamine, three different stereoisomers (**2**, **3**, **4**) were suggested but not identified. In that study no attempt was made to obtain enantiomerically pure NTB. Only chromatographic resolution of **2** has been reported.[6]

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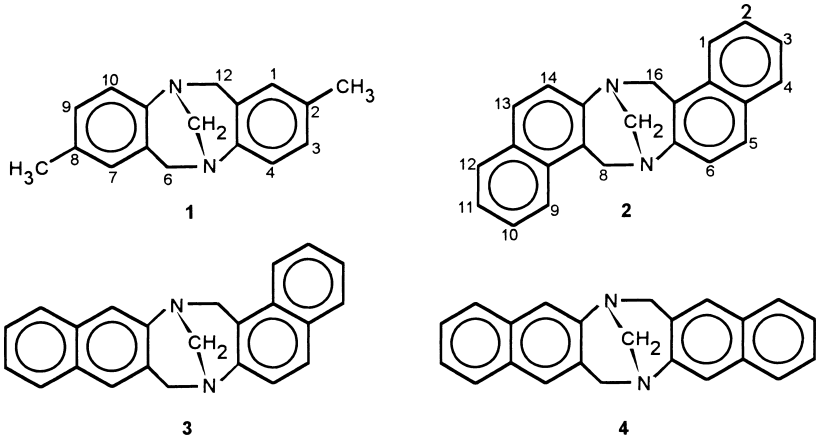

Although resolution of TB has often been carried out by chromatography,[7] even in the pioneering work of Prelog,[3] classical resolution via diastereomer salt formation caused difficulties because in acidic media (e.g. using 10-camphorsulfonic acid as a resolving agent) the partially resolved samples undergo racemization. An iminium ion mechanism has been suggested as a possible mechanism for racemization.[3] Greenberg et al. were unable to find evidence for such an intermediate, but their study showed that racemization might be more favourable in dilute acid rather than in concentrated acid.[8] Using (−)-1,1′-binaphthalene-2,2′-diyl hydrogenphosphate as the resolving agent the resolution was attended by a crystallization-induced asymmetric transformation.[9] Ethano-Tröger's base (2,8-dimethyl-6*H*,12*H*-5,11-ethanodibenzo[*b*, *f*][1,5]-diazocine) was successfully resolved by di-*p*-toluoyl-tartaric acid while resolution of the methoxy derivative of the above compound failed.[10]

Due to the very pronounced asymmetric character of TBs, these types of compounds have both theoretical and practical interest, as molecular receptors,[11] chiral solvating agents,[9] and as chiral modifiers in enantioselective reactions.[12]

The aim of this work was to prepare and resolve NTB to get a new chiral compound in order to induce supramolecular interactions. This may then be utilized in different fields, for instance in the formation of host–guest type complexes[13] and enantioselective hydrogenations.

2. Results and discussion

NTB was obtained by condensation of 2-naphthylamine with formaldehyde according to Farrar's methods.[5] The work with 2-naphthylamine needs special care due to the strong carcinogenic effect of this compound. In method (1) reactants were heated in the presence of concentrated HCl. The brown–yellow gum formed was subsequently digested with methanol. After basification, the MeOH solution gave a pale brown precipitate (sample A, yield 67%). In the course of method (2) 2-naphthylamine was mixed with hot dilute HCl and formaldehyde was added to the reaction mixture after cooling to room temperature. In this case the reaction time was longer. The gum formed was digested with ethanol. The EtOH solution was basified giving a brown–white precipitate (sample B, yield 40.9%). The residue of the digestion (a green material) was dissolved in chloroform then basified to get sample C (yield 23.6%). Samples A, B and C were recrystallized from hot methanol to give white crystals. HPLC measurements proved that each sample contained only one main component (more than 90%). The NMR measurements including NOE difference spectra provided firm evidence that the three samples have identical structures to **2**. On irradiation of H16A, H16B (which are equivalent to H8A, H8B) NOE with the proton giving a doublet of

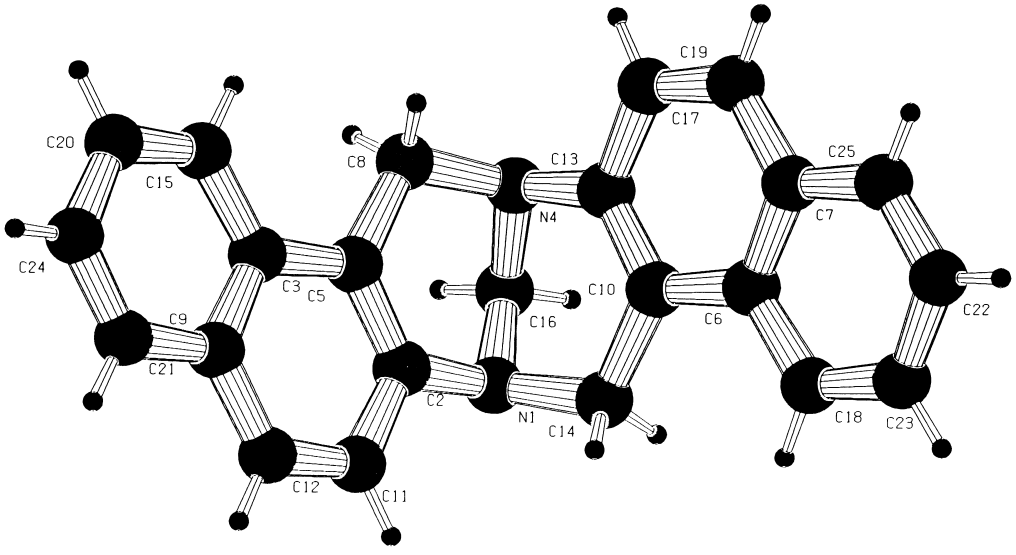

Figure 1. Absolute molecular structure of (+)-NTB as determined by X-ray diffraction

doublet signal (and not a singlet) was observed. This NOE was assigned to H1 and this confirms structure **2**. Assignment of the spectra was achieved by ^{1}H decoupling and by HETCOR experiments. In contrast to a previous result[5] formation of **3** and **4** was not observed.

Resolution of (±)-NTB was carried out by salt formation with (−)-di-*p*-toluoyl-D-tartaric acid [(−)-DTTA] according to the literature.[10] In acetone pre-dried over $CaCl_2$ and freshly distilled from K_2CO_3, (±)-NTB and [(−)-DTTA] gave [(−)-NTB·(−)-DTTA] as colourless crystals. If water was present in the solvent the resolution failed. Exclusion of air is advisable because otherwise a red colour appeared suggesting an undesirable oxidation process. After recrystallization and base treatment, pure (−)-NTB (98% ee) was obtained in 21% yield based on (±)-NTB. The enantiomeric excess was determined by HPLC with a chiral column. The mother liquor above was basified and the (+)-NTB enriched material was treated with (+)-di-*p*-toluoyl-D-tartaric acid [(+)-DTTA] to get the [(+)-NTB·(+)-DTTA]. From this salt pure (+)-NTB was obtained (100% ee) with 19% yield based on (±)-NTB. The absolute configuration of the (+)-NTB enantiomer was determined by a single-crystal X-ray diffraction determination (Fig. 1). This gave (7*S*,15*S*) in accord with the literature data for the axial chirality of TB.[9]

The specific rotation of (−)-NTB and (+)-NTB is extremely high {$[\alpha]_D^{24}$ +1166, $[\alpha]_D^{24}$ −1150 (*c* 0.1, $CHCl_3$)} compared with TB {$[\alpha]_D^{20}$ +280, $[\alpha]_D^{20}$ −280 (*c* 0.5, hexane) Aldrich Chem. Co.}. Only helicenes show specific rotations of this magnitude.[14] In the series of [5][14]-, [6]-, [7]-, [8]- and [9][15]-helicenes $[\alpha]_{D_{max}}$ was found to increase as the number of rings increases. In the case of NTB the rigid [1,5]-diazocine skeleton of C_2 molecular symmetry also contains condensed aromatic rings. In this sense there is a definite similarity to helicenes.

3. Experimental

*3.1. Preparation of (±)-8*H,*16*H-*7,15-methanodinaphtho[2,1-bis][2′,1′-f]-diazocine [(±)-NTB]*

(1) 2-Naphthylamine (14.5 g, 0.1 mol), concentrated hydrochloric acid (10 cm^3) and formaldehyde (12 cm^3, 37% solution) were heated together at 100°C for 20 min. The formed gum was digested with

warm MeOH. The methanol solution was basified with NH_4OH and the precipitate obtained was filtered, washed with a small portion of cold MeOH, and dried in a dessicator over P_2O_5, giving sample A (10.8 g, 67%): mp after MeOH recrystallization 212–213°C. Anal. calcd for $C_{23}H_{18}N_2$: C, 85.68; H, 5.63; N, 8.69. Found: C, 85.01; H, 5.08; N, 8.63.

(2) 2-Naphthylamine (14.5 g, 0.1 mol) was dissolved in hot HCl (2 N, 120 cm^3). The mixture was allowed to cool to room temperature. The slurry was treated with formaldehyde (10 cm^3, 37% solution) and left to stand at room temperature for 1 day. The resulting gum was digested with EtOH. The EtOH solution was basified and the precipitate obtained was washed with a small portion of EtOH, and dried in a dessicator over P_2O_5, giving sample B (6.6 g, 40.9%): mp after MeOH recrystallization 209–211°C. Anal. calcd for $C_{23}H_{18}N_2$: C, 85.68; H, 5.63; N, 8.69. Found: C, 86.29; H, 5.40; N, 8.65. The residue of the digestion was dissolved in chloroform, and basified with NH_4OH. The organic layer was washed with water, dried over Na_2SO_4 and evaporated giving sample C (3.8 g, 23.6%): mp after MeOH recrystallization 213–215°C. Anal. calcd for $C_{23}H_{18}N_2$: C, 85.68; H, 5.63; N, 8.69. Found: C, 85,64; H, 5.54; N, 8.63. ^1H and ^{13}C NMR spectra for samples A, B, C, (+)-NTB and (−)-NTB were identical. ^1H NMR (400 MHz, $CDCl_3$, 30°C) δ 7.69 (2H, dd, *J*=8.1, 1.4 Hz), 7.65 (2H, dd, *J*=8.3, 1.3 Hz), 7.64 (2H, d, *J*=8.8 Hz), 7.43 (2H, ddd, *J*=8.3, 6.9, 1.4 Hz), 7.35 (2H, d, *J*=8.8 Hz), 7.34 (2H, ddd, *J*=8.1, 6.9, 1.3 Hz), 5.02 (2H, d, *J*=−16.7 Hz), 4.75 (2H, dt, *J*=−16.7, 1.1 Hz), 4.52 (2H, t, *J*=1.1 Hz); ^{13}C NMR ($CDCl_3$+DMSO) δ 145.77, 131.35, 130.83, 128.53, 127.82, 126.43, 124.67, 124.65, 121.18, 121.16, 67.06, 55.80.

*3.2. Resolution of (±)-8*H,*16*H-*7,15-methanodinaphtho[2,1-bis][2′,1′ -f][1,5]-diazocine [(±)-NTB]*

(±)-NTB (10 g, 31 mmol) and (−)-di-*p*-toluoyl-L-tartaric acid (7.19 g, 18 mmol) were dissolved in hot acetone (200 cm^3) under argon. The mixture was allowed to stand at room temperature for ten days. The precipitate was filtered and recrystallized from acetone under argon, giving [(−)-NTB·(−)-DTTA] (5.57 g): mp 163–164°C, $[\alpha]_D^{24}$ −399 (*c* 0.1, $CHCl_3$); IR ν_{max} (KBr): 753.4, 1105.5, 1266.6, 1732.5 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$+DMSO, 30°C) δ 8.01 (4H m, DTTA), 7.70 (2H, dd, *J*=8.1, 1.4 Hz), 7.66 (2H, dd, *J*=8.5, 1.2 Hz), 7.64 (2H, d, *J*=8.9 Hz), 7.44 (2H, ddd, *J*=8.5, 6.9, 1.4 Hz), 7.36 (2H, d, *J*=8.9 Hz), 7.35 (2H, ddd, *J*=8.1, 6.9, 1.2 Hz), 7.25 (4H, m, DTTA), 5.96 (2H, s, DTTA), 5.05 (2H, d, *J*=−16.7 Hz), 4.74 (2H, d, *J*=−16.7 Hz), 4.53 (2H, s), 2.16 (6H, s, DTTA); ^{13}C NMR ($CDCl_3$+DMSO) δ 168.07 (DTTA), 165.28 (DTTA), 144.22 (DTTA), 144.95, 131.18, 130.78, 130.05 (DTTA), 129.13 (DTTA), 128.48, 127.85, 126.51, 126.43 (DTTA), 124.78, 124.42, 121.18, 121.04, 71.72 (DTTA), 66.53, 55.46, 21.66 (DTTA). Anal. calcd for $C_{23}H_{18}N_2 \cdot C_{20}H_{18}O_8$: C, 72.87; H, 5.12; N, 3.95. Found: C, 72.37; H, 5.13; N, 3.97.

The [(−)-NTB·(−)-DTTA] obtained (5.57 g) was decomposed with saturated aqueous $NaHCO_3$ in CH_2Cl_2. The mixture was extracted with CH_2Cl_2 and washed with brine. The organic layer was dried over Na_2SO_4, filtered and evaporated. The remaining material (2.1 g, 21%, 98% ee) was recrystallized from MeOH under argon atmosphere: mp 258–260°C, $[\alpha]_D^{24}$ −1150 (*c* 0.1, $CHCl_3$); IR ν_{max} (KBr): 748.9, 756.6, 939.6, 1212.0 cm^{-1}. Anal. calcd for $C_{23}H_{18}N_2$: C, 85.68; H, 5.63; N, 8.69. Found: C, 85.66; H, 5.64; N, 8.90.

The mother liquor from the above described separation of (−)-NTB was evaporated. The remaining solid was treated with saturated aqueous $NaHCO_3$ in CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated to give a pale brown material. Thus the obtained material and (+)-di-*p*-toluoyl-L-tartaric acid (7.2 g 19 mmol) were dissolved in hot acetone (200 cm^3) under an argon atmosphere. The solution was allowed to stand at room temperature for ten days. Pale yellow crystals of [(+)-NTB·(+)-DTTA] were obtained (5.26 g), mp 164–165°C, $[\alpha]_D^{24}$ +412 (*c* 0.1, $CHCl_3$); IR ν_{max} (KBr): 753.3, 1105.7,

1266.4, 1732.2 cm^{-1}; ^1H and ^{13}C NMR spectra of [(+)-NTB·(+)-DTTA] were identical with those of [(−)-NTB·(−)-DTTA]. Anal. calcd for $C_{23}H_{18}N_2 \cdot C_{20}H_{18}O_8$: C, 72.87; H, 5.12; N, 3.95. Found: C, 72.42; H, 5.20; N, 4.05.

The [(+)-NTB·(+)-DTTA] obtained (5.26 g) was decomposed with saturated aqueous $NaHCO_3$ in CH_2Cl_2. The mixture was extracted with CH_2Cl_2 and washed with brine. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The remaining white material (1.9 g, 19%, 100% ee) was recrystallized from MeOH under an argon atmosphere: mp 257–259°C, $[\alpha]_D^{24}$ +1166 (*c* 0.1, $CHCl_3$); IR ν_{max} (KBr): 748.9, 756.6, 939.6, 1212.0 cm^{-1}. Anal. calcd for $C_{23}H_{18}N_2$: C, 85.68; H, 5.63; N, 8.69. Found: C, 86.01; H, 5.66; N, 8.85.

3.3. General

Samples A, B and C were analyzed by HPLC on a PGC column with 90% MeOH–10% H_2O eluent, UV detector at 250 nm. The enantiomeric excesses of (−)-NTB and (+)-NTB were measured by HPLC analysis on a CHIRAL-AGP column, with 30% acetonitrile–phosphate buffer (pH 7.0) eluent, and a UV detector at 225 nm.

3.4. Single crystal X-ray diffraction study

A suitable single crystal of (+)-NTB was mounted on a 4-circle automated X-ray diffractometer using Cu-K_α radiation at ambient temperature. Crystal data indicated the orthorhombic space group $P2_12_12_1$ (No. 19) with a=6.454(1), b=9.450(1) and c=27.150(1) Å. A total of 4283 intensities were collected of which 3331 were unique. The initial structure model was obtained from direct methods and smoothly refined via full matrix least-squares for all non-hydrogen atoms treated with anisotropic displacement parameters. Hydrogen atoms were placed in calculated positions and kept riding on their respective anchor atoms. The final R and wR^2 values are 0.031 and 0.092 for 3331 data values. The value of the Flack parameter, x=−0.01(5), indicates the correct choice of the coordinate system. All computer programs used in the data treatment and refinement are listed.[16]

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