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Tetrahedron Letters 45 (2004) 3309–3311
Tetrahedron Letters

Synthesis and chiroptical properties of two new planar-chiral macrocycles ☆

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Received 22 December 2003; revised 3 February 2004; accepted 13 February 2004

Abstract—Could simple intraannular-arm macrocyclic systems exist in enantiopure stable forms? The effective synthesis of two representative compounds of such a class, their resolution into enantiomers, and experiments justifying their stability toward racemization are presented.

Structural studies of molecules possessing an element of planar chirality started in the 1940s with the synthesis and resolution of 1,12-dioxa[12]paracyclophane (the first chiral 'ansa' compound).[1] Up to now, there have been many examples of planar-chiral compounds including cyclophanes,[2] metallocenes,[3] bridged annulenes,[4] *trans*-cycloalkenes,[5] and miscellaneous structures.[6] Interest in the synthesis of planar-chiral compounds is rapidly growing since they are used as ligands for transition metal complexes. Ligands of this type are usually based on ferrocene or [2,2]paracyclophane backbones. Complexes consisting of such planar-chiral ligands and transition metals such as rhodium,[7] iridium,[8] and palladium[9] have been developed as catalysts for various asymmetric reactions.[10]

In this communication we present the synthesis and structure elucidation of compounds **8** and **9**, the planar chirality of which originates from a suitably substituted macrocyclic amide. Designed planar-chiral systems of this type are similar to metacyclophanes,[11] however, macrocyclic amides could interact with cations via ethereal oxygen atoms or with anions through amide groups.[12]

A structure under consideration should consist of a macro-ring containing an intraannular group. There are two indispensable requirements for such systems to exist in chiral form. The first is related to preventing an intraannular group from threading through the macro-ring plane; thus a relatively small macro-ring and an appropriately large intraannular substituent are needed. The second condition requires prochiral differentiation of the macrocyclic unit.

For the preparation of compounds **8** and **9**, as well as their analogs, we planned to apply the double-amidation reaction, developed recently in our laboratory.[13] In this reaction, dimethyl, α,ω-dicarboxylates react with primary, α,ω-diamines in the presence of MeO^- under ambient conditions (methanol as solvent, room temperature, several hours, and a reagent concentration of 0.1 mol dm^{-3}) to afford macrocyclic diamides in good to excellent yields. Thus, the initial stage of the synthesis is the preparation of appropriate dimethyl dicarboxylates and α,ω-diamines (Scheme 1 and Supplementary material). Starting from 2-nitroresorcinol **1**, after catalytic reduction of the nitro group and acylation of the resulting amino group, we obtained compound **2**,[14] that in turn was elongated with methyl bromoacetate to give the corresponding dimethyl dicarboxylate **3**. Compound **3** was then examined in a model reaction with unsubstituted diaminoether **4**,[15] to afford macrocyclic compound **7** in 23% isolated yield. Examination of the molecular model of **7** shows that the macrocyclic ring and intraannular group are located on different faces of the aromatic plane, because the cavity of the macro-ring is not large enough to accommodate the intraannular

Keywords: Macrocycles; Planar chirality; Chiroptical properties; Synthesis.
☆ Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tetlet.2004.02.063
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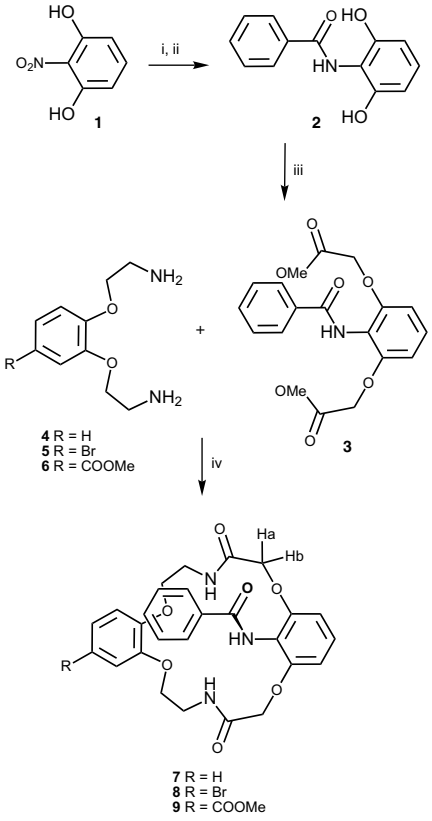
doi:10.1016/j.tetlet.2004.02.063



Scheme 1. Reagents and conditions: (i) H_2, Pd/C, MeOH; (ii) benzoyl chloride, MeOH, 65%; (iii) methyl bromoacetate, K_2CO_3, 2-butanone, 90%; (iv) Na, MeOH, rt: 23% **7**, 19% **8**, 10% **9**.

group. A very important feature of this type of chirality is that the energy barrier of rotation must be high enough to permit resolution into enantiomers. To justify our assumption we carried out a temperature-dependent ^{1}H NMR experiment, which showed AB-type splitting for the isolated methylene group (Fig. 1).

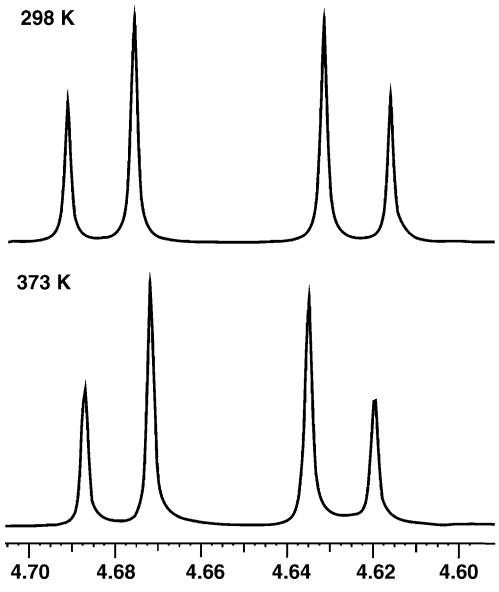


Figure 1. The temperature-dependent ^{1}H NMR spectrum of isolated CH_aH_b protons of compound **7** in DMSO-d_6.

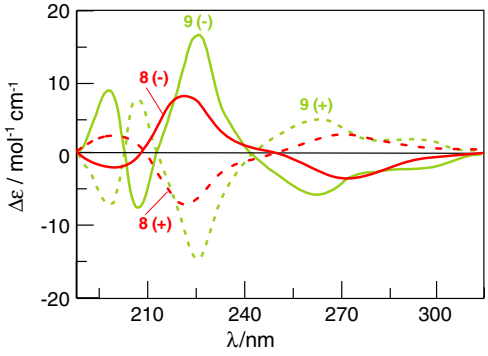


Figure 2. CD spectra of the enantiomers **8** and **9** in acetonitrile.

Even at 373 K, the benzamide group cannot pass through the macro-ring plane. In order to introduce an element of planar chirality, we carried out an analogous reaction of dimethyl dicarboxylate **3** with substituted diaminoethers **5** and **6**, which led to the desired compounds **8** and **9**, respectively, in satisfactory yields (Scheme 1).

Racemic compounds **8** and **9** were successfully resolved into enantiomers employing analytical chiral HPLC (Chiralcel OD-H®). The separation factors α were found to be 1.25 and 1.38, respectively, and were high enough to allow a semi-preparative resolution. The pure enantiomers of compounds **8** and **9** obtained were subjected to CD experiments (Fig. 2).

It is noteworthy that acetonitrile solutions of (−)**8**, (+)**8** and (−)**9**, (+)**9** retained their enantiopurity for at least two months at room temperature and even extended boiling of solutions in acetonitrile did not lead to any racemization.

In summary, we have shown that *N*-benzoyl substituted macrocyclic diamides can be readily synthesized and resolved into enantiomers, which are stable toward racemization. Such compounds, showing planar chirality could serve as chiral ligands for inclusion complexes with neutral as well as cationic and anionic guests.

Acknowledgements

Financial support from the State Committee for Scientific Research (Project T09A 087 21) is gratefully acknowledged.

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