ORGANIC LETTERS

2004
Vol. 6, No. 11
1697−1700

Isolation and Epimerization Kinetics of the First Diastereoisomer of an Inherently Chiral Uranyl–Salophen Complex

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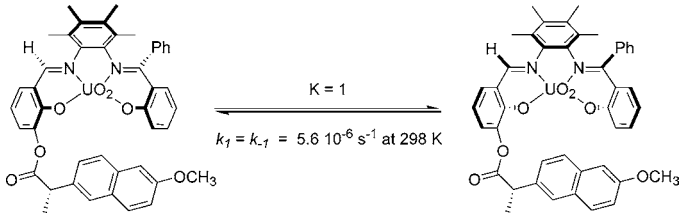
Received February 9, 2004

ABSTRACT



The first diastereoisomeric mixture of an inherently chiral uranyl–salophen complex was prepared using (*S*)-naproxen as a chiral derivatizing agent. Slow crystallization from diisopropyl ether–chloroform afforded one pure diastereoisomer in 45% yield. Kinetic studies allowed the determination of the epimerization rate.

Salophen ligands strongly bind to the uranyl dication UO_2^{2+}, and the resultant robust complexes[1] have found a variety of applications in the molecular recognition of anions,[2] ion pairs,[3] and neutral molecules[4] and also in catalysis[5] and transport.[6]

The large ionic radius of the uranium imposes a nonplanar, highly puckered conformation to the salophen ligand, as shown by a large number of X-ray structures[3b,4a,7] and easily reproduced by molecular mechanics calculations (Figure 1).

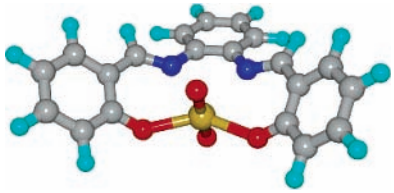


Figure 1. Computer-calculated structure of the parent compound **1** (R = R′ = H).

This structural feature makes nonsymmetrically substituted complexes[4c] (e.g., **1**, R ≠ R′) devoid of any symmetry element and therefore inherently chiral.[8,9]

We have recently shown[8] that a flipping motion of the salicylaldehyde units (eq 1) inverts the curvature and causes

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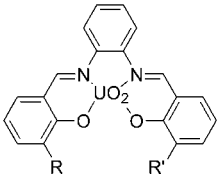
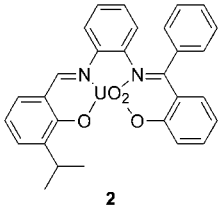
10.1021/ol049769x CCC: $27.50
Published on Web 04/29/2004

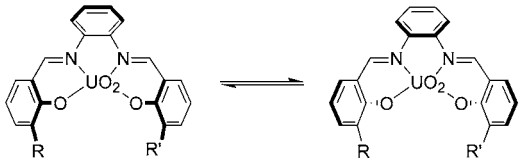


1



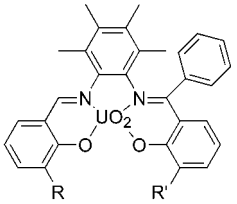
2

topomerization/racemization of symmetrically/nonsymmetrically substituted compounds.

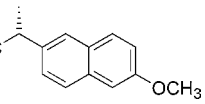


(Eq. 1)

In sterically unhindered compounds, the flipping motion is fast on the NMR time scale even at 233 K, but bulky substituents in suitable positions slow the motion and make the chirality detectable. Complex **2**, equipped with a phenyl group on one imine carbon, is the first compound in which the flipping motion could be detected by ^{1}H and ^{13}C NMR ($\Delta G^{\ddagger} = 15.7$ kcal mol^{-1}, $k = 20$ s^{-1} at 298 K). In the search for configurationally stable receptors and catalysts, the height of the barrier was significantly increased by the introduction of methyl groups on the *o*-phenylenediamine nucleus. Interconversion of enantiomers of **3a** (R = ^{i}Pr and R′ = H) was found to be slow on the NMR time scale even at 385 K ($\Delta G^{\ddagger} \geq 21$ kcal mol^{-1}), but a precise determination of the height of the barrier is still an open task. At the racemic mixture level, a viable route would be dynamic HPLC on a chiral stationary phase.[10] Unfortunately, unlike sterically unhindered uranyl−salophen complexes,[4c,5a] compound **3a** did not tolerate any chromatographic treatment. Therefore, preparative resolution without resorting to chromatographic separation turned out to be a necessary prerequisite not only in view of future applications of chiral uranyl−salophen complexes to chiral recognition and asymmetric catalysis but also for a preliminary study of their configurational stability.



3a R' = H, R = iPr

3b R' = H, R = OOC 

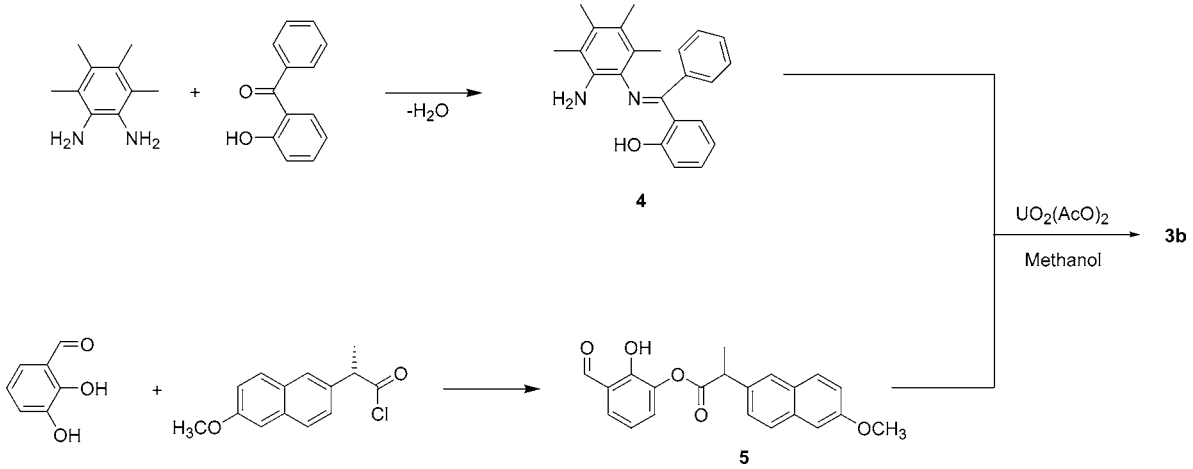
Here we describe the synthesis of the diastereoisomeric mixture **3b** using (*S*)-naproxen as the resolving agent,[11] the isolation of one diastereoisomer in pure form, and the kinetics of its epimerization.

The Schiff base **4** obtained from the tetramethyl derivative of *o*-phenylenediamine and *o*-hydroxybenzophenone was condensed with the (*S*)-naproxen derivative of 2,3-dihydroxybenzaldehyde in the presence of $UO_2(OAc)_2$ in methanol, as depicted in Scheme 1. Complex **3b** was obtained in 71% yield. The presence of two diastereoisomers was revealed by a number of split signals in the ^{1}H NMR spectrum (Figure 2a). The composition of the mixture is 1:1 or very nearly so, which shows that the (*S*)-naproxen pendant has little influence, if any, on the equilibrium position.

Crystallization of a dilute solution of **3b** (15 mg) in chloroform (10 mL), induced by slow diffusion of diisopropyl ether at room temperature, gave after a couple of weeks 7 mg of dark red crystals, which were recovered and washed with *n*-pentane.[12] Comparison of the ^{1}H NMR spectrum (Figure 2b) with that of the diastereoisomeric mixture showed that only one diastereoisomer had been isolated in a high level of purity ($[\alpha]^{20}_{D} = 152.0\ 10^{-1}$ deg cm^2 g^{-1}, $CHCl_3$).[13] Its circular dichroism spectrum is shown in Figure 3. It is significantly different from that of the model compound **5** as well as from that of the diastereoisomeric mixture.

Whereas a solid sample of the isolated diastereoisomer of **3b** is configurationally stable for at least one month at room temperature, slow epimerization takes place in solution.

Scheme 1. Synthesis of Chiral Uranyl−Salophen Complex **3b**.



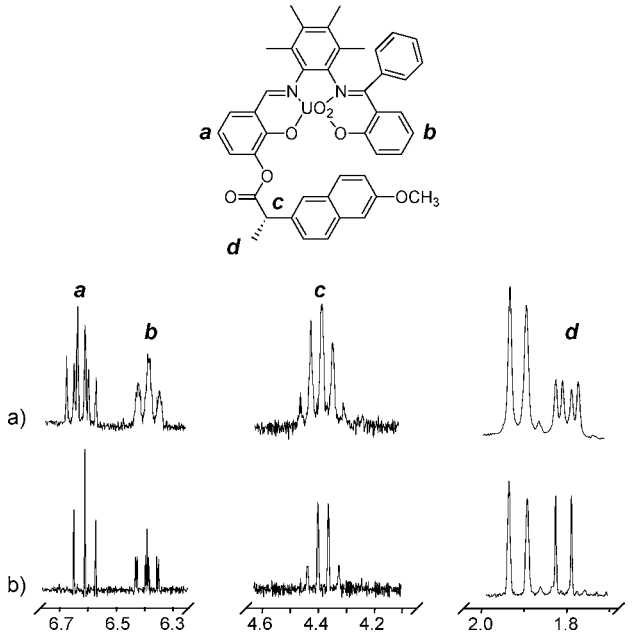


Figure 2. Portions of ^{1}H NMR spectra (200 MHz, acetone-d_6) of the diastereoisomeric mixture of **3b** (a) and of the pure isolated diastereoisomer (b).

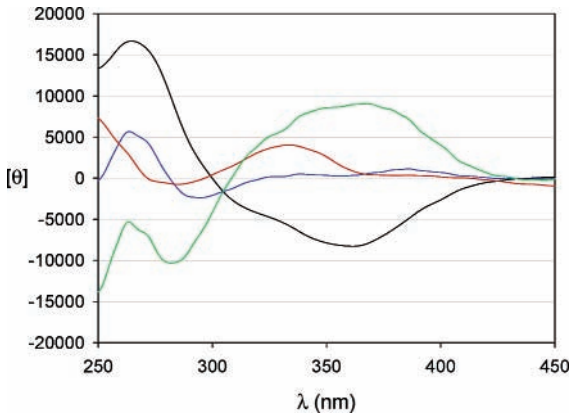


Figure 3. Circular dichroism spectra ($CHCl_3$, 5.0×10^{-5} M) of **5** (red), the diastereoisomeric mixture of **3b** (blue), and the pure isolated diastereoisomer of **3b** (black) and calculated circular dichroism of the other diastereoisomer (green). [θ] is given in deg cm^2 dmol^{-1}.

Figure 4 shows the time evolution of the mole fraction of the pure diastereoisomer, as determined at 298 and 318 K.

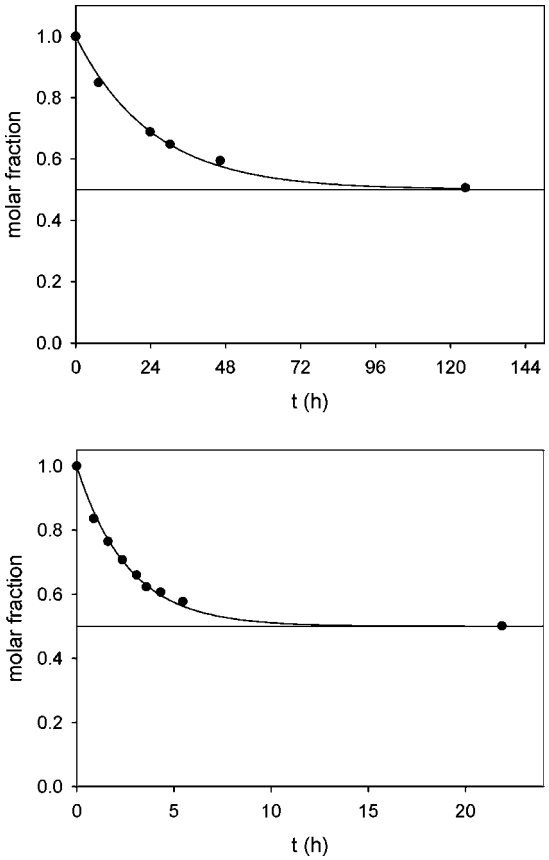


Figure 4. ^{1}H NMR time−concentration data (***d*** protons in Figure 2) for the epimerization of the pure isolated diastereoisomer of **3b** at 298 K (up) and 318 K (bottom).

A nonlinear least-squares fit of experimental points to the standard equation for a reversible reaction first-order in both directions with $K = 1$ gave a value of 5.6×10^{-6} s^{-1} at 298

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(12) Mother liquor contained an equilibrated mixture of the two diastereoisomers. Thus, although the yield of the isolated pure diastereoisomer was less than 50%, the system underwent a crystallization-induced asymmetric transformation (see: Eliel, E. L.; Wilen, S. K. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; p 364). Crystallizations from more concentrated solutions and/or from other solvent systems afforded mixtures.

(13) Diastereoisomeric mixture has a specific rotatory power $[\alpha]^{20}_D$ = 21.1 10^{-1} deg cm^2 g^{-1}, $CHCl_3$.

K ($\Delta G^{\ddagger} = 24.6$ kcal mol^{-1}) for the rate constants ($k_1 = k_{-1}$) of epimerization. A similar treatment of data obtained at 318 K gave $k_1 = k_{-1} = 5.3 \times 10^{-5}$ s^{-1}. Since the naproxen unit has a negligible influence on the epimerization equilibrium, it is very likely that it does not affect the kinetics as well. It appears therefore that the above results can be extended with confidence to the flipping motion in compounds of general structure **3**, independent of the nature of R and R′ within wide limits.

In summary, a new inherently chiral uranyl−salophen complex was synthesized in the form of a pair of diastereoisomers using (*S*)-naproxen as a chiral derivatizing agent. One pure diastereoisomer was isolated in good yield by crystallization and fully characterized. This compound is configurationally stable for at least one month at room temperature in the solid state. A kinetic study of its epimerization in solution led to a first estimate of the height of the barrier of the flipping motion, which is believed to apply to a large variety of complexes of general structure **3**. The results indicate that the configurational lability of these complexes would require fast and mild deprotection procedures. For the same reason, their use as asymmetric catalysts should be compatible with those reactions that are complete within 1 h at 298 K.

Acknowledgment. We thank Dr. Simona Rotella and Prof. Mario Barteri from this department for assistance in the CD measurements and useful discussions. This work was supported by MIUR (Progetto Dispositivi Supramolecolari).

Supporting Information Available: Experimental details for synthetic procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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