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Dynamic Equilibration of Diastereomeric Salts of Atropisomers. Proton NMR Spectra of 1,8-Di(3'-pyridyl)naphthalene in the Presence of R-Camphorsulfonic Acid

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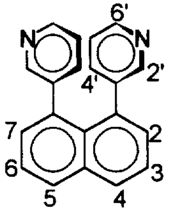
Abstract: *In the presence of chiral camphorsulfonic acid (CSA) the anti and syn atropisomers of the title compound in acetone-d_6 form diastereomeric salts detectable at ambient temperatures by proton NMR. Comparison of these spectra with those generated in the presence of racemic CSA provides evidence for the formation of the diastereomers.* Copyright © 1996 Elsevier Science Ltd

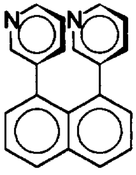
Traditional chemistry has focused on the formation of covalent bonds. But with recent investigations of large molecular assemblies such as nucleic acids and proteins there has come a need to understand the factors important in the noncovalent interactions responsible for molecular recognition. Molecular assemblies often are aggregates and equilibrating structures where electrostatic interactions are important.[1] These products at times may be made simply by mixing the appropriate reagents in a selected solvent.[2]

We introduce a model substrate designed to probe chiral recognition involving ion aggregates of π-π stacked rings in moderately polar solvents. 1,8-Di(3'-pyridyl)naphthalene[3] **(1)** due to restricted rotation about its two stereogenic axes exists as a rapidly equilibrating mixture of *anti* (racemic, R-R and S-S) and *syn* (*meso*, R-S) atropisomers in a number of solvents at ambient temperatures, Eqn 1, the *anti* diastereomer being favored.[3] Each of these two diastereomers in acetone-d_6 in the presence of *(R)*-10-camphorsulfonic acid (CSA) is converted into its own distinguishable diprotonated diastereomeric salt.

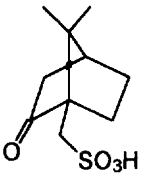
$$R\text{-}R \rightleftharpoons R\text{-}S \rightleftharpoons S\text{-}S \quad (1)$$



1 anti



1 syn



***R*-CSA**

The *anti* pair of equilibrating enantiomers of diprotonated **1** has homotopic[4] *si* or *re* pyridyl faces (C_2 symmetry) that on association with one or two chiral CSA anions *(R)* is made diastereotopic[4] and thereby is converted into a diastereomeric pair of salts, represented as the salts of the dianion, *R*,R-R,*R* and *R*,S-S,*R*. The *syn-meso* form (σ plane) has heterotopic *si* and *re* pyridyl faces and on association with the chiral anion also becomes a chiral salt with diastereotopic faces, represented as the dianion complex, *R*,R-S,*R*. Equation 2 presents the equilibria involved for the complexes of the dianions but we do not yet have experimental evidence to distinguish between complexes with one or two of these anions or whether the mono and dianionic salts are in equilibrium with each other or higher aggregates.

Others have reported the formation of a diastereomer of a meso compound in the presence of a chiral solvating agent[5] and of equilibrating enantiotopic groups made distinguishable by NMR in such a solvent.[6] Diastereotopic salts of a simple pyridine and chiral carboxylic acids detectable by ^{15}N NMR[7] have been recorded as well as proton NMR of diastereotopic salts of chiral amines.[8] Reviews of the use of dynamic NMR to study conformational chirality of uncharged materials[9] and to determine optical purity[10,11] are available.

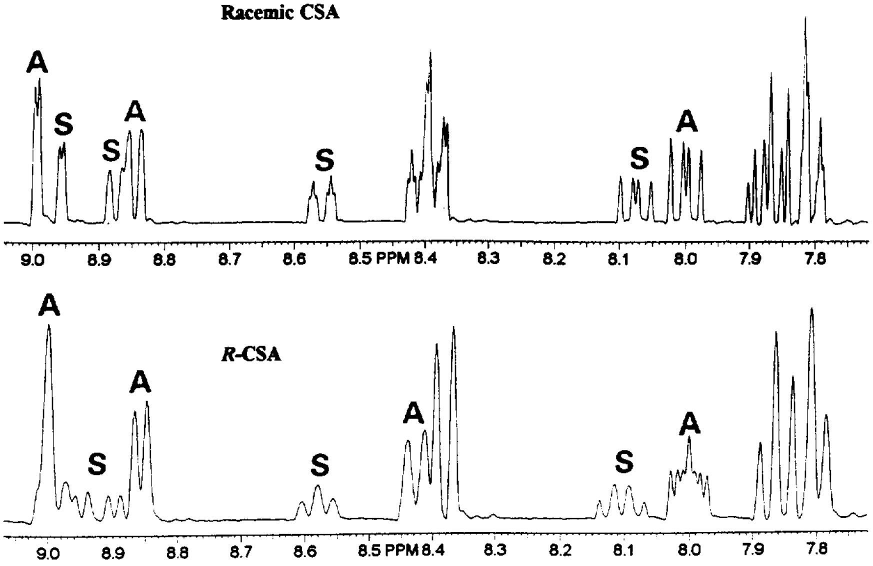
$$R\text{,R-R,}R \rightleftharpoons R\text{,R-S,}R \rightleftharpoons R\text{,S-S,}R \quad (2)$$

Two 300 MHz spectra of 0.05 M diprotonated **1** in acetone-d_6 at 19 °C containing 0.3 M CSA and a small amount of water are shown in the Figures. The first spectrum is that of a control sample containing racemic CSA; the second has *R*-CSA. The smaller multiplets in each are associated with the *syn* and the larger with the *anti* diastereomers here present in about a 1 to 1.6 ratio in both samples. The 3'-pyridyl protons are readily identified by their chemical shifts and multiplicities and appear in the usual order of increasing field, H2', H6', H4' and H5'; their low field positions are consistent with diprotonation. The order for the naphthalene protons is that commonly found in 1,8-diarylnaphthalenes, H4,5 (8.4), H3,6 (7.86) and H2,7 (7.8 ppm) and are largely unremarkable with the exception of the signals for H3,6 (racemic CSA) that are clearly split into two overlapping pairs of triplets; their relative intensities suggest they are associated with *anti-syn* forms. The higher field positions of H4' (8.4 ppm) and H5' (8.0 ppm) may confidently be assigned to the *anti* structure because the naphthyl ring is distorted and the pyridyl rings are situated off center to each other in order to minimize strain; this geometry causes these positions to be shielded.[3]

A comparison of the two spectra provides evidence for the formation of diastereomeric salts. With racemic CSA the signals for the diastereomers rapidly average to give a simple spectrum. The *anti* (A) and *syn* (S) forms of H6' (8.85 ppm) overlap and the *anti* signal of H4' overlaps that for H4,5 of naphthalene (8.4 ppm), otherwise individual multiplets are apparent.

The signals for the individual protons of a pair of diastereomers contain extra lines that are not present in the spectrum with racemic CSA. With (*R*)-CSA the diastereomeric pairs *R*,R-R,*R* and *R*,S-S,*R* (or the pairs *R*,R-R and *R*,S-S) formed from the racemic *anti* mixture are present in apparently equal amounts as are the

H NMR Spectra of 1 in acetone-d_6 at 19° Showing the Effects of CSA on *Syn* (S) and *Anti* (A) Multiplets.



diastereotopic faces in *R*,R-S,*R* (or *R*,R-S and *R*-S,D) from the *syn* isomer. There is only a suggestion that the H2' doublet at the lowest field (9.0 ppm) is separated into several doublets due to extensive overlap but the signals for H6' (8.85-8.95 ppm) show extra multiplicity in the form of two equally intense doublets for the minor *syn* form. The additional structure for H4' (an apparent triplet, 8.58 ppm) of the *syn-meso* form again suggests that the two faces are different. Clearly definitive information comes from a consideration of the *syn-anti* multiplets for H5' which are cleanly separated (8.1 and 8.0 ppm). Each one of these multiplets represents **two** partially overlapping sets consisting of four lines (dd). By contrast, the racemic CSA shows only the expected single dd pattern.

At 45 ^{0}C the spectrum simplifies considerably, now showing a single multiplet for the individual sites which can be assigned easily. This signal collapse is consistent with rapid *anti-syn* interconversion and ion pair dissociation. At -60 ^{0}C a rigorously dried sample clearly shows two well separated pairs of equally intense signals for the *syn* complex, a pair for H4' and another pair for H5'. These pairs of signals are associated with the *si* and *re* faces of the dication and are unequivocally identified by their multiplicities The *anti-syn* ratio increases to 2.4 (room temperature) in the absence of water.

A highly linear correlation exists between the inverse of the temperature (^{0}K) over an 80^{0} range and the logarithm of the width of an overlapped multiplet, a measure of the separation between the individual multiplets for each diastereomer. But such correlations were found only for the *syn* protons, perhaps in part because there is extensive signal overlap of the *anti* and the naphthyl protons limiting the range of study and the apparently smaller difference in signal separation between the diastereomers. The slopes of such plots are expected to be related to the intrinsic shift difference between the equilibrating structures[10] and the mole fraction of associated substrate.

Although (*R*)-CSA always gives spectra with more complex multiplets than racemic CSA, the observed multiplicity and chemical shifts are highly dependent on the method of sample preparation, concentration, substrate ratio, water content and temperature, all consistent with the idea that the spectra reflect a time-dependent, population-weighted, averaged collection of associated and dissociated ion pairs and individual ions. In $CDCl_3$ **1** and (*R*)-CSA consists largely of the *anti* diastereomer at ambient temperatures.

The complex stereodynamics of mixtures of **1** and CSA provide a novel system to study ion pairing of rapidly equilibrating π-stacked substrates, interactions of some importance in molecular recognition.[1]

EXPERIMENTAL SECTION

Samples were freshly prepared by mixing **1** and CSA with acetone-d_6. The ratio of the two was established by comparing the areas of the two diastereotopic protons of the CH_2SO_3H group (3.3 and 2.7 ppm) of CSA with any of the several multiplets of **1**. A minimum amount of water was estimated from the HOD signal usually about 4 ppm but often at higher field in drier samples. Deliquescent CSA introduces variable amounts of water. Some samples were prepared by mixing the two reactants in an NMR tube and then drying the tube at 100 °C under a vacuum before adding the acetone-d_6.

REFERENCES

1. Hunter, C. A. *Chem. Soc. Rev.* **1994**, *23*, 101.
2. Whitesides, G. M.; Simanek, E. E.; Mathias, J. P.; Seto, C. T.; Chin, D. N.; Mammen, M.; Gordon, D. M. *Acc. Chem. Res.* **1995**, *28*, 37.
3. Zoltewicz, J. A.; Maier, N. M.; Fabian, W. M. F. *Tetrahedron* **1996**, *52*, 8703.
4. Eliel, E.L.; Wilen, S.H. *Stereochemistry of Organic Compounds*; J.Wiley & Sons: New York, 1994.
5. Kainosho, M.; Ajisaka, K.; Pirkle, W. H.; Beare, S. D. *J. Am. Chem. Soc.* **1972**, *94*, 5924.
6. Mannschreck, A.; Jonas, V.; Kolb, B. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 909.
7. Dyllick-Brenzinger, R.; Roberts, J. D. *J. Am. Chem. Soc.* **1980**, *102*, 1166.
8. Fulwood, R.; Parker, D. *Tetrahedron:Asymmetry* **1992**, *3*, 25.
9. Gasparrini, F.; Lunazzi, L.; Misiti, D.; Villani, C. *Acc. Chem. Res.* **1995**, *28*, 163.
10. Pirkle, W. H.; Hoover, D. J. *Top. Stereochem.* **1982**, *13*, 263.
11. Parker, D. *Chem. Rev.* **1991**, *91*, 1441.

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