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### ENANTIOSELECTIVE EFFECTS IN ASSOCIATION II

Eberhard Wenschuh<sup>a</sup>; Heidrun Winter<sup>a</sup>; Gisela Mendel<sup>a</sup>; Alfred Kolbe<sup>a</sup>

<sup>a</sup> Sektion Chemie der Martin-Luther-Universität Halle-Wittenberg,

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# ENANTIOSELECTIVE EFFECTS IN ASSOCIATION II<sup>1</sup>

## Synthesis and Association Behaviour of (+)-N-Cyclohexyl-*p*-Tolylsulfinamide

EBERHARD WENSCHUH, HEIDRUN WINTER, GISELA MENDEL und  
ALFRED KOLBE

*Sektion Chemie der Martin-Luther-Universität Halle-Wittenberg  
DDR-402 Halle/S., Weinbergweg 16*

Dedicated to Prof. Dr. K. Issleib on the occasion of the 60th anniversary of his birthday November 19th, 1979.

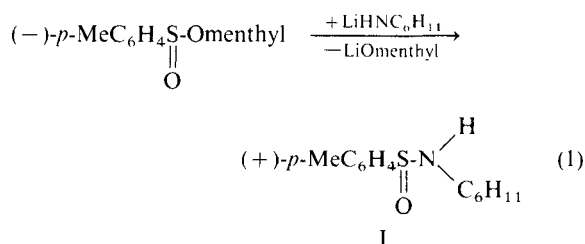
(Received April 18, 1979)

The title compound (I) has been synthesized for the first time. The ir spectra of the pure enantiomer and the racemic mixture (both dissolved in CCl<sub>4</sub> to an association allowing concentration) are different from each other in characteristic features. The differences vary on changing the temperature and/or concentration and are discussed in terms of thermodynamic properties of the H bond, linking the molecules by NH—OS-bridges. In particular, the free NH bands of the pure enantiomer are about 10 % less intensive than those of the racemic mixture under the same conditions, the case of high, association-free dilution excluded. Rather dramatic findings can be reported describing the association between the pure (R)-butan-2-ol and I. Only by change of the configuration of one of the partners differences of about one order of magnitude in the equilibrium constants are obtained.

### INTRODUCTION AND SCOPE

Recently we have published a paper concerning an enantioselective effect appearing in the homoassociation of optically active alcohols.<sup>1</sup> The results, presented there, are believed to be appropriate to initiate similar investigations on other compounds. Therefore we have extended our studies on the homo- and heteroassociation behaviour of the title compound. The synthesis and results of (I) are given in the following.

(I) has been prepared according to a method described by NUDELMAN and CRAM<sup>3</sup> for the synthesis of (+)-*p*-tolyl-sulfinanilide from (–)-menthyl-*p*-tolyl-sulfinate<sup>4</sup> and lithiumcyclohexylamide (Eq. 1).



### RESULTS

#### a) The Homoassociation of (I)

The pure enantiomer as well as the racemic mixture of N-cyclohexyl-*p*-tolyl-sulfinamide show two free NH bands due to conformational isomerism originated by rotation on the S-N axis. We have given an extensive description of the conformational behaviour of this class of substances in a former publication.<sup>2</sup> In this paper we compare the intensities of the free NH bands and the intensity of the associated band for the racemic mixture and one of the pure enantiomers. The results are given in Figures 1 and 2.

In Figure 1 it is clearly to be seen, that, in the special case chosen, the free NH bands as well as the associated one of the racemic mixture has turned out to be the more intensive, but the shift of its associated band is smaller than that of the pure enantiomer. The lower shift may be explained using the assumption, that the conformation, which is represented by the higher frequency NH band, acts preferably as a donor in the hydrogen bond. (Unfortunately, the associated band cannot

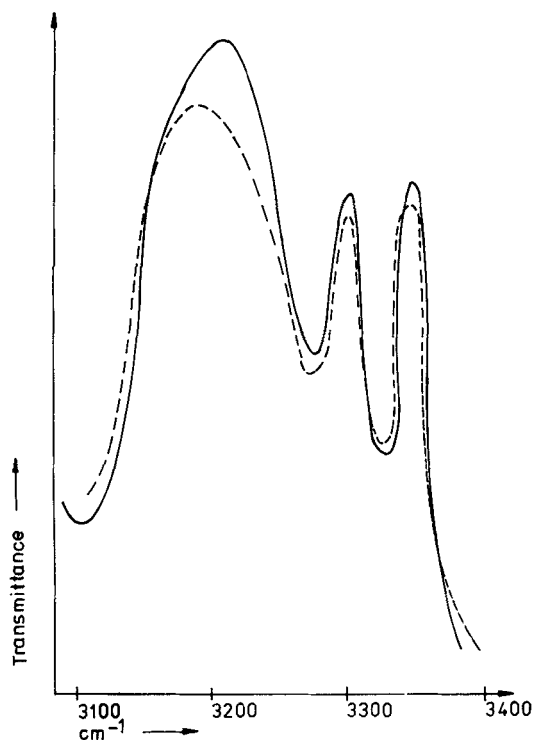


FIGURE 1 Absorption profiles of the pure enantiomer (—) and the racemic mixture (---) in the NH stretching range at 15°C (0.05 mol. l<sup>-1</sup>).

be resolved to obtain knowledge about its conformational origin). Then in the case of the optically active compound, the NH band belonging to the other conformation and possessing the lower NH stretching frequency predominantly takes part in the H bond. This explanation allows us to find out the usual parallelism between the NH shift and the intensity change of the associated band.

Figure 2 shows almost similar curves, which characterize the intensities of the free NH bands, but beyond this similarity there remain some differences. Firstly, in the range of low concentrations, the intensities of the free NH bands of the racemic mixtures are always higher, this means a greater quantity of free NH bonds and consequently a lower degree of association. Secondly, with increasing concentration the intensities of the free NH bands of the racemic mixture decrease more strongly than those of the pure enantiomer. Evidently the length of the association chains of the racemic mixture also increases more strongly with increasing concentration than in the case of the pure enantiomer. This behaviour is hardly due to

enthalpic parameters only, but chains formed by molecules with different configurations should be preferred by statistical reasons.

Further we deduce from Figure 2, that in both cases the intensities of the longer wave NH bands decrease somewhat more strongly than those of the shorter wave band (more than 50% for the first band, about 30–35% for the second one). The strongest decrease is found in the case of the long wave band of the racemic mixture. This effect can only be due to the terminal NH groups of chain associates, the signals of which appear in the spectra like those of free groups. The quantitative relation between the different conformers of the free molecules is determined by thermodynamic rules, and this relation is the same for the pure enantiomer as well as the racemic mixture. But the positions of the free NH groups of the terminal molecules of chain associates are determined by the enthalpic and steric condition of the chain. This situation may be different for pure configurational and configurationally mixed associates. This may be the reason causing such different concentration behaviour of the free NH bands as given in Figure 2.

#### b) The Heteroassociation of (I)

In the other part of this work we paid attention on the hetero-association between butan-2-ol and the title compound. The R-enantiomer of this alcohol (about 94% optical purity) was at our disposal. Only 1:1 associates have been found. We investigated the following systems:

Alcohol	R	R	R + S	R + S
(I)	R	R + S	R	R + S

The equilibrium constants were determined by measurements of the decrease of the free OH band. The decrease of the quantity of the acceptor molecules by homoassociation demonstrated by Figure 2 has been taken into account. The results were not corrected to 100% optical purity of butan-2-ol. We found in the sequence of the systems, given above, the following equilibrium constants valid for 15°C: 13.1; 7.4; 9.9; and 9.2, respectively. From these results the equilibrium constants may be deduced for the system formed by the pure enantiomers:

$$K_{RR} = 13.1 = K_{SS}; \quad K_{RS} = 1.6; \quad K_{SR} = 6.6.$$

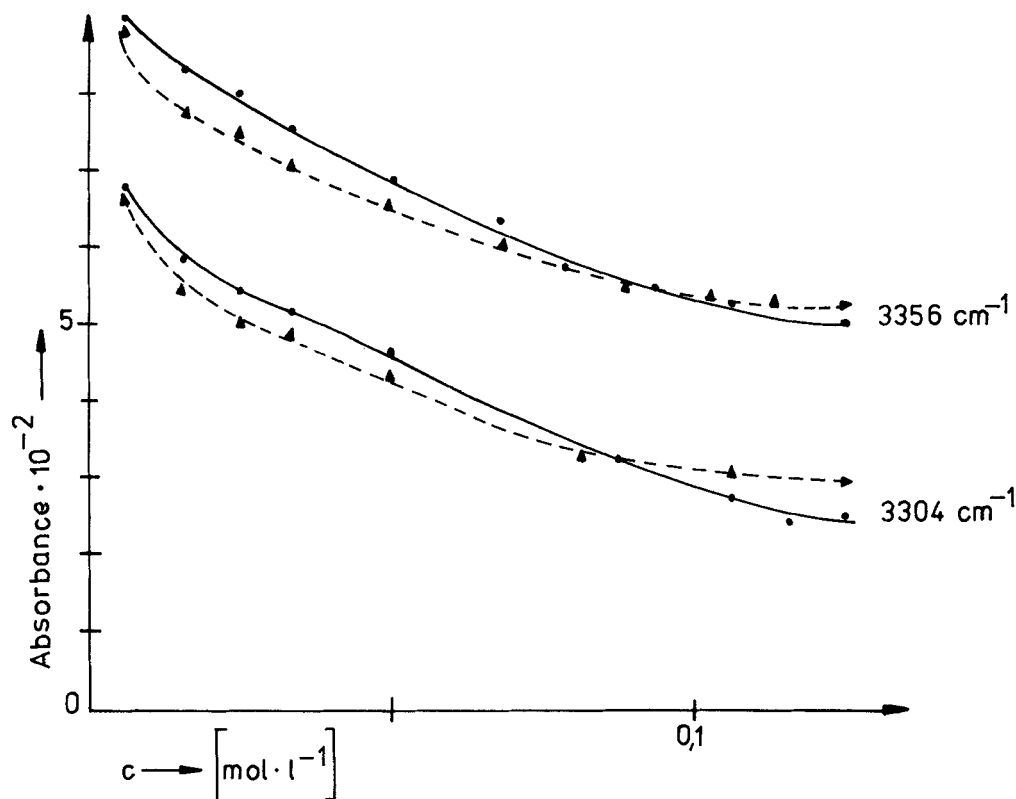


FIGURE 2 Absorbance of the free NH bands of the pure enantiomer (▲) and the racemic mixture (●) at 15°C in homassociation.

The reliability of the results is additionally supported by the following investigations: Exactly equal quantities of racemic as well as of optically active sulfides were dissolved to the same fixed volume by the same solution of optically active butan-2-ol in  $\text{CCl}_4$ . Both solutions were directly compared with each other by using them, in cells of the same path length, as sample and reference in the ir spectrometer. If the solution of the pure enantiomers had been placed into the reference beam, there remained in the spectrum a free OH band of considerable intensity, as it was to be expected with regard to the results given. Further, the equilibrium constant of 9.9 for all-enantiomer association of both racemic compounds is in good accordance with that one to be calculated from the equilibrium constants of the single systems.

Clearly, the assignment given for the absolute configuration of the optically active sulfinamide, namely R is an arbitrary one, but the assumption, that the equilibrium constant of the first system ( $K = 13.1$ ) belongs to a configurationally mixed system, leads to considerably higher differences

between the equilibrium constants of the systems discussed here. Only because of this fact, the assignment given was chosen. Measurements at 40°C apparently give evidence of about 20% difference in the association enthalpy, the system of equally configured enantiomers is formed in favour of the all-configuration system. More precise results in this field should be one of the subjects of following investigations. At the present stage, we cannot give an adequate discussion of the facts reported here, because such a discussion should imply a detailed description of the different conditions, which are responsible for the steric relations between different associate diastereomers. We feel only this point of investigation now reached as a starting point to extend our investigations to other substances and other conditions.

#### EXPERIMENTAL

*Preparation of (I)* 2.7g cyclohexylamine, dissolved in 50 ml of absolute ether were stirred, cooled to  $-20^\circ\text{C}$  and then 1.75g *n*-butyl-lithium was added dropwise. After finishing the metalation of cyclohexylamine the mixture was stirred for one hour

and then an ethereal solution of 8.0g (–)-menthyl-*p*-tolylsulfinate<sup>4</sup> was dropped into the reaction mixture. After warming up to room temperature, the precipitate was filtered off and dried. 2.5g (=39.0%) (+)-*N*-cyclohexyl-*p*-tolylsulfonamide could be extracted with absolute ether from this product. All operations were carried out under argon atmosphere. The resulting substance melts at 64°C. The specific rotatory power in CCl<sub>4</sub> amounts to 369.0°, 303.6°, 179.8° and 174.5° using the wave lengths 406, 436, 546 and 578 nm, respectively.

The spectroscopic measurements were done on a BECKMAN IR 12. In some cases investigating the homoassociation, the absorption scale was ten times expanded. Concentrations are

about 0.01 to 0.05 (l) and 0.05 (butan-2-ol) mol. l<sup>-1</sup>, CCl<sub>4</sub> of MERCK "uvasol" quality was used.

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