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ENANTIOSELECTIVE EFFECTS IN THE ASSOCIATION BEHAVIOUR OF OPTICALLY ACTIVE ALCOHOLS

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Abstract—The association behaviour of four optically active secondary alcohols with chiral C atoms in the α-position was investigated by means of IR spectroscopy and calorimetry. CCl_4 was used as a solvent. As compared to the racemic compounds, the corresponding optically active alcohols have slightly higher concentrations of free OH groups, i.e. lower degrees of association, but somewhat higher enthalpy of association. Consequently, the H-bonding of racemic alcohols is favoured by entropy. Differences have been found also in the absorption coefficients of the associated OH groups. Optically active solvents exert some influence on the association behaviour of optically active alcohols. No differences could be observed in the H-bonding of optically active monocarboxylic acids, as compared with the racemic ones.

INTRODUCTION AND SCOPE

It is generally believed that optically active compounds and the corresponding racemic mixtures give almost identical IR spectra, at least in highly dilute solution. However, in the case of preponderately associated chiral molecules, some differences in the solution spectra appear possible. In particular this seems plausible, if the association constants of molecules of equal and opposite configuration are not exactly equal. In order to learn, whether such differences between diastereoisomeric associates produce measurable effects, we have studied by means of IR and calorimetric methods the association behaviour of some optically active and the corresponding racemic alcohols. The compounds we have chosen possess a chiral centre attached to the OH group, and bearing substituents with strongly differing bulkiness.

Furthermore, we have tentatively investigated the influence of an optically active solvent upon the association of both enantiomers of an optically active alcohol, as well as the association behaviour of diastereoisomeric pairs of monocarboxylic acid molecules. Finally, we have looked into some consequences of enantioselective association with respect to the relationship between optical rotatory power and enantiomeric composition of a chiral alcohol.

Compounds

In Table 1 all the compounds investigated are given. The references given in this Table contain instructions for the preparation of the respective substances. Our values of rotatory power in all cases are the same as given, except for one case, when it is slightly higher.

RESULTS

In Fig. 1 the different α values of the compounds **1**–**3** are plotted vs the concentration, using the temperature as a parameter. α Means the actual intensity of the free OH band at the concentration c in respect to that at infinite dilution. In the case of **1** and **2** the expected difference between the α's of the optically active and the racemic compounds can clearly be recognized. In the case of the compound **3** this difference is scarcely out of the limits of our experimental error; nevertheless, it could be reproduced in several experiments and seems to be real. Investigating alcohol **4**, we did not find any difference in the α's when comparing the spectra of racemic and optically active compounds. A check on our results has been performed in the following manner: Equal quantities of R and S enantiomers of the compound **1** were mixed. The α values, observed for the solution of this mixture, differed from that of the optically active components to exactly the same extent as the latter differed from that obtained by using the alcohol prepared by means of a Grignard reaction without further treatment. This excluded the possibility that impurities, contained only in the racemic samples, had any influence on our results.

Table 1. Compounds used for association studies

1	1-Phenyl-2-methylpropan-1-ol	racemic compounds and both of its optically active enantiomers[1–4]
2	2,2,4-Trimethylpentan-3-ol	rac. and R compound[1,5,6]
3	1-Phenylpropan-1-ol	rac. and S compound[2,4,7,8]
4	1-Cyclohexylpropan-1-ol	rac. and R compound[9,10,11]
5	L-(+)-1-Chloro-2-methylbutan	[12,13]
6	L-(+)-1-Bromo-2-methylbutan	[14,15,16]
7	Cyclohexylphenyl acetic acid	rac. and R compound[17]
8	Phenyl ethyl acetic acid	rac. and R compound[18]

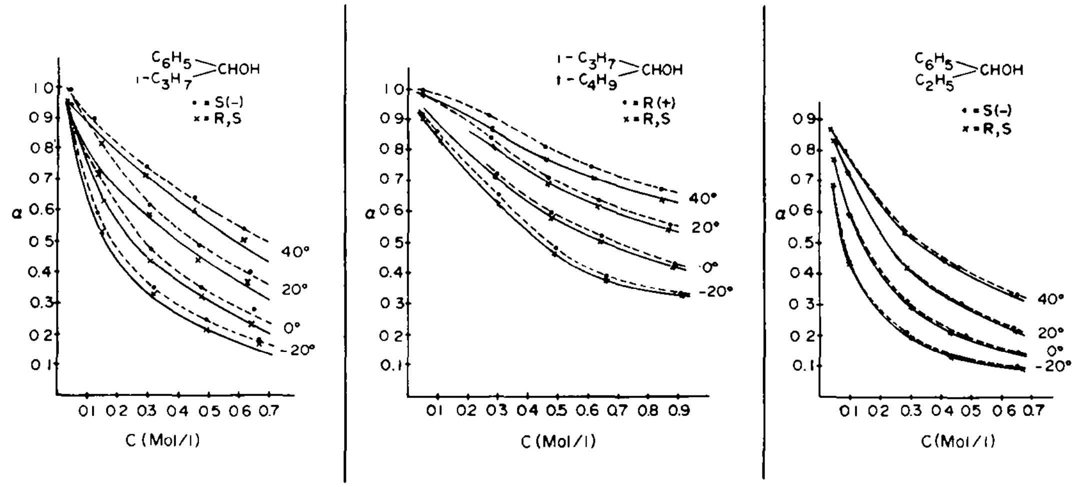

Fig. 1. $\alpha = \epsilon_c/\epsilon_\infty$ as a function of concentration for several alcohols at different temperatures.

The complete spectra of optically active and racemic alcohols in the case of association-free dilution showed no difference at all. On the other hand, studying solutions containing association complexes, we obtained differences in the frequencies as well as in the intensities of the absorption of the associated OH band. In the spectrum of the compound 1 we found $\Delta\nu_{OH}$ about 20 cm^{-1} greater for the optically active compound than for the racemic mixture. The other alcohols, however, exhibited no enantiomeric difference in the $\Delta\nu_{OH}$ values, except perhaps a very small one in the case of compound 3. As a rule, the associated bands of the optically active components increased to an intensity larger than that of the racemic alcohols. Thus the cases described here have a common feature, namely that both the free and associated OH band of the optically active component, exceed the corresponding bands of the racemic compound in intensity, if there is any association at all. The differences of the absorbances of the associated OH bands of the optically active vs racemic alcohols 1 and 2 under identical conditions amounted to about 10–15%.

Our method was not sensitive enough, to show the existence of corresponding differences in the region between 400 and 1700 cm^{-1}; such differences ought to be related to the effects occuring in the OH stretching region.

Considering the small magnitude of the enantioselective effects, we do not deduce any further reaching conclusions from the present results. Nevertheless, it can be stated that in our cases the degree of association *f* is slightly lower for optically active alcohols or equals that for the corresponding racemic ones, but does not exceed these values. The highest differences we found in the case of compound 1 amounts to about 8–10%.

Another result worth considering is the dependence of the apparent absorption coefficient of the free OH band on temperature. Qualitatively we found that this dependence is somewhat stronger for the optically active compared with the racemic alcohols. Therefore we concluded that the enthalpy of association ΔH is slightly higher for the optically active alcohols. Additionally, we have also performed calorimetric measurements using compound 1. The results obtained here, refer to the enthalpy which is needed to break all H-bonds (only free OH bands in the spectra), and therefore it is reasonable that they differ from our spectroscopic data.

The most important enthalpy results are presented in Fig. 2, containing only values of the compound 1. High dependence on concentration and on temperature is clearly to be recognized, the sign of ΔΔH being in accordance with the Badger-Bauer rule.[19]

There are analogous dependences in the other systems, but because these are not the main object of our paper, we give only the standardized average values for the compound 2, namely ΔH = −5500 J mole^{-1} for the racemic and −5700 J mole^{-1} for the optically active alcohol.† 3 (ΔH = −9900 J mole^{-1}) and 4 (ΔH = −9100 J mole^{-1}) show no significant differences in ΔH between the optically

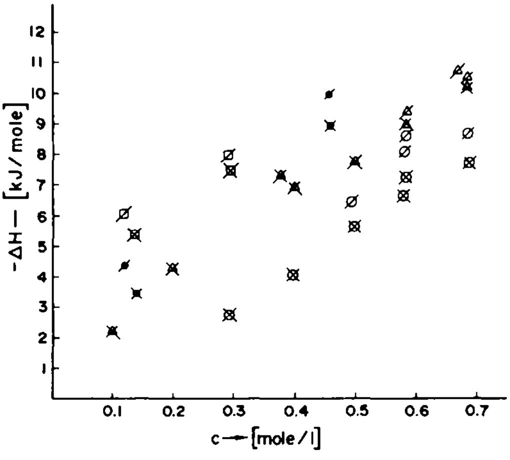

Fig. 2. −ΔH values for the association of alcohols. The calorimetric results were obtained by diluting solutions of the concentration given in the abscissa to "infinite dilution", which is characterized by possessing only a free OH band in the IR spectrum. These ΔH values refer only to the amount of associated OH bonds, which has been determined by IR spectroscopy.[20] The meaning of the points are as follows: ⊠ and ✗ racemic mixture of compound 1 at 30 and 15°, respectively ∅ and ⨯R-enantiomer of compound 1 at 30 and 15°, respectively all obtained by calorimetry. The values marked by ⊠ and × for the racemic mixture and ⧄ and / for the *R* enantiomer were obtained by spectroscopic measurements using the formula given. The different temperatures used in the case of ⊠ and ⧄ were 20 and −20° and in the case of × and ⁄ 40 and 0°, respectively.

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†The high dependence of the association enthalpy on temperature has been found also in other cases. We are just describing such behaviour of cyclohexanols in another paper.[20]

active vs racemic specimens, this corresponding to the results based on α-measurements.

For both of the configurationally homogeneous components of the compound **1** we tentatively investigated the association behaviour using the optically active solvents **5** and **6**. Although in this case the absorption coefficient of the free OH band is practically the same for both of the enantiomers, in both solvents the (*S*) component of the alcohols possesses an absorption coefficient of the associated band, which is about 5% greater than that of the (*R*) component. Values of $\Delta\nu_{OH}$ turned out here to be only 60% of those obtained with CCl_4 as a solvent, namely 120–135 cm^{-1}.

Investigating the behaviour of the acids **7** and **8**, we did not find any effects due to enantioselective association. This may be explained by the greater distance between the chiral centre and the associating group. The finding of Horeau and Guette[21] who reported calorimetric effects due to optical activity in the cases of α-methyl, α-ethyl succinic acid and of α-methyl, α-isopropyl succinic acid may be due to other associate structures of these dicarboxylic acids.

DISCUSSION

Clearly, attempts for any interpretation of the enantioselective association of chiral molecules should be based on differences in the steric arrangement of the interacting groups. Unfortunately, a detailed analysis of non bonding interactions in the diastereoisomeric associates would be extremely difficult because of the distance of the interacting groups and their conformational freedom. From this reason, we will not discuss the enantiomeric differences in ΔH in terms of such non bonding interactions. Nevertheless, it seems interesting, that in two cases the "isoconfigurational" associates as compared with the "heteroconfigurational" ones exhibit higher negative enthalpy of formation, higher intensity of the associated OH bands, and also greater $\Delta\nu_{OH}$. The parallelism of these 3 properties is to be expected, if ΔH is an appropriate expression of the strength and the distance of the $OH\cdots O$ bond.

From the observation that associates with higher $-\Delta H$ show lower f values compared with their diastereoisomers, we concluded that "heteroconfigurational" associates are connected with higher ΔS (or lower $-\Delta S$) values, than the isoconfigurational ones. This may be understood in a rather general way, taking into account that the construction of an associated chain from 2 different enantiomeric units allows more possible arrangements than the construction of isoconfigurational chains. Clearly, these differences in statistic probability of formation (i.e. in ΔS) should increase with increasing chain length of associates.

Our result may have some consequences for experiments in the field of natural and related compounds. Thus, the IR spectrum of an optically active natural compound and that of its synthesized racemic analogue can differ, even equally concentrated solutions, provided that one deals with strongly associated compounds like alcohols. Such differences are to be expected only in the frequencies and intensities of the associated group vibrations, the other parts of the molecule not being influenced by diastereoisomeric effects under these conditions.

Furthermore, deviations from the linear relationship between enantiomeric excess and optical rotation might arise from such enantioselective association phenomena. Indeed, we have observed such deviations in the cases of butan-2-ol[22] and of compound **1**,[23] whereas Horeau and Guette[21] noticed similar effects using a chiral dicarboxylic acid. A more detailed study of these effects will be presented later.

EXPERIMENTAL

The spectroscopic investigations were performed with preference for the range of the free and associated stretching vibration of the OH group (3100–3800 cm^{-1}) at four different temps, namely −20°, 0°, +20° and +40°. NaCl cells with 0.40 mm and 1.00 mm thickness were used. CCl_4 of Merck uvasol quality was used as a solvent. The Peltier apparatus used has been previously described.[24] All spectroscopic work was done on the Beckman IR 12, usually using a recording speed of 3.2 $cm^{-1} \cdot min^{-1}$: The calorimetric procedure described in detail in Ref. 23 was used. In the present work we also diluted a solution of an exactly known concentration to infinite dilution, characterized by the disappearance of any association band. The amount of associated OH bonds in the starting solution were determined by IR spectroscopy. The calorimetric data are average values, and refer to the complete dissociation of the different association complexes to monomers only.

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