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## OPTICAL PROPERTIES OF MANNICH BASES INFLUENCED BY CYCLODEXTRIN COMPLEXATION

Mannich bases are model systems for the study of intramolecular hydrogen bonding and proton transfer processes. Both phenomena can be investigated by changes of optical properties of these molecules and it could be shown that particularly the proton transfer is highly sensitive to the environment, e.g. the solvent. Inclusion of this type of molecules by cyclodextrins (CDs) influences therefore the proton transfer equilibria significantly, which can be used for a characterization of the cavity of the complexing agent.

CDs are widely used as excipients and additives in pharmacy as hosts to form inclusion complexes with small and medium sized organic molecules. The mainly hydrophobic cavity of the host molecules surround the guest molecules to some extent, depending on the geometry of the complexes, and the guests are shielded against the external moiety, e.g. highly polar aqueous solvents. As a consequence of the inclusion reaction the reactivities of the guest molecules, their solvent dependent spectroscopic and physicochemical properties are strongly influenced. As driving forces for the complexation process have been suggested: (a) electrostatic interactions, (b) van der Waals interactions, (c) hydrophobic interactions, (d) hydrogen bonding between polar groups of the "guest" and the hydroxyl groups of the "host", (e) relaxation by release of high-energy water from the CD cavity upon substrate inclusion, (f) relief of the conformational strain in a CD-water adduct and (g) induced fit (CDs undergo significant conformational changes upon complex formation to optimize opportunities for other modes of interactions) (Connors, 1997, Guo, 1998, Szejtli, 1998, Hedges, 1998).

The association of the Mannich base piperidino-methyl-2-naphthol (P2N) with  $\beta$ -CD is a very convenient system to study the influence of the

complexation on the intramolecular proton transfer between the neutral and zwitterionic structures, due to the strong dependence of that intramolecular equilibrium on the environment.

### MATERIAL AND METHODS

The Mannich bases used in the experiments were synthesized according to literature (Haslinger, 1980).  $\beta$ -CD (research grade, Serva, Heidelberg) was used without further purification. All solutions were prepared using bidistilled water. Concentrations of Mannich bases solutions were in the range of  $(4-8) \times 10^{-5}$  M and those of  $\beta$ -CD were  $(3-10) \times 10^{-3}$  M. The pH of the solutions was adjusted using either HCl or NaOH solution (both p.a., Merck, Darmstadt) and was measured by pH-meter PHM85 radiometer equipped with a standard glass electrode. Absorption spectra were recorded on a Hitachi U3501 spectrophotometer. In each measurement, a blank solution with corresponding concentration of  $\beta$ -CD was used as a reference. The association constants of the Mannich bases with  $\beta$ -CD in aqueous solution were estimated by the modified Hildebrand-Benesi method. (Köhler, 1992). The acid dissociation constants ( $K_a$ ) and  $K_{PT}$  of the Mannich bases were determined spectrophotometrically, and that of the corresponding  $\beta$ -CD complexes were obtained through extrapolation to 100% complex formation. The first  $pK_a$  was also determined by pH potentiometric titration.

### RESULTS AND DISCUSSION

Mannich bases are condensation products of the *Mannich* reaction of naphthols with aromatic amines in the presence of formaldehyde. They possess an intramolecular hydrogen bond between the hydroxyl group and the nitrogen of the amine. Proton transfer induced changes of the chromophoric system allow investigations by electron absorption, fluorescence and induced circular dichroism spectra. A scheme for the proton transfer equilibria is given in Figure 1.

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Paper presented as a poster.

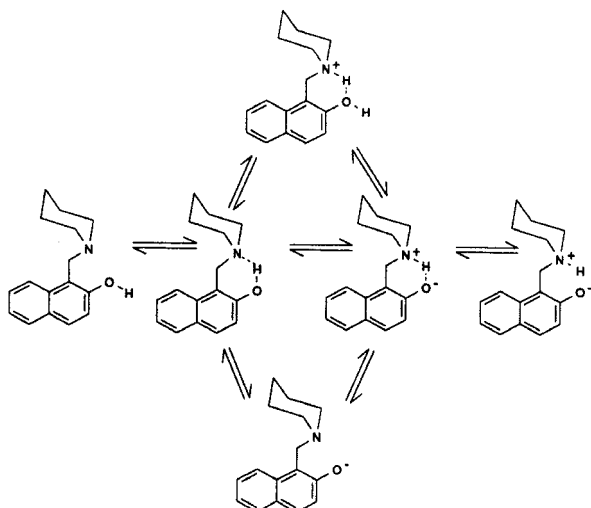


Figure 1. Protonation scheme of P2N in protic solvents

Mannich bases generally form short intramolecular hydrogen bonds between the proton donor, which is the phenolic or naphtholic group, and the amine, the acceptor moiety. In apolar medium intramolecular hydrogen bonding is more pronounced than intermolecular hydrogen bonds with water molecules. Moreover the high polarity of water as solvent stabilizes polar molecules like the zwitterionic form of P2N. Evidently, there is a dependence of the proton transfer equilibria on the pH-value. The various protonated forms of P2N associate with CDs with different complexation constants, leading to a pH dependence of the overall association constant. In neutral aqueous solution the association constant of P2N with  $\beta$ -CD was determined as  $265 \text{ M}^{-1}$  indicating an affinity of medium strength between host and guest molecules (Figure 2).

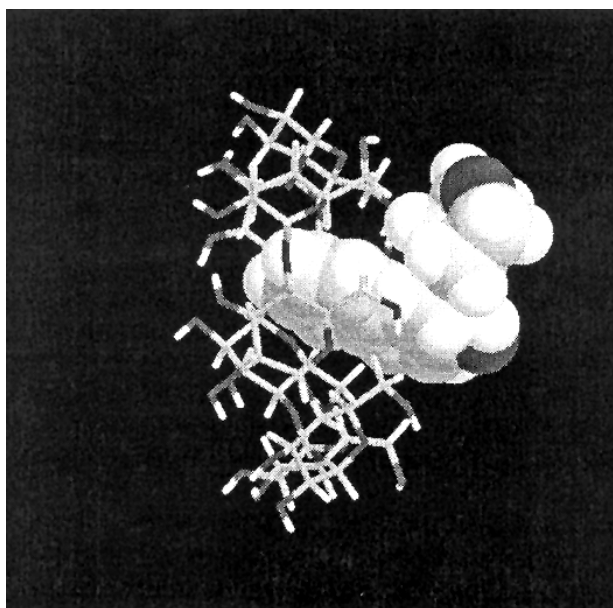


Figure 2. Complexation of  $\beta$ -CD with P2N

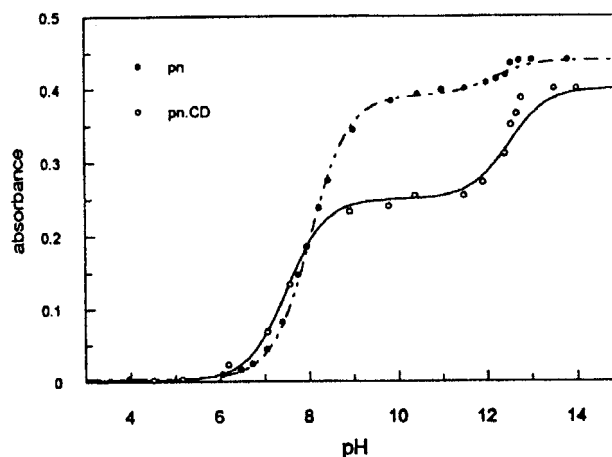


Figure 3. pH dependence of the extinction coefficient of P2N and P2N- $\beta$ -CD complexes at 351 nm.

Temperature dependent measurements of the association reaction allow the determination of the thermodynamic parameters.

Generally, P2N is a twobasic acid and both experimentally observed  $pK_a$  values are influenced by the complexation with  $\beta$ -CD. The respective profiles for P2N and the inclusion complex with  $\beta$ -CD are given below (Figure 3). The  $pK_{a1}$  and  $pK_{a2}$  values as well as the proton transfer equilibrium constants for both the free and the complexed compound  $K_{PT}$  are presented in Table 1.

Table 1.  $pK_{a1}$ ,  $pK_{a2}$  and  $K_{PT}$  of P2N in aqueous solution and in complexation with  $\beta$ -CD

	P2N	P2N- $\beta$ -CD
$pK_{a1}$	7.64	7.23
$pK_{a2}$	12.36	12.49
$K_{PT}$	9.79	2.34

The  $pK_{a1}$  for the deprotonation of the cation, which is 7.64 for noncomplexed P2N, decreases in the association complex to a value of 7.23, which was determined by extrapolation to 100% complexation. The second  $pK_{a2}$ , however, i.e. the protonation constant of the anionic form, is only slightly shifted from 12.36 for free P2N to 12.49 in the complex. In acidic solution, below  $pH = 5$ , P2N exists only in the protonated cationic form and in basic solution, as the pH exceeds 13, the anionic deprotonated form dominates. In neutral solution proton transfer equilibrium between the neutral and the zwitterionic form exists, and the proton transfer equilibrium constant  $K_{PT}$  can be estimated from the extinction coefficient of the plateau between  $pH = 9$  and 11.5. It is assumed, that the chromophor of the neutral form has a similar spectrum to that of the cation, as in both cases the absorbing species is a naphthol moiety; the spectrum of the zwitterionic structure should correspond to that of the anion.

For aqueous P2N a  $K_{PT}$  constant of 9.79 was estimated. This  $K_{PT}$  value decreases drastically on complexation with  $\beta$ -CD: The  $K_{PT}$  value of the complexed form evaluates to  $K_{PT} = 2.34$ . This change in the proton transfer equilibrium can be explained by higher interaction energy of the neutral form of P2N with the hydrophobic interior of the  $\beta$ -CD cavity in comparison to that of the polar, doubly charged zwitterion. This is supported by the calculation of the individual association constants of the neutral and the zwitterionic structure with  $\beta$ -CD. Equilibrium constants and the thermodynamic parameters of P2N at 25°C are given in Table 2.

Table 2. Proton transfer equilibrium constants ( $K_{exp}$  in  $M^{-1}$ ) of P2N complexed with  $\beta$ -CD, together with thermodynamic parameters and calculated association constants ( $K_{calc}$  in  $M^{-1}$ ) of the neutral and the zwitterionic form of P2N with the reaction enthalpies (in kcal/mol) and entropies (in cal/mol K).

	$K_{exp}$	$K_{calc}$	$\Delta H$	$\Delta S$
P2N	9.79		-2.1	-2.5
P2N- $\beta$ -CD	2.34		-2.8	-7.6
Neutral P2N		858	-6.9	-7.2
Zwitterion		205	-7.4	-11.8

## CONCLUSION

The proton transfer in Mannich bases is influenced by the polarity of the environment. In the inclusion

complex with  $\beta$ -CD decreases the extent of both intra- and intermolecular proton transfer processes, which is comparable with results obtained in non polar solvents. This effect can be explained by the hydrophobic cavity, which interacts better with the neutral form than with the charged zwitterionic form and leads to some shielding effect against the polar water molecules. The change of the proton transfer constant between free and complexed PN can be used for a characterisation of the cavity properties of various hosts.

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