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Short Communication

The Influence of Cyclodextrin Complexation on Proton Transfer in Piperidinomethyl-2-naphthol

G. Köhler, H. Martinek, W. Parasuk, K. Rechthaler, and **P. Wolschann**

Institut für Theoretische Chemie und Strahlenchemie, Universität Wien, A-1090 Wien, Austria

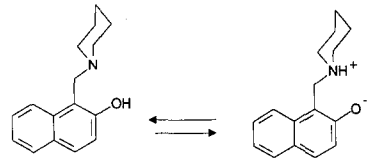
Summary. Piperidinomethyl-2-naphthol forms inclusion complexes with β-cyclodextrin with an equilibrium constant of 265 M^{-1} in aqueous solution. The proton transfer equilibrium between the neutral and the zwitterionic form is strongly influenced by the association.

Keywords. β-Cyclodextrin; Piperidinomethyl-2-naphthol; *Mannich* base; Host-guest complex; Inclusion complex; Proton transfer.

Der Einfluß der Komplexierung mit β-Cyclodextrin auf das Protontransfer-Gleichgewicht in Piperidino-2-naphthol (Kurze Mitt.)

Zusammenfassung. Piperidinomethyl-2-naphthol bildet Einschlußkomplexe mit β-Cyclodextrin mit einer Gleichgewichtskonstante von 265 M^{-1}. Das Protontransfer-Gleichgewicht zwischen neutraler Form und zwitterionischer Struktur wird durch diese Assoziation stark beeinflußt.

Cyclodextrins are widely used as hosts to form inclusion complexes with small and medium sized organic molecules. Changes of spectroscopic and physicochemical properties as well as of reactivities result from such host-guest interactions. In the present paper the association of the *Mannich* base piperidinomethyl-2-naphthol with β-cyclodextrin is reported. Alkylaminomethylphenols and naphthols are model systems for the study of intramolecular proton transfer processes. In particular, the proton transfer equilibrium of piperidinomethyl-2-naphthol (*P2N*) was investigated extensively in its ground as well as in its excited state [1–3]. *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 aqueous solution, intramolecular hydrogen bonding is widely replaced by intermolecular interactions with the solvent [1]. It was shown that solvent properties influence strongly the rate of proton transfer between the neutral and the zwitterionic structures [2].



P2N forms a host-guest complex with β-cyclodextrin with an association constant of $265 \pm 20\, M^{-1}$ in neutral aqueous solution. This is clearly shown by distinct changes on the absorption spectrum as the host concentration is increased: a shift of the spectrum from 348 nm to 345 nm and a decrease of the extinction coefficient is observed. The equilibrium constant was therefrom estimated by a modified *Hildebrand-Benesi* method [3]. The large change of the absorption spectrum of *P2N* due to the complexation with β-cyclodextrin is the result of a shift of the proton transfer equilibrium from the zwitterionic structure to the neutral form of *P2N*. The resulting observed spectral shift is much larger than expected for the environmental influence of the cyclodextrin cavity on the naphthol chromophor, and for 2-naphthol complexation with β-cyclodextrin the spectra shift, in the contrary, to lower energies [4,5].

P2N is a two basic acid and both pK_a values are influenced by the complexation. These pK_a values are measured by the variation of the extinction coefficient in dependence on the *pH*-value. The respective profiles for *P2N* and the association complex are given in Fig 1.

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.

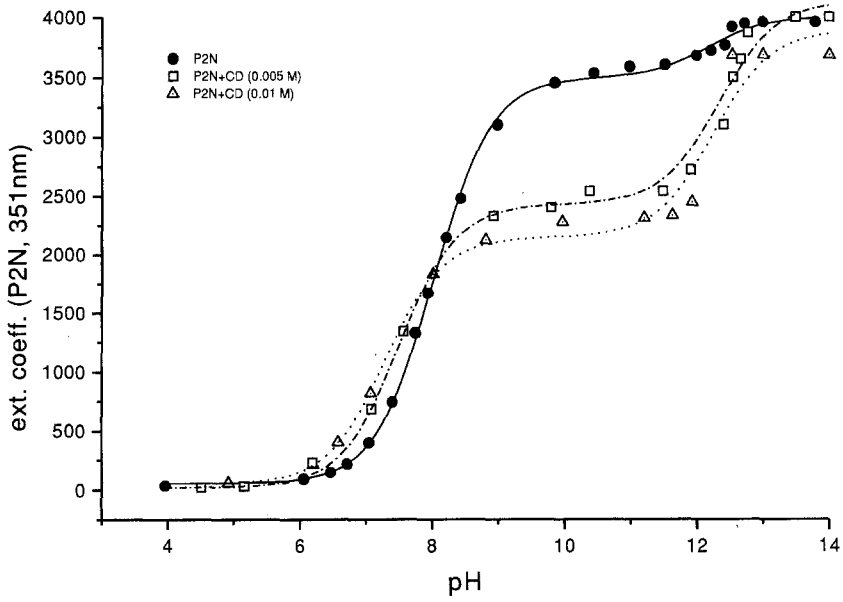


Fig. 1. *pH* dependence of the extinction coefficient of *P2N* and *P2N*-β-cyclodextrin complexes at 351 nm

In acidic solution (below $pH = 5$) *P2N* exists only in the protonated cationic form, whereas 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} of 9.79 was estimated. As shown in Fig. 1, this K_{PT} value decreases drastically on complexation with β-cyclodextrin: 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 a higher interaction energy of the neutral form of *P2N* with the hydrophobic interior of the β-cyclodextrin 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 β-cyclodextrin. From the overall association constant K', equilibrium constants $K_N = 858\,M^{-1}$ for the neutral molecule and $K_Z = 230\,M^{-1}$ for the zwitterion were evaluated. The formation of a complex with the neutral form of *P2N* is, therefore, favoured. The respective difference in the free energy must additionally be overcome to activate proton transfer. This proton transfer equilibrium is thus very sensitive to inclusion of the aromatic moiety into the hydrophobic cavity of cyclodextrins and this effect might be used for a characterization of the interior properties of various hosts.

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