Photochemical Behaviour of β-Carbolines. Part 5.[1] Ground and Excited State Interactions of *nor*-Harmane and Harmane with Alcohols and Ethers

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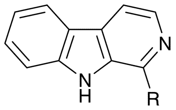
The formation of complexes of harmane and *nor*-harmane with a variety of alcohols and ethers in a non polar solvent (cyclohexane) is studied by absorption spectroscopy using chemometrics to calculate the stoichiometry and formation constants.

β-Carbolines are naturally occurring alkaloids that are widely distributed in nature. They are phototoxic and have a wide pharmacological activity. Although there are not conclusive studies, the hypothesis that is often proposed is that the interactions between the β-carbolines and their biological receptors involve the formation of reversible molecular association complexes. The study of the β-carboline–alcohol interaction is especially interesting because these molecules can form H-bonds acting simultaneously as donors and acceptors because of their NH indolic and N pyridinic groups. The most investigated class of compounds with these H-bonding properties are the 7-azaindoles.[16,17] A similar behaviour has been also described for other molecules, *e.g.* 1-azacarbazoles,[18] hydroxyquinolines[19] and 2-(2′-pyridyl)indoles.[20] In such systems, the formation of cyclic complexes usually with alcohols may lead to excited state tautomerization involving the cooperative movement of two or more protons. The stoichiometry of these complexes usually is 1:1 but is sometimes 1:2.[18–20]



nor-harmane R = H
harmane R = Me

Fig. 1 Structure of *nor*-harmane and harmane

The absorption and fluorescence emission and excitation spectra of *nor*-harmane and harmane in different organic solvents are presented in Tables 1 and 2 (see full text). In the case of the pure organic solvents the bands of the neutral species are observed and there is enough evidence that the low energy band is due to a π–π^* transition which is displaced to longer wavelength when protonated.

When the fluorescence and absorption maxima are plotted against the values of the local solvent polarity parameter (π^*)[26] they fall on a straight lines only for non-H bonding solvents. In the case of alcohols, DMSO, DMF and ethers (diethyl ether, THF, 1,4-dioxane) the absorption and fluroescence maxima are shifted to the red more than could have been expected on the basis of the π^* parameter. These results indicate that there is a specific interaction between the solvent and the solute both in the ground and excited states,being more pronounced in the latter [Figs. 2(*b*) and 3(*b*), see full text]. β-Carbolines, owing to their structure, can act as H-bond acceptors and H-bond donors yielding complexes of definite stoichiometry with solvents.

When a small quantity of alcohol (or any suitable solvent) was added to a solution of β-carboline in cyclohexane there was a change in the absorption spectrum. If successive additions were made the growth of new bands was observed as a function of alcohol concentration, with the clear formation of isosbestic points (Fig. 4, see full text). This fact indicates that a new species forms

$$B + nR \rightleftarrows BRn \qquad (1)$$

where B is the β-carboline and R the added solvent.

In order to establish the stoichiometry of the complex formed, and taking advantage of having data digitalized, a chemometric method[29] was applied.

The procedure involves the application of a defined chemical model for the evolution of the conventration profiles. In this case

$$[B] = [B]^0/(1 + K[R]^n) \qquad (9)$$

$$[BR_n] = [B]^0 K[R]^n/(1 + K[R]^n) \qquad (10)$$

as $[B]^0 = [B] + [BRn]$ and $K = [BRn]/[B][R]^n$.

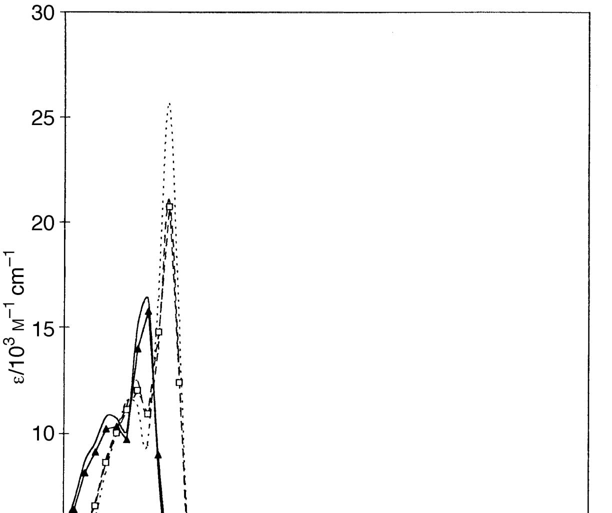


Fig. 5 Absorption spectra of *nor*-harmane. Uncomplexed *nor*-harmane (——); *nor*-harmane complexed with EtOH (– – –); predicted spectrum for uncomplexed *nor*-harmane (—▲—); predicted spectrum for *nor*-harmane–EtOH (1:2) complex (- - - - -); predicted spectrum for *nor*-harmane–EtOH (1:3) complex (- -□- -)

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Table 3 K and n values for the formation of the complex β-carboline–RH (1:n)

β-Carboline	RH	n	K^a
nor-Harmane	1,4-Dioxane	1	6.5
	Diethyl ether	1	6.6
	THF	1	12.0
	MeOH	3	43×10^{3}
	EtOH	3	35×10^{3}
	PrOH	3	97×10^{3}
	$Pr^{i}OH$	3	26×10^{3}
	$Bu^{t}OH$	3	24×10^{3}
	BuOH	3	65×10^{3}
	$C_6H_{13}OH$	3	70×10^{3}
Harmane	1,4-Dioxane	1	5.6
	Diethyl ether	1	5.3
	THF	1	10.5
	MeOH	3	11×10^{3}
	EtOH	3	8.5×10^{3}
	PrOH	3	$14\times10^{3}2$
	$Pr^{i}OH$	3	5.5×10^{3}
	$Bu^{t}OH$	3	7.0×10^{3}
	BuOH	3	9.0×10^{3}
	$C_6H_{13}OH$	3	15×10^{3}

[a] The estimated error is ±15%.

In the case of *nor*-harmane in cyclohexane with the addition of ethanol, the best n value obtained was 3. In Fig. 5 are shown the experimental spectra and the spectra predicted using the values obtained after global analysis. As can be seen, the agreement between the experimental and predicted ε values using $n = 3$ is excellent. If the value of $n = 2$, the agreement is not that good. It is interesting to point out that this type of global analysis is more complete and sensible to variation in the stoichiometric coefficient that the popularly used methods which take into account only wavelengths were only one of the species absorbs.[27,28]

The results obtained for the different solvents are presented in Table 3. Note that when the solvent has a Taft α value equal to zero (diethyl ether, 1,4-dioxane, THF) the stoichiometric coefficient is 1. When solvents with a low β value were used, such as benzyl cyanide, acetonitrile and dichloromethane, the formation of the complex was not detected. In the case of chloroform and carbon tetrachloride a photochemical reaction was observed which is described elsewhere.[32,33]

There does not seem to be a clear correlation between the K value and a property of the alcohols such as Taft α hydrogen bond donor ability or β hydrogen bond acceptor ability (see Table 3, full text).

In all the cases studied the K of *nor*-harmane is higher than that of harmane. It is reasonable to assume that steric factors are responsible.

The fluorescence quantum yields and lifetimes of *nor*-harmane and harmane were measured in different organic solvents. The results are presented in Tables 4 and 5 (see full text). It can be seen that neither in the quantum yield nor in the lifetimes is there a great difference between the hydroxylic and non hydroxylic solvents. This fact is different to that observed in the case of α-carbolines[18] and 2-(2′-pyridyl)indoles.[20] In these latter cases the fluorescence is strongly quenched in polar protic solvents such as alcohols.

In the case of the β-carbolines the fluorescence lifetimes are longer in hydroxylic solvents. This indicates that the complex between the β-carbolines and the alcohol is more polar than the β-carboline as it is stabilized more in polar solvents.

When the ground state complex is excited it has a distinctive emission. If the fluorescence emission spectra are registered at the wavelength of the isosbestic point, a new band appears slightly shifted red with respect to the band of the β-carbolines in pure cyclohexane, as can be seen in Fig. 7 (see full text).

K^* was calculated using a modification of the Foster-Hammick-Wardley expression[28] assuming that the equilibrium between the excited species B^* and BRn^* is established during their lifetime and the stoichiometry of the complex is the same as in the ground state. The comparison of the K values in the ground state with those of the first excited singlet state reveals that the complexation is favoured in the latter state. It is known that the pyridinic N becomes more basic in this state and the pyrrolic NH group more acidic. These acid–base enhanced properties make the interaction with the solvents more favourable. Further work must be done in order to prove that equilibrium is established during their lifetimes.

Techniques used: UV–VIS, stationary and time resolved fluorescence emission spectroscopy

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Fig. 2: Frequency maxima of *nor*-harmane in organic solvents *vs.* the local polarizability parameter

Fig. 3: Frequency maxima of harmane in organic solvents *vs.* the local polarizability parameter

Fig. 4: Absorption spectra of *nor*-harmane in cyclohexane with added EtOH

Fig. 6: CPK spheres of *nor*-harmane–BuOH (1:3) complex with its geometry optimized by PM3 semiempirical method

Fig. 7: Fluorescence emission spectra of *nor*-harmane in cyclohexane and with added BuOH

Tables 1 and 2: Electronic absorption and fluorescence emission and excitation spectral data for *nor*-harmane and harmane in organic solution

Table 4: Fluorescence quantum yields of *nor*-harmane and harmane in organic solvents

Table 5: Fluorescence lifetimes of *nor*-harmane and harmane in organic solvents

Table 6: Excited state K values for the formation of the complex β-carboline–RH (1:n) in cyclohexane

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