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ORIGINAL ARTICLE

Enantioselective phosphorescence behavior of naproxen in β-cyclodextrin supramolecular complex

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Abstract In the presence of small amount of 1-iodo butane (IBu) (0.1 % (v/v)), Naproxen (Nap) displays strong room temperature phosphorescence (RTP) in β-cyclodextrin (β-CD) solution without deoxygenation because of the formation of ternary complex of β-CD, Nap, and IBu. The results indicate that β-CD shows good enantiodiscrimination for (R)-Nap and (S)-Nap. The RTP intensity of (R)-Nap is larger than that of (S)-Nap, the difference being 29.2 %. Both (R)-Nap and (S)-Nap exhibit single exponential phosphorescence decay with different lifetimes of 2.535 ± 0.056 and 1.798 ± 0.076 ms for (R)-Nap and for (S)-Nap, respectively. The corresponding association constants evaluated for (R)-Nap/β-CD/IBu and (S)-Nap/β-CD/IBu ternary complexes are (8.02 ± 0.15) × 10^3 and (2.50 ± 0.06) × 10^3 L mol^{-1}, respectively. Thus, the observation of RTP differences between (R)-Nap and (S)-Nap can be attributed to their different ability to form complexes with chiral β-CD.

Keywords Naproxen · β-cyclodextrin · Room temperature phosphorescence · Lifetime · Chiral discrimination

Introduction

Naproxen [2-(6-methoxy-naphthyl) propanoic acid] is a non-steroidal, anti-inflammatory drug that has been widely used for the treatment of osteoarthritis, rheumatoid arthritis and acute pain in musculoskeletal disorders [1, 2]. The drug works by blocking the enzyme cyclooxygenase-2, and thereby reducing the levels of prostaglandins whose mission is to act as messengers in the process of inflammation, fever, and pain [3]. Naproxen contains a chiral carbon atom and therefore occurs as two optical isomers. The clinical studies have shown that the pharmaceutical activity of (S)-Naproxen is 28 times stronger than that of (R)-Naproxen, while the R-enantiomer can cause some adverse effects [4, 5]. So Naproxen is the drug sold as its pure S-enantiomer. To facilitate drug processing and production and reduce the side effects of drugs, chiral separation and recognition of (R) and (S)-enantiomers as well as the determination of optical purity have become important issues. Since (R) and (S)-Naproxen differ only in the disposition of a small methyl group and a hydrogen atom at the chiral center, the chiral recognition of Naproxen enantiomers involves certain special difficulties and remains a challenging task [6].

Cyclodextrins (CDs), a group of oligosaccharides, are well-known host molecules. They are chiral and are thus able to distinguish between enantiomers by forming diastereomeric host–guest complexes through dipole–dipole, hydrophobic, Vander Waals, electrostatic as well as hydrogen bonding interaction. Therefore, CDs have been widely used as chiral selector in chiral separation and recognition based on various approaches including phosphorescence sensing [7–19].

The interaction between Nap and β-CD has been investigated in solution and in the solid state [20–23]. Several methods for the determination of Nap by RTP using organized media such as CDs and micelles have also been reported [24–30]. However, no report of the chiral recognition of Nap by room temperature phosphorimetry has been presented. In addition, the observation of RTP

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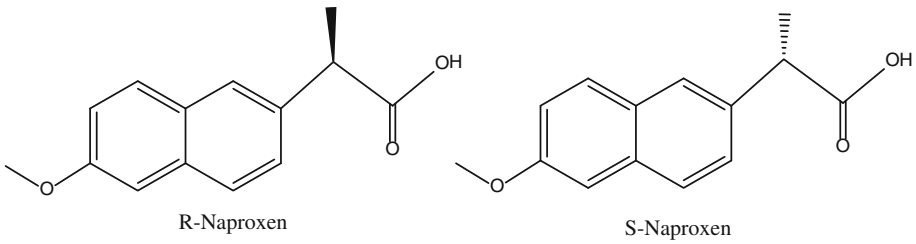
Chart 1 Structures of (R)- and (S)-Naproxen



in the above-mentioned reports required deoxygenation using an oxygen scavenger such as sodium sulfite, which produces some inconveniences. In this work, we investigated the RTP of Nap in β-CD aqueous solution without deoxygenation, using 1-iodo butane as both heavy atom perturber and space-regulator. We found that the RTP signals differed significantly for the two enantiomers of Nap, while absorption and fluorescence hardly show any difference. The observed RTP intensity and lifetime differences enabled easy spectroscopic discrimination between this pair of enantiomers based on simple time-resolved detection.

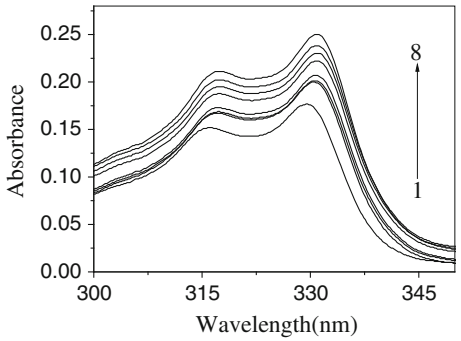


Fig. 1 Absorption spectra of (R)-Nap in different concentrations of β-CD. [(R)-Nap] = 1×10^{-4} M; [β-CD](mM): (*1–8*) 0; 1.6; 3.2; 4.8; 6.4; 8.0; 9.6; 11.2

Experimental

Chemicals

(R)-(-)-Naproxen ((R)-Nap) and (S)-(+)-Naproxen ((S)-Nap), as shown in Chart 1, were purchased from Alfa Aesar (Lancaster, UK) and used as received. Stock solutions of (R)-Nap and (S)-Nap were prepared in ethanol at 1.0×10^{-2} mol L^{-1}. α-CD, β-CD, γ-CD, HP-β-CD (average degree of substitution D.S. = 4.2, MW = 1,380) and Me-β-CD (average degree of substitution D.S. = 12.5, MW = 1,310) were obtained from Wacker Co. (Munich, Germany) and used without further purification. Absolute ethyl alcohol (≥99.7 %), 1,2-dibromoethane (1,2-DBE), 1,4-dibromobutane (1,4-DBB), 1-iodobutane (IBu), bromocyclohexane (BrCH), 1, 2, 3-tribromopropane (1, 2, 3-TBP), 1, 2-dibromopropane (1, 2-DBP) and dibromomethane (DBM) (≥98.0 %) were purchased from Beijing Chemicals Factory (Beijing, China). Britton–Robinson (B–R) buffer solutions were used to adjust the acidity of solution. The water used to prepare the solution was double-distilled.

Apparatus

The UV absorption spectra were obtained on a TU-1901 spectrophotometer (Puxi instrument Co., China). The phosphorescence measurements were performed on a LS-55 luminescence spectrometer (Perkin-Elmer) with excitation wavelength of 334 nm. The excitation and emission slits were set at 10 and 20 nm, respectively. The delay time and the gate width were set at 0.04 and 2.00 ms, respectively. Phosphorescence lifetimes were determined with a cary eclipse fluorescence spectrophotometer (Varian, Palo Alto, USA). The first delay time was set at 0.05 ms while the gate time was set at 6.00 ms. The phosphorescence lifetime values were obtained by fitting the phosphorescence decay curves to single or bi-exponential curve. pH values were measured with a pHS-3C digital pH meter (Shanghai Precision Scientific Instrument Co., Ltd., Shanghai, China).

Experimental procedure

Typically, appropriate amount of stock solutions of (R)-Nap and (S)-Nap was transferred into a comparison tube of 10 ml, and then proper volumes of β-CD and IBu solution were added. The mixed solution was diluted to the final 5 ml with doubly distilled water and shaken thoroughly. The working solutions were left to equilibrate for 1 h at room temperature before making measurements. Enantiomeric mixtures of Nap were made by mixing known amounts of single enantiomeric stock solutions by weight. All the other CD systems follow the same procedure.

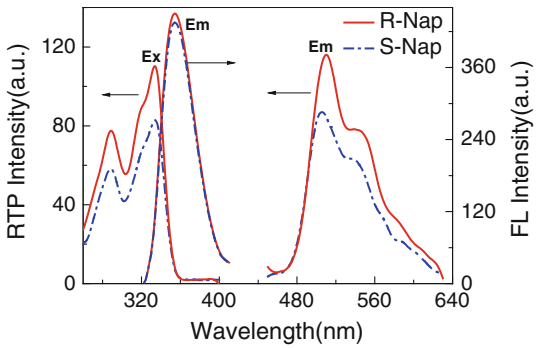


Fig. 2 Phosphorescence and fluorescence spectra of (R)-Nap and (S)-Nap in β-CD solution. [(R)-Nap] = [(S)-Nap] = 1.00×10^{-4} M; [β-CD] = 5.00×10^{-3} M; pH = 2.78; For phosphorescence measurement, [IBu] = 0.1 %(v/v)

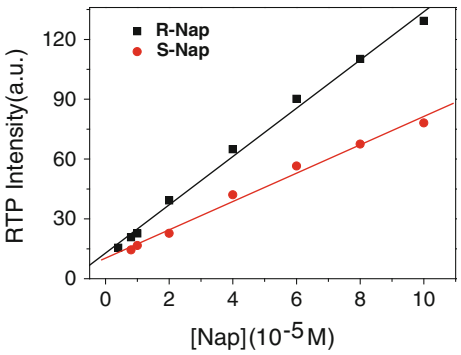


Fig. 3 RTP intensity as a function of Nap concentration. [IBu] = 0.1 %(v/v); [β-CD] = 5.00×10^{-3} M

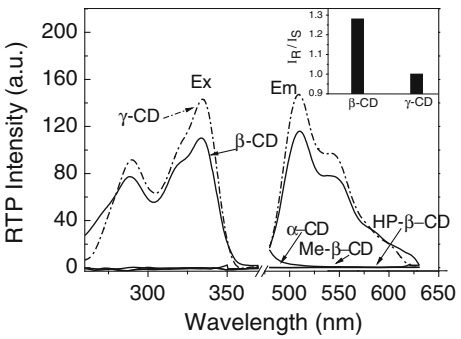


Fig. 4 Phosphorescence spectra of (R)-Nap in different cyclodextrins. [(R)-Nap] = 1.00×10^{-4} mol L^{-1}; [CDs] = 5.0×10^{-3} M; [IBu] = 0.1 %(v/v). Inset: the ratio of RTP intensity of (R)-Nap to (S)-Nap

Results and discussion

Spectral characteristics

UV absorption and fluorescence spectra

Absorption spectra of (R)-Nap upon adding of β-CD are shown in Fig. 1. Like other 2-substituted Naphthalene chromophores, the absorption spectrum of Nap shows a typical fine-structured band above 300 nm, corresponding to the $S_0 \rightarrow S_1$ transition [31]. The absorbance of Nap increased with the increase of β-CD concentration and the absorption peaks at 316 and 330 nm red-shifted by 2 nm, indicating that the drug was in a less polar microenvironment and an inclusion complex between Nap and β-CD was formed. The addition of β-CD produced very similar effects on the UV absorption behaviour of (S)-Nap (data not shown).

Fluorimetric measurements were also performed in aqueous solutions of β-CD. Emission spectra were recorded in the 325 nm $< \lambda$em $<$ 425 nm range, with excitation at λex = 330 nm. As described in previous papers [32, 33], the emission spectrum of Nap aqueous solution presents a non-structured band centered around 353 nm (Fig. 2). The fluorescence changes upon addition of β-CD are very similar for both R and S enantiomer. The difference in fluorescence emission intensity of the peak at 355 nm was too small to be used for chiral discrimination.

Phosphorescence spectra of the three-component inclusion system

In the presence of oxygen, no RTP signals from Nap were produced when it is individually included in the cavity of β-CD. Upon addition of IBu as a third component, however, strong RTP emission of Nap was observed. Thus, it can be inferred that the three-component inclusion complex, namely, β-CD/Nap/IBu complex, really comes into existence. It is reasonable to infer that Nap is solubilized into the β-CD cavity together with the hydrophobic space-regulator IBu so that Nap is experiencing a sufficiently rigid enough microenvironment to produce strong RTP emission. Herein IBu also acts as a heavy atom perturber, which can enhance the probability of S1 $\rightarrow$ T1 intersystem crossing by interacting with Nap and induce strong phosphorescence.

The RTP spectra are shown as Fig. 2 for the inclusion system. It's clear that β-CD shows good enantiodiscrimination for (R)-Nap and (S)-Nap. The maximum excitation peak of both enantiomers is at 334 nm, while the emission of (R)-Nap and (S)-Nap showed a slight difference with their maximum emission at 510 and 506 nm, respectively. Moreover, the RTP intensity of (R)-Nap was greater than that of (S)-Nap, the difference being 29.2 %. The results indicate that (R)-Nap is better protected against quenching than (S)-Nap in the inclusion system. Under optimal conditions, the RTP intensity is linear with the concentration of R-Nap or S-Nap in the range of 4.00×10^{-6}–1.00×10^{-4} M ($R^2 = 0.9972$) and 8.00×10^{-6}–1.00×10^{-4} M ($R^2 = 0.9948$), respectively (Fig. 3). The limits of detection are

1.68×10^{-7} and 2.87×10^{-7} M (signal to noise ratio of 3:1) for R-Nap and S-Nap, respectively. This sensitivity is comparable to or better than that reported for other phosphorescence methods.

The experiments were also examined in other CDs systems including α-CD, HP-β-CD, Me-β-CD and γ-CD. The results show that the resultant RTP signals were very low or undetectable in other CDs systems except for γ-CD (Fig. 4). No remarkable differences in the RTP intensity, however, were observed for (R)-Nap and (S)-Nap in the case of γ-CD, indicating that γ-CD shows little enantiodiscrimination for this pair of enantiomers. According to the so-called three-point interaction model between one enantiomer and the chiral selector, the interaction between the chiral β-CD cavity and Nap may be modified by IBu to achieve a better fit and a stronger interaction. (R)-Nap and (S)-Nap fit differently into the cavity of the β-CD and chiral discrimination then takes place. By contrast, the size of γ-CD may be too large to produce chiral discrimination. Therefore, the following studies were carried out in the β-CD solutions.

Factors affecting RTP intensity

Effect of pH

Naproxen has a carboxyl group and exists in different forms, i.e., as anionic, and neutral species, as a function of pH (the pKa value of Naproxen is 4.9 [34]). Our result shows that changes in the pH do not produce significant changes in the fluorescence intensities of Nap (data not shown), in good agreement with that reported by Escandar et al. [29]. In contrast, the influence of pH on the RTP intensity of Nap was notable. As shown in Fig. 5, the RTP emission of Nap decreased in intensity as pH increased and disappeared when pH was over 6.0. It is known that the presence of a heavy atom is an important factor for RTP

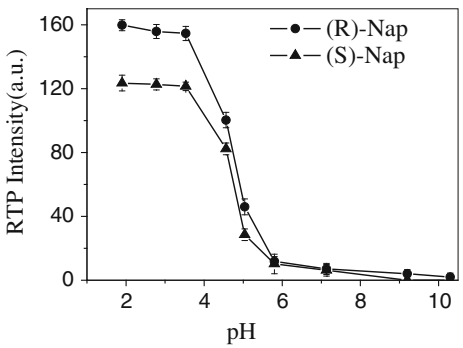


Fig. 5 Effect of pH on phosphorescence intensity of (R)-Nap and (S)-Nap. [(R)-Nap] = [(S)-Nap] = 1.00×10^{-4} M; [IBu] = 0.1 % (v/v); [β-CD] = 5.00×10^{-3} M

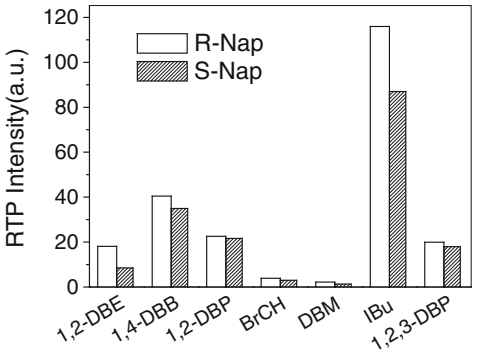


Fig. 6 Effect of HAP on the RTP intensity of (R)-Nap and (S)-Nap. [(R)-Nap] = [(S)-Nap] = 1.00×10^{-4} M; [β-CD] = 5.00×10^{-3} M; [IBu] = 0.1 %(v/v); pH = 2.78

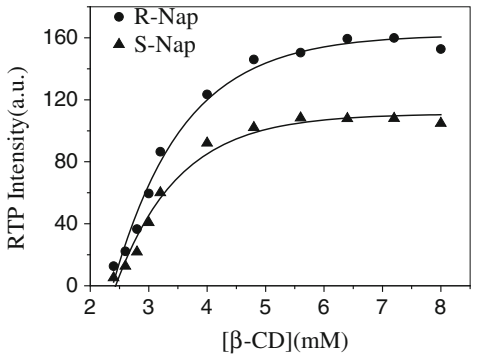


Fig. 7 Effect of increasing concentration of β-CD on the phosphorescence of Nap [(R)-Nap] = [(S)-Nap] = 1.00×10^{-4} M; [IBu] = 0.1 % (v/v); pH = 2.78

detection and in order to obtain significant CD-stabilized RTP signals, the analyte and the heavy atom need to be in close proximity to produce effective population of the triplet state of the former. According to Bettinetti et al. [22], the affinity of the CD cavity for the neutral form of a given guest is preferred to that for the ionized form. At lower pH, Nap is a neutral molecule and it can interact with β-CD via hydrophobic interactions as well as hydrogen bonding between the carboxylic proton and an external hydroxy group of the CD, which enhanced the degree of inclusion. At pH > 6, Nap mainly exists as anion with more hydrophilic character, leading to a reduction in the binding affinity of Nap to β-CD. Moreover, the neutral Nap is much more lipophilic and could be more strongly attracted to BuI inside the CD cavity, which induced a much stronger RTP emission. Similar results were observed in our previous studies with quinine and quinidine as well as 1,1′-binaphthol, where the RTP emissions mainly come from the neutral luminescent species [17, 18]. A pH of 2.78 was selected for the subsequent studies.

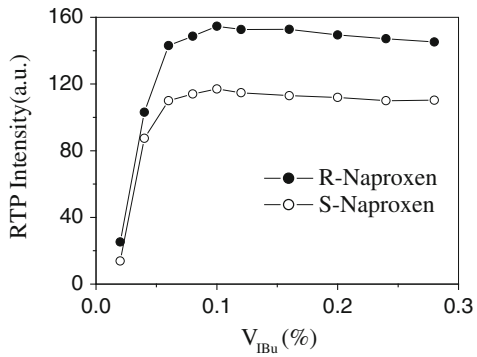


Fig. 8 Effect of the volume of IBu on the phosphorescence intensity. [(R)-Nap] = [(S)-Nap] = 1.00×10^{-4} M; [β-CD] = 5.00×10^{-3} M; pH = 2.78

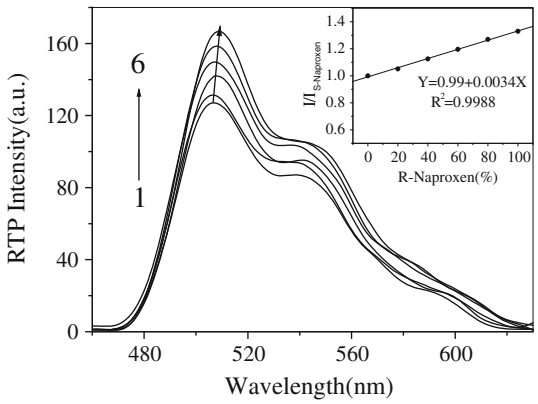


Fig. 9 The RTP spectra of different ratios of (R)-Nap and (S)-Nap. [β-CD] = 5.00×10^{-3} M; [IBu] = 0.1 %(v/v); pH = 2.78, [(S)-Nap]/[(R)-Nap]: (1) 1:0, (2) 4:1, (3) 3:2, (4) 2:3, (5) 1:4, (6) 0:1. Inset: Phosphorescence enhancement of Nap versus the enantiomeric composition of Nap

Effect of heavy atom perturbers

Some haloalkanes, including 1, 4-DBB, DBM, 1, 2-DBP, BrCH, 1, 2, 3-TBP, IBu and 1, 2-DBE were investigated as heavy atom perturbers (HAP). As shown in Fig. 6, all the HAP studied, except for DBM and BrCH, can induce RTP of Nap in β-CD solution but to a different degree. However, only IBu showed the most intense RTP signals as well as a high level of enantioselectivity. Thus, IBu was selected as a HAP for the chiral discrimination of Nap in this work.

Effect of both β-CD and IBu concentrations

With the purpose of optimizing RTP signals, the influences of both β-CD and BrCH concentrations on the RTP intensity of Nap were investigated. As seen in Fig. 7, the RTP intensity of Nap increased sharply with the increase of β-CD concentration and this change became slow and tended to reach a plateau when the concentration of CD was more than around 4.8×10^{-3} M, indicating the formation of Nap/β-CD/IBu inclusion complexes.

The variation in the RTP with IBu concentration is shown in Fig. 8. It can be seen that the RTP intensity increased with the increase of IBu, and reached a maximum value when portion of IBu in the working solution was more than 0.1 % (the ratio of the volume of IBu to the total volume of the sample solution) and then remains almost constant at higher concentrations of this compound. Therefore, in the subsequent experiments the β-CD and IBu concentrations were kept constant at 5 mM and 0.1 % (8.78 mM), respectively.

RTP spectra of (R)- and (S)-Nap mixtures

Under optimal conditions, RTP spectra obtained from mixtures of (R)- and (S)-Nap at different R/S ratios were shown in Fig. 9. As is seen in the inset of Fig. 9, the RTP intensity can be correlated linearly with the enantiomeric composition of Nap. In addition, the emission peak around 506 nm is progressively red shifted to around 510 nm with the increasing of (R)-Nap. Therefore the proposed method enables the determination of the enantiomeric composition of a Nap mixture.

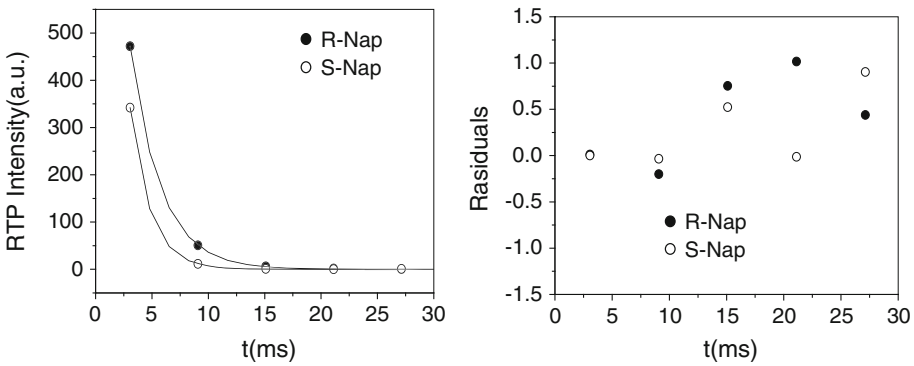


Fig. 10 (*Left*) Phosphorescence decay curves of (R)-Nap and (S)-Nap. (*Right*) residual analysis of phosphorescence decay fitting of (R)-Nap and (S)-Nap. [(R)-Nap] = [(S)-Nap] = 1.00×10^{-4} M; [β-CD] = 5.00×10^{-3} M; [IBu] = 0.1 %(v/v); pH = 2.78

Measurements of phosphorescence decay and lifetime

Figure 10 presents the phosphorescence lifetime decay and the residual analysis for (R)-Nap and (S)-Nap, respectively. Under aerated conditions, both (R)-Nap and (S)-Nap in aqueous β-CD solution in the presence of IBu displayed a single exponential phosphorescence decay with lifetimes of 2.535 ± 0.056 ms for (R)-Nap and 1.798 ± 0.076 ms for (S)-Nap, respectively. The observed lifetime values are comparable to the earlier reported values of 1–3 ms for Nap in deoxygenated CDs solutions [29], implying that Nap can be better protected against oxygen quenching in the present system. The lifetime difference between (R)-Nap and (S)-Nap was 34.02 %, which indicated a distinct chiral discrimination of β-CD toward this pair of enantiomers. It can be inferred that the different stereochemical structures of (R)-Nap and (S)-Nap lead to their different ability to form complexes with the chiral β-CD. It is clear that (R)-Nap/β-CD/IBu complex is more stable so that its triplet lifetime is much longer than that for (S)-Nap.

Complexation equilibria

The complexation stoichiometry between β-CD and Nap was found to be 1:1 [22]. Assuming that a 1:1:n ternary complex Nap/β-CD/IBu is formed, the formation of the complex can be described by several equilibria:

$$\mathrm{Nap} + \beta - CD \overset{K1}{\leftrightarrow} \mathrm{Nap} \cdot \beta - CD$$

$$\mathrm{Nap} \cdot \beta - \mathrm{CD} + n\mathrm{IBu} \overset{K2}{\leftrightarrow} \mathrm{Nap} \cdot \beta - \mathrm{CD} \cdot \mathrm{IBu}_n$$

The formation constant of the binary complex K_1 was first calculated from the fluorescence data by use of the modified Benesi–Hildebrand equation (Eq. 1) [35].

$$\frac{1}{F - F_0} = \frac{1}{K[\beta - \mathrm{CD}][F_\infty - F_0]} + \frac{1}{F_\infty - F_0} \quad (1)$$

where F is the observed fluorescence intensity of Nap solution at each β-CD concentration, F_0 represents fluorescence intensity of Nap solution in the absence of β-CD. The calculated formation constant K_1 are $(8.97 \pm 0.30) \times 10^2$ and $(8.21 \pm 0.25) \times 10^2$ L mol^{-1} for (R)-Nap and (S)-Nap, respectively. These values are somewhat smaller than the value reported for Nap at pH 2.5, log $K = 3.32 \pm 0.02$ [29]).

When the concentrations of both β-CD and IBu are much greater than that of Nap, their free and analytical concentrations are similar and therefore the mass balance for Nap can be written as:

$$\mathrm{C_{Nap}} = [\mathrm{Nap}](1 + K_1 C_{\mathrm{CD}} + K_1 K_2 C_{\mathrm{CD}} C_{\mathrm{IBu}}^n) \quad (2)$$

where C_{Nap}, C_{CD} and C_{IBu} are the analytical concentrations of Nap, β-CD and IBu, respectively, and [Nap] is the free concentration of Nap.

If the RTP emission is predominantly from the triplet-state ternary inclusion complex, then the increase in the intensity of phosphorescence should be proportional to the ternary complex concentration:

$$\mathrm{I_p} - \mathrm{I_0} = m[\mathrm{Nap} \cdot \beta - \mathrm{CD} \cdot \mathrm{IBu}_n] \quad (3)$$

where I_{P} and I_0 are the phosphorescence intensities of Nap in the presence and in the absence of IBu, respectively; m is a proportionality constant. Assuming that at high β-CD concentrations essentially all of the Nap molecules are complexed, the following equation can be written:

$$I_{\mathrm{p}\infty} - I_0 = mC_{\mathrm{Nap}} \quad (4)$$

where $I_{\mathrm{P}\infty}$ is the RTP intensity when the complex is completely formed. Combining Eqs. (2)–(4) gives:

$$I_p - I_0 = [K_1 K_2 C_{\mathrm{CD}} C_{\mathrm{IBu}}^n (I_{P\infty} - I_0)]/(1 + K_1 C_{\mathrm{CD}} + K_1 K_2 C_{\mathrm{CD}} C_{\mathrm{IBu}}^n) \quad (5)$$

when $1/I_{\mathrm{p}} - I_0$ is plotted versus 1/[IBu], a good linear relationship is observed for both (R)-Nap and (S)-Nap systems, indicating the formation of a 1:1:1 ternary complex Nap/β-CD/IBu according Eq. 5. The values for K_2, calculated from the ratio of the intercept to slope, are $(8.02 \pm 0.15) \times 10^3$ and $(2.50 \pm 0.06) \times 10^3$ L mol^{-1} for (R)-Nap and (S)-Nap, respectively. These overall association constant values are much higher than that for the binary complexes, indicating that the presence of IBu enhanced the inclusion ability of β-CD to Nap. Moreover, the difference in the inclusion efficiency was much more pronounced for the two isomers in the presence of a third component. It can be concluded that the mobility of the (R)-Nap in β-CD cavity should be lower than that of the (S)-Nap in the presence of IBu, suggesting that there is a more precise stereochemical matching between (R)-Nap and β-CD in the presence of IBu.

Conclusions

Strong RTP of Nap is induced synergetically by β-CD and IBu without removal of oxygen dissolved in the solution because of the formation of ternary complex of Nap/β-CD/IBu. β-CD and Nap enantiomers can form two diastereomeric complexes with different stabilities. Thus, the Nap/β-CD/IBu complexes exhibit enantiomeric differentiation in both RTP intensity and RTP lifetime, enabling easy spectroscopic discrimination between (R)-and (S)-Nap enantiomers based on simple time-resolved detection.

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