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Is sodium cinnamate a photoswitchable hydrotrope?

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Photoswitchable hydrotropic solubilization has been investigated by *cis–trans* isomerization about the olefinic bond of sodium cinnamate (Na-CIN) for various solutes such as cinnamic acid, aspartic acid, curcumin, thymol, and benzocaine. The extent and rate of isomerization depend on the concentration of Na-CIN and temperature. The *cis–trans* isomerization of Na-CIN by UV irradiation allows recovery of the solute from aqueous Na-CIN solutions, without dilution by water. Extraction of forskolin and curcumin from *coleus forskholii* and *curcuma longa*, was also studied for recovery under UV irradiation.

1. Introduction

Small molecular weight amphiphilic molecules such as sodium and potassium salts of alkyl group substituted benzoic and aryl sulfonic acids are known as hydrotropes because of their remarkable ability to dissolve other sparingly soluble organic compounds in aqueous solutions. [1–4] Non-aromatic and non-ionic hydrotropes also have been reported with similar solubilization capacities and thus aromatic structure may not be an essential criteria to exhibit hydrotropic behavior. [5] The strong dependence of solubility of an organic solute on hydrotrope concentration has been used in several applications: drug solubilization, detergent formulations, household applications and technological applications for enhancing rates of reactions and separations. [6–19] Several reviews have appeared for the mechanism of hydrotropy and applications of hydrotropes in recent years. [2,20,21] Since solute recovery can be done by simple dilution by water, the hydrotrope solutions provide an excellent method at ambient conditions for heat labile compounds although temperature has a significant effect on the hydrotropic solubilization. Solvent extraction is an alternative but the product still needs to be recovered from the organic solvent and the loss of solvent itself into hydrotropic solutions can be prohibitive. [17]

Since hydrotropic solubilization is a result of cooperative aggregation behavior driven by amphiphilic molecular structure of a hydrotrope, any change in its molecular structure can induce a change in the aggregation pattern and thus in the environment experienced by the dissolved solute. The self assembly of such molecules, as soft matter, is now a subject of intense research in different laboratories. [2,20] To explore an alternate method for a better recovery, we explore sodium cinnamate (Na-CIN) as a photoswitchable hydrotrope. Licht and Wiener [22] in 1950 were the first to investigate Na-CIN as a hydrotrope, but to the best of our knowledge there has been no report in the literature on influence of light on its hydrotropic behavior.

The *cis–trans* isomerization of olefinic compounds under ultraviolet irradiation is a well known phenomenon. [23]. Due to the isomerization taking place across the double bond, the equilibrium position of hydrophilic and hydrophobic centers in an aggregate can get disturbed due to the change in the aggregation pattern. These changes eventually can lead to modification of the hydrotropic solubilization of a solute. We, therefore, looked at the possibility of using Na-CIN as a hydrotrope which can show structural changes as a result of exposure to either visible or ultraviolet electromagnetic radiation. We believe that such a photo-induced reversible solubilization can have direct application in drug formulations and site directed drug delivery.

2. Materials and methods

2.1. Materials

Cinnamic acid (AR grade) was procured from Molychem India Ltd, Mumbai. The sodium salt of cinnamic acid was prepared by neutralizing cinnamic acid with sodium hydroxide in stoichiometric quantity. Benzocaine was obtained as gift sample from Mesha Pharma Ltd, Mumbai. All other solutes were of analytical grade and were sourced from S.D fine chemicals (I) Ltd.

Dried roots of *Coleus forskholii* were obtained from Godavari Biorefineries Ltd, Mumbai, India, while turmeric powder was procured from

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local market and used as such for extraction studies. The extraction methods using hydrotrope solutions are described in previous communications. [13–17].

2.2. Analytical methods

Cis and *trans* isomers of cinnamic acid were characterized by high performance liquid chromatography (HPLC) using 5 μm Hypersil C-18 column of length 250 mm, equilibrated with a methanol–water (60:40) mixture containing 0.1% acetic acid as the mobile phase. The column was mounted on a JASCO PU-2080 plus HPLC Chromatograph equipped with a 20 μL loop injector and a photodiode array detector (MD-2010).

The LCMS analysis was performed on Finnigan LCQ Advantage Max (LCQ Adv max, LCQAD 30000, Thermoelectron Corporation) using a Hypersil C18 column which was equilibrated with the mobile phase as given above at a flow rate of 0.5 cm^3/min followed by MS detection on an electron spray ionization source. Pure and dry nitrogen was used as a sheath gas or nebulizer gas with flow rate of 40 cm^3/min and auxiliary nitrogen flow rate was maintained at 15 cm^3/min. The capillary temperature was maintained at 275 °C with the voltage at 13 V and ion spray voltage at −5 kV.

2.3. Surface tension measurements

The surface tension of aqueous sodium cinnamate (Na-CIN) solutions was measured using a semi-automatic Fischer surface tensiometer (Model-21) by the Du Nouy ring method. The instrument was calibrated with distilled water at 25 °C. The aqueous hydrotrope solutions were prepared in distilled water.

2.4. Cis–trans isomerization of Na-CIN

An aqueous solution of *trans*-Na-CIN (20 cm^3) was placed in a 25 cm^3 quartz beaker (ID: 3 cm) and irradiated with ultraviolet radiation of long wavelength range (>254 nm) in a dark chamber. The kinetics of the isomerization reaction was studied by analysis of samples taken at specified intervals of time using HPLC.

2.5. Solubilization in Na-CIN solutions

The solubility of cinnamic acid, curcumin, thymol and benzocaine was measured by equilibrating Na-CIN solutions of different concentrations ranging from 0.2 to 1.0 mol/dm^3 with an excess amount of the solute in a cylindrical stirred glass vessel of volume 100 cm^3, in a constant temperature water bath. After a typical equilibration time of 2 h, the suspension was allowed to settle for 10 min. A glass pipette with its tip protected by a micro filter was used to withdraw a clear sample from the upper portion of the solution. The solute was back extracted from the aqueous sample (1 cm^3) into chloroform (3 cm^3). The extraction was done twice to ensure complete extraction of the solute. A third step of extraction with chloroform did not yield any further significant solute from the aqueous phase. The combined chloroform extract was then evaporated to recover the solute which was then dissolved in methanol for HPLC analysis.

2.6. Recovery of solute under UV irradiation

Na-CIN solution (1.0 mol/dm^3), saturated with a solute, was taken in a quartz beaker (length: 6 cm, diameter: 5 cm) and placed in a UV chamber having a long wavelength range (>254 nm) ultraviolet lamp. The solution was subjected to UV irradiation for 18 h. The precipitated solute was recovered by centrifugation and dried in oven at 60 º C for 2 h and then analyzed by HPLC.

2.7. Hydrotropic extraction and recovery of active components from natural products

Extraction of forskolin and curcumin from *forskholii coleus* and *curcuma longa* (turmeric) was studied kinetically in a fully baffled cylindrical glass vessel of capacity 250 cm^3 equipped with a four-bladed flat blade turbine impeller (2 cm ID). The pulverized roots of either *Coleus forskholii* (0.8–1.0 mm) or turmeric powder were suspended in 1 mol/dm^3 Na-CIN solution with 10% (w/w) solid loading and agitated vigorously at 1200 rpm at 30 °C for 2 h. Samples were withdrawn from the solution using a micro-filter fitted pipette at definite time intervals for the analysis. The extracted material was recovered from the respective Na-CIN solution using ultraviolet irradiation as described above without dilution.

3. Results and discussion

3.1. Characterization of Na-CIN for surface activity

Fig. 1 shows surface tension of *trans* Na-CIN solutions decreasing with increasing concentration of the hydrotrope and with an apparent break at 0.45 mol/dm^3. This concentration can be treated as MHC of Na-CIN beyond which the surface tension of the solutions remains constant at 32 dyn/cm. The amphiphilicity is considered as a prerequisite for a molecule to function as a hydrotrope. [1,3]. The amphiphilic nature and consequently the surface activity of Na-CIN are evident from its molecular structure. The ability of a hydrotrope to increase the solubility of organics in water is often better when the hydrotrope concentration is sufficient to induce the formation of associated structures. The self-association becomes prominent near MHC and is often indicated by abrupt changes in the solution properties such as surface tension or solubility. [3]. Since the effect of a surface active agent on an interfacial phenomenon is a function of its concentration, the effectiveness of any surface active agent in reducing interfacial tension depends on the maximum concentration that it can attain at the interface.

Surface tension curve for *cis*-Na-CIN could not be obtained due to non-availability of pure *cis*-isomer. However, surface tension of 1 mol/dm^3 Na-CIN solution at a photo-equilibrium condition containing 12% of the cis-isomer is 46 dyn/cm. This increase in the surface tension has to be because of the presence of *cis*-isomer in the solution and it clearly suggests the change in the surface properties which can be greatly exploited for easy recovery of the solute.

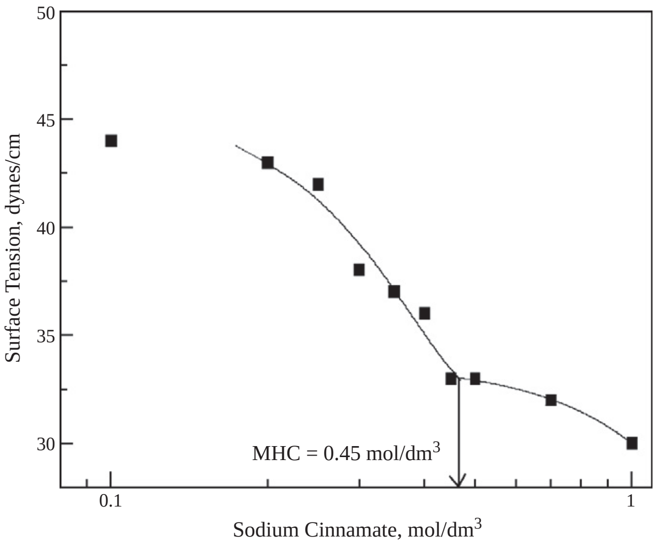

Fig. 1. Effect of concentration on the surface tension of aqueous sodium cinnamate solution.