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Thermodynamic evidence for nano-heterogeneity in solutions of the macrocycle *C*-butylresorcin[4]arene in non-aqueous solvents

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ABSTRACT

Partial molar volumes and isentropic compressibilities of the macrocyclic calixarene *C*-butylresorcin[4]arene have been determined as functions of solute concentration and temperature in five non-aqueous solvents of widely differing character: ethanol, 1-propanol, acetonitrile, *N,N*-dimethylformamide and dimethylsulfoxide. Both thermodynamic parameters indicated the presence of solute aggregation in all of the studied solvents. Detailed analysis of the data implied that the aggregates formed contained significant amounts of solvent, suggesting that the solutions were nano-heterogeneous rather than conventional micellar. Differences among the solvents were consistent with their hydrogen-bond donor and acceptor properties.

1. Introduction

The occurrence of micelles (or, more generally, nano-heterogeneity) is usually considered to be a special feature of aqueous solutions, arising from the characteristic properties of water as a solvent, reflecting its unique structure and hydrogen-bonding capabilities. However, evidence exists for similar phenomena occurring in purely non-aqueous systems [1–4]. The present paper provides evidence for the formation of aggregates of the *C*-butylresorcin[4]arene calixarene: 2,8,14,20-tetrabutyl-4,6,10,12,16,18,22,24-octahydroxo-resorcin[4]arene (CBRA, Fig. 1), using simple thermodynamic measurements, in a selection of protic and aprotic non-aqueous solvents of widely differing character.

Resorcin[4]arenes and their derivatives are versatile macrocycles with many actual or prospective applications in chemistry and biology [5–6]. For example, they have been used for corrosion control [7] and in catalytic studies [8–9]. In biological systems, the binding of a resorcin[4]arene with bovine serum albumin has been used to investigate antibody interactions [10]. Their uses in drug delivery and drug targeting [7,11] have also been examined.

Because of their chemical diversity and structural variety the *C*-alkylresorcin[4]arenes are useful solutes for probing the behaviour of supramolecular systems in solution. Previous studies [12–13] reported solution enthalpies of some *C*-alkylresorcin[4]arenes in alcohols. In this paper, apparent molar volumes and isentropic compressibilities of CBRA in five solvents have been determined from density and speed of sound measurements, respectively, at temperatures from 278.15 to 308.15 K.

2. Experimental

2.1. Chemicals

CBRA was synthesized in acid media from resorcinol and pentanal using literature procedures [14–15]. The compound so obtained was recrystallized from 1:1 (v/v) ethanol-water, dried under reduced pressure of ~5 kPa at 360 K for 24 h, and then stored in dark flasks in a desiccator over freshly activated silica gel. The final purity of the compound was determined by HPLC to be >0.99 mass fraction. Thermogravimetric analysis, TGA, of the purified CBRA showed that the compound was not solvated (Figure S1).

The solvents ethanol (EtOH), *n*-propanol (1-PrOH), acetonitrile (ACN), *N,N*-dimethylformamide (DMF) and dimethylsulfoxide (DMSO) were purchased from Alfa Aesar, USA (all >0.99 in mass fraction) and were employed without further purification; EtOH and DMSO were stored under dry nitrogen and dried using freshly

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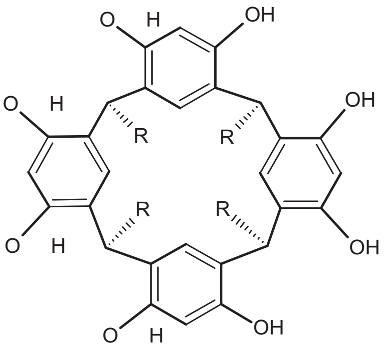

Fig. 1. Chemical structure of C-butylresorcin[4]arene, CBRA; R = $CH_2CH_2CH_2CH_3$.

activated 3 Å molecular sieve pellets. Solvent densities were checked periodically and were found to be reproducible to about $\pm 5 \times 10^{-6}$ g·cm^{-3}). Other details of the chemicals used are listed in Table 1.

2.2. Apparatus and procedures

Densities (ρ) of, and speeds of sound (υ) in, the solvents and solutions were measured using an Anton Paar (Austria) DSA 5000 M instrument. The experimental reproducibility was better than $\pm 1\times10^{-5}$ g·cm^{-3} and ±0.1 m·s^{-1}, respectively, at all temperatures. All solutions were prepared by mass, without buoyancy correction, using an Ohaus (Germany) Analytical Plus balance with a precision of 0.01 mg. Thermograms were obtained with a Netzsch (Germany) TG-DTA/DSC STA 409, at temperatures from (288 to 820) K. The applied scan rate was 10 K·min^{-1} and nitrogen at 60 mL·min^{-1} was used as the purge gas.

3. Results

3.1. Density of and speed of sound in the neat solvents

The present experimental densities and speeds of sound for the chosen solvents at $278.15 \le T/\text{K} \le 308.15$ are listed in Table S1 in the Supporting Information. For DMSO the measurements were restricted to $T \ge 293.15$ K, consistent with its melting point. Table S1 also lists for these solvents the corresponding literature values, which are in good agreement (typically better than ±0.1% relative) with the present results.

3.2. Apparent molar volumes and isentropic compressibilities

The densities of CBRA solutions in EtOH, 1-PrOH, ACN, DMF and DMSO at the target temperatures are listed as a function of solute concentration in Tables S2 to S8 in the Supporting Information. The apparent molar volumes, V_ϕ, were calculated at each concentration and temperature using the usual equation:

$$V_\phi = \frac{M_2}{\rho} - \frac{1000(\rho-\rho_0)}{m\rho\rho_0} \tag{1}$$

where m is the molal concentration (mol·kg^{-1}) of the CBRA, M_2 = 712.9 g·mol^{-1} is its molar mass (the molecular formula is $C_{44}H_{56}O_8$) and the subscript $_0$ denotes a neat solvent quantity. The V_ϕ values so obtained are also given in Tables S2 to S8, along with their uncertainties.

The speeds of sound υ, in the same solutions are listed in Tables S9 to S15 in the Supporting Information. The isentropic compressibilities of the solvents, $\kappa_{S,0}$, and of the solutions, κ_S, were calculated respectively as:

$$\kappa_{S,0} = \frac{1}{\upsilon_0^2\rho_0} \tag{2}$$

$$\kappa_S = \frac{1}{\upsilon^2\rho} \tag{3}$$

In addition, the apparent molar isentropic compressibilities of the solutions $\kappa_{S,\varphi}$ were calculated as:

$$\kappa_{S,\phi} = \frac{M_2\kappa_S}{\rho} + \frac{(\kappa_S\rho_0 - \kappa_{S,0}\rho)}{m\rho\rho_0} \tag{4}$$

The values of $\kappa_{S,\phi}$ with their respective uncertainties are also included in Tables S9 to S15.

3.3. Aggregation concentration, m_{agg}

Plots of V_ϕ and $\kappa_{S,\phi}$ against solute concentration exhibit two more-or-less linear branches with significantly differing slopes for all of the studied systems. Figs. 2 and 3 illustrate this phenomenon for CBRA in ACN. This type of behaviour is reminiscent of that observed for long chain alkyltrimethylammonium salts in water, which has been attributed to micellization of the strongly hydrophobic RMe_3N^+ cations [16]. As CBRA is not expected to be particularly hydrophobic and, as noted in the Introduction, hydrophobic behaviour is quintessentially a phenomenon of aqueous solutions, it is reasonable to assume that the present behaviour is related to some type of aggregation (nano-heterogeneity) in these mixtures akin to, but not necessarily identical with, micelle formation (see later). The concentration at which this aggregation occurs, m_{agg}, was determined using Phillips' criteria [17–18] based on the solute concentration at which there is an abrupt change in some solution property, Y, i.e., where $\partial^3 Y/\partial m^3 = 0$. The numerical Y (m) data ($Y = \upsilon$, V_ϕ and $\kappa_{S,\phi}$) were analyzed by means of spline regression using the TableCurve V5.01 software. Values of m_{agg} (Table 2) were found to be virtually independent of the measured property and so were averaged for all three properties at each temperature. These averaged values were also independent of temperature.

Table 1
Specification of chemical samples.

Compounds	Source	CAS No.	Purification method	Mass fraction purity	Analysis method
CBRA*	Synthesis		Precipitation and vacuum dried	>0.99	HPLC
EtOH	Merck	64-17-5	Dried with 3 Å sieves	0.999	
1-PrOH	Alfa Aesar	71-23-8	None	>0.99	
DMF	Alfa Aesar	68-12-2	None	>0.997	
DMSO	Alfa Aesar	67-68-5	Dried with 3 Å sieves	>0.99	
ACN	J.T.Baker	75-05-8	None	0.999	

*CBRA samples were powders.