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LETTERS

A Volumetric Study of Molecular Inclusion by α-Cyclodextrin

Neil S. Isaacs[a] and David J. Young[b]*

[a]Department of Chemistry, University of Reading, PO Box 224, Reading, RG6 6AD, U.K.

[b]School of Science, Griffith University, Nathan 4111, Australia. Email: D.Young@sct.gu.edu.au

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Abstract: The reaction volume ($\Delta \bar{V}_{c \rightarrow 0}$) associated with inclusion of 3-nitrophenol by α-cyclodextrin was determined by densitometry to be -9 $cm^3\ mol^{-1}$ while the corresponding value for encapsulation of methyl orange by two molecules of α-cyclodextrin is +27 $cm^3\ mol^{-1}$. These volume changes can be interpreted in terms of displacement of solvent from the cavity of α-cyclodextrin and/or changes in solvation of the "guest" molecule.

Keywords: Cyclodextrins, Inclusion.

Introduction: The association of two or more chemical entities by non-covalent, intermolecular interactions is an area of intense research interest.[1] Although a wide – ranging and diverse field, the different facets of this discipline share the common need for physical techniques for characterising the stoichiometry, structure, stability and binding properties of large, and often dynamic, "host – guest" complexes in solution. Commonly employed techniques include optical absorption, fluorescence, NMR spectroscopy, conductivity and circular dichroism.[2] Each of these are very useful, but none is generally applicable to all systems. A more general method is the measurement of heats of formation by microcalorimetry[3] but this technique is restricted to relatively few laboratories. The objective of this research was to investigate a general and experimentally simple method for probing "host - guest" interactions in solution, making use of a fundamental property of all molecules, the volume of space they occupy in solution ("partial molar volume", $\bar{V}$). There have been relatively few volumetric studies of molecular inclusion, and some scepticism expressed about the interpretation of results from these studies.[4] More recent investigations have gone some way to support the validity of this approach.[5] We have reported[6] a volumetric study of the molecular complexation of C_{60} with *p*-benzylcalix[5]arene in toluene. Formation of this "ball and cup" supramolecular assembly was associated with a partial molar volume change ($\Delta \bar{V}_{c \rightarrow 0}$) of +195 $cm^3\ mol^{-1}$ which is consistent with the displacement of two toluene molecules from the cavity of the calixarene, an interpretation consistent with molecular modelling. Volume change may be a useful technique for observing host – guest interactions in solution, but further investigations are required to engender confidence in the interpretation of results.[4] To this end we now report

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the results of a volumetric study of the formation of two, very well known and well characterised supramolecular assemblies; (i) the 1 : 1 complex of α-cyclodextrin and 3-nitrophenol[7] and (ii) the 2 : 1 complex of α-cyclodextrin and methyl orange[8].

Experimental: α-Cyclodextrin hydrate (**1**) was dried for 3 h at 105 °C under dynamic vacuum (1 mm Hg)[9]. 3-Nitrophenol (**2**) was used as supplied and aqueous solutions of the 1 : 1 complex (**3**) were prepared from equimolar quantities of **1** and **2** in doubly deionised water. Methyl orange (**4**) was recrystallised from water and dried under vacuum. The 2 : 1 complex (**5**) was prepared *in situ* from **1** and **4**. Density measurements of degassed, dilute solutions of **1** - **5** were performed in doubly deionised water as solvent using a Paar high precision, vibrating tube density meter at 29.65 ± 0.05 °C. Between 2 and 5 density measurements were made at 4 - 5 concentrations over the range 2.00×10^{-3} - 8.44×10^{-2} M and extrapolated to c = 0 (Figure 1). Density values were converted to partial molar volumes as previously described[10]. The standard deviation in these values at each concentration was less than 2% and typically 1%. The partial molar volumes of complexes **3** and **5** were calculated assuming negligible dissociation[7a, 8a].

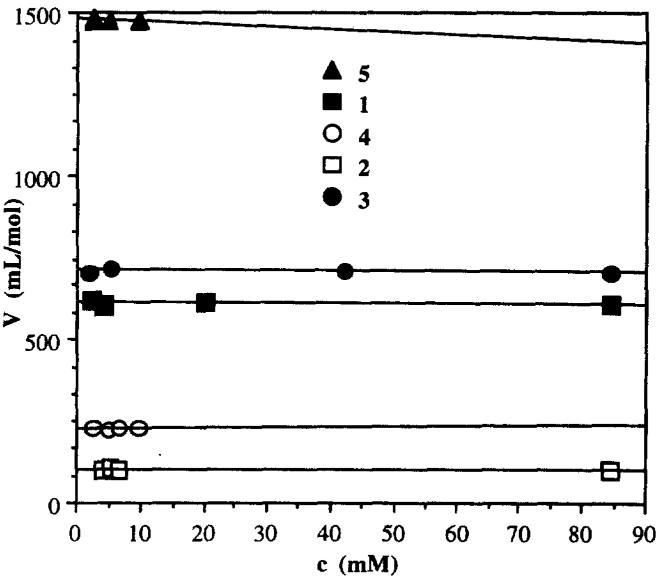
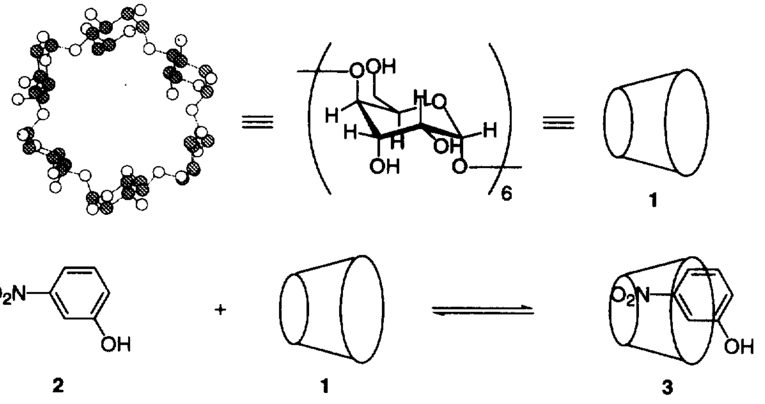


Figure 1: Partial molar volume ($\bar{V}$) versus concentration for compounds **1** to **5**.

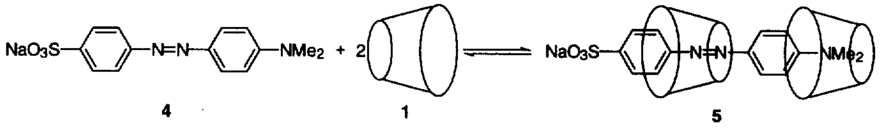
Results and Discussion: The partial molar volumes of **1**, **2** and **3** are given in Scheme 1. The reaction volume ($\Delta \bar{V}_{c\rightarrow 0}$) on complex formation is calculated to be -9 cm^3 mol^{-1}. This is a relatively small difference, but can be interpreted in terms of displacement of solvent from the α-cyclodextrin cavity. The partial molar volume of water at this temperature is 18.1 cm^3 mol^{-1} and the cavity of **1** has been estimated to hold between four[5] and six[11] water molecules in aqueous solution. The value of -9 cm^3 mol^{-1} is consistent with displacement of 5.4 water molecules by the substrate which agrees well with these estimates.



$\bar{V}_{c\rightarrow 0}$ = 106 ± 2 cm^3 mol^{-1} $\bar{V}_{c\rightarrow 0}$ = 613 ± 5 cm^3 mol^{-1} $\bar{V}_{c\rightarrow 0}$ = 710 ± 5 cm^3 mol^{-1}

Scheme 1

By comparison, the complexation of methyl orange (**4**) with two equivalents of **1** (Scheme 2) resulted in a positive volume change; $\Delta \bar{V}_{c\rightarrow 0}$ = +27 cm^3 mol^{-1}. A simple displacement of ten or twelve water molecules from the cavities of two molecules of **1** would result is a volume change of $\Delta \bar{V}_{c\rightarrow 0}$ = -48 or -12 cm^3 mol^{-1}, respectively. Rather, this relatively large, positive value of $\Delta \bar{V}_{c\rightarrow 0}$ can be interpreted in terms of a loss of solvation from the ionic sodium sulfonate group on complexation. The replacement of water solvation by hydrogen bonding between the sulfonato group and primary hydroxyl groups on **1** is observed in the crystal structure of **5**[8b].



$\bar{V}_{c\rightarrow 0}$ = 229 ± 3 cm^3 mol^{-1} $\bar{V}_{c\rightarrow 0}$ = 1482 ± 4 cm^3 mol^{-1}

Scheme 2

The volume changes associated with these host - guest assemblies of α-cyclodextrin are small but, interestingly, are of opposite sign, depending on the nature of the substrate. A larger difference, as was observed for calixarene inclusion of C60[6], could possibly be exploited for determining equilibrium constants. Nevertheless, even small volume changes can be observed by high precision densitometry and provide an unambiguous indication of an interaction between molecules in solution. These volume changes can be interpreted in terms of changes in the solvation of the host or guest.

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References:

1. For recent issues devoted to these topics see *Chem. Rev.* **1997**, *97*, 1231 – 1734 and *Chem. Rev.* **1998**, *98*, 1741 – 2076.
2. Wenz, G. *Angew. Chem., Int. Ed. Engl.,* **1994**, *33*, 803.
3. Bastos, M.; Briggner, L. E.; Shehatta, I.; Wadsoe, I. *J. Chem. Thermodyn.* **1990**, *22*, 1181.
4. Connors, K. A. *Chem. Rev.* **1997**, *97*, 1325.
5. Takaizumi, K.; Wakabayashi, T.; Ogino, H. *J. Solution Chem.* **1996**, *25*, 947.
6. Isaacs, N. S.; Nichols, P. J.; Raston, C. L.; Sandoval, C. A.; Young D. J. *J. Chem. Soc., Chem. Commun.* 1997, 1839.
7. (a) Harata, K. *Bull. Chem. Soc. Jpn* **1978**, *51*, 2737; (b) Harata, K.; Uedaira, H.; Tanaka J. *Bull. Chem. Soc. Jpn* **1978**, *51*, 1627.
8. (a) Cramer, F.; Saenger, W.; Spatz, H. -Ch. *J. Am. Chem. Soc.* **1967**, *89*, 14; (b) Harata, K. *Bull. Chem. Soc. Jpn* **1976**, *49*, 1493.
9. Connors, K. A.; Pendergast, D. D. *J. Am. Chem. Soc.* **1984**, *106*, 7607.
10. Isaacs, N. S. "Liquid Phase High Pressure Chemistry", Wiley, Chichester, **1981**, Ch 4.
11. Bergeron, R. J.; Meeley M. P. *Bioorg. Chem.* 1976, **5**, 197.