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Luigir. Nassimbeni[a]
[a] Department of Chemistry, University of Cape Town, Rondebosch, South Africa

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Useful Techniques in Host-Guest Chemistry

LUIGI R. NASSIMBENI*

Department of Chemistry, University of Cape Town, Rondebosch, 7701, South Africa

While crystal structure analysis remains the most powerful analytical tool for the elucidation of host-guest structures, a greater understanding of the behaviour of these compounds is achieved by studying their thermal stabilities and kinetics of formation and desolvation.

Various analytical techniques for the study of inclusion compounds are outlined and evaluated.

Keywords: Host-guest compounds, structure, thermodynamics, kinetics

The process of molecular recognition lies at the core of supramolecular chemistry, a subject of increasing interest and relevance in recent years. This is clearly demonstrated by the appearance of specialised journals in this field: the *Journal of Inclusion Phenomena* (1983), *Supramolecular Chemistry* (1992), *Crystal Engineering* (1998), and the publication of *Supramolecular Chemistry,* Vols 1–11 (1996) [1–4].

Host-guest or inclusion compounds have been classified by Weber according to their molecular interactions as well as their topologies [5]. In this paper we briefly review some useful analytical techniques that may be employed to measure various physical and chemical properties of host-guest systems, in order to understand these in terms of their molecular structures and intermolecular interactions.

These techniques may broadly be divided into three main categories:

a) Structure Analysis
b) Thermodynamics
c) Kinetics

STRUCTURE

Single crystal x-ray diffraction remains the most important technique for determining the structure of inclusion compounds. Since inclusion compounds which contain volatile guests are often unstable, the use of diffractometers equipped with CCD detectors has become popular. These allow one to capture intensity data relatively fast (typically 5000 reflections may be captured in 60 minutes) and thus minimise the problems associated with crystal decay. For very small crystals, or crystals which scatter poorly because of structural complexity or disorder, synchrotron radiation is particularly useful but is generally less accessible [6].

A well defined crystal structure analysis allows one to measure the intramolecular and intermolecular parameters of interest. This is usually the starting point for molecular mechanics calculations, and in particular for the estima-

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* Proofs To: L R Nassimbeni, Department of Chemistry, University of Cape Town, Rondebosch 7701, South Afric. FAX: 27–21–685 4580, Email: xrayluig@psipsy.uct.ac.za

tion of lattice enthalpies. Hydrogen bonding remains the most important inter-molecular interaction, and a recent book by Jeffrey [7] reviews this important subject and has an extensive bibliography. Of particular interest to host-guest systems are the interactions with C-H as the donor group, which have received considerable attention. Nishio [8] has carried out a study of the CH... π interaction which occurs in organic compounds. Steiner, [9], has discussed the nature of short C-H...π contacts and related these to spectroscopic and quantum mechanical results. C-H...O hydrogen bonds have been characterised from accurate results obtained from neutron data [10–14], and their patterns have been studied by Desiraju in terms of molecular recognition and the formation of supramolecular assemblies [15–17]. More generally, the whole question of supramolecular synthons, pattern recognition and their applications in the design of targeted structures has recently been reviewed [18].

THERMODYNAMICS

Thermal Gravimetry (TG) and Differential Scanning Calorimetry (DSC) are the most accessible tools for the quantitative study of the thermal stability of inclusion compounds and have been previously reviewed [19]. TG is a suitable method of obtaining accurate host:guest ratios of inclusion compounds when the guest is relatively volatile. We feel this is important because inclusion compounds are often non-stoichiometric. Crystal structure analysis is not a suitable tool for establishing the host:guest ratio because the site occupancies and temperature factors are correlated in the process of least-squares refinement.

DSC measurements yield the onset temperatures of the guest-release reaction, T_{on}, and their associated enthalpy change, ΔH. Such measurements should be treated with caution, and accurate values are only achieved if care is taken with regard to calibration of the DSC, flow rate of the purging gas, heating rate and the particle size distribution of the sample. The latter is crucial, but is sometimes difficult to achieve because the inclusion compound may be labile and not lend itself to crushing and sieving. In our laboratory we have overcome this difficulty by preparing samples of the host-guest compound under conditions of fast-stirring, which yields powders with small particles with a narrow size distribution. We note however that crystals grown under dissimilar conditions may yield inclusion compounds with different host:guest ratios, with differing structures or different polymorphs of the same structure. We therefore monitor the structure by x-ray powder diffraction to ensure consistency.

Figure 1 shows idealised curves of an inclusion compound $H{\cdot}A_nB_m$ which decomposes stepwise to yield an intermediate $H{\cdot}A_n$ and the uncomplexed, non-porous phase of the host compound H (apohost). The areas under the first two endotherms yield the enthalpies of the guest-release reactions ΔH_1 and ΔH_2, which are generally different, while the third endotherm yields the enthalpy of the host melting. The precision of the weight losses are generally ± 1% in successive experiments, giving accurate host:guest ratios of the compound under study.

When an inclusion compound decomposes, the guest release reaction is made up of two components: the desorption of the guest and the rearrangement of the "empty cage", or β_o, structure of the host to its non-porous α – phase [20]. The DSC measures the sum of these, generally with a precision of about 10%.

In order to obtain accurate, reproducible results for the desorption step, we have devised an apparatus which measures the vapour pressure of a volatile guest over a large temperature range. The apparatus is a simplified version of the one we used previously to measure the vapour pressure of bis (9,9′- dihydroxy – 9,9′-difluorene) · 0.5 EtOH over the temperature range 30°C – 80°C [21,22]. Schematic results for

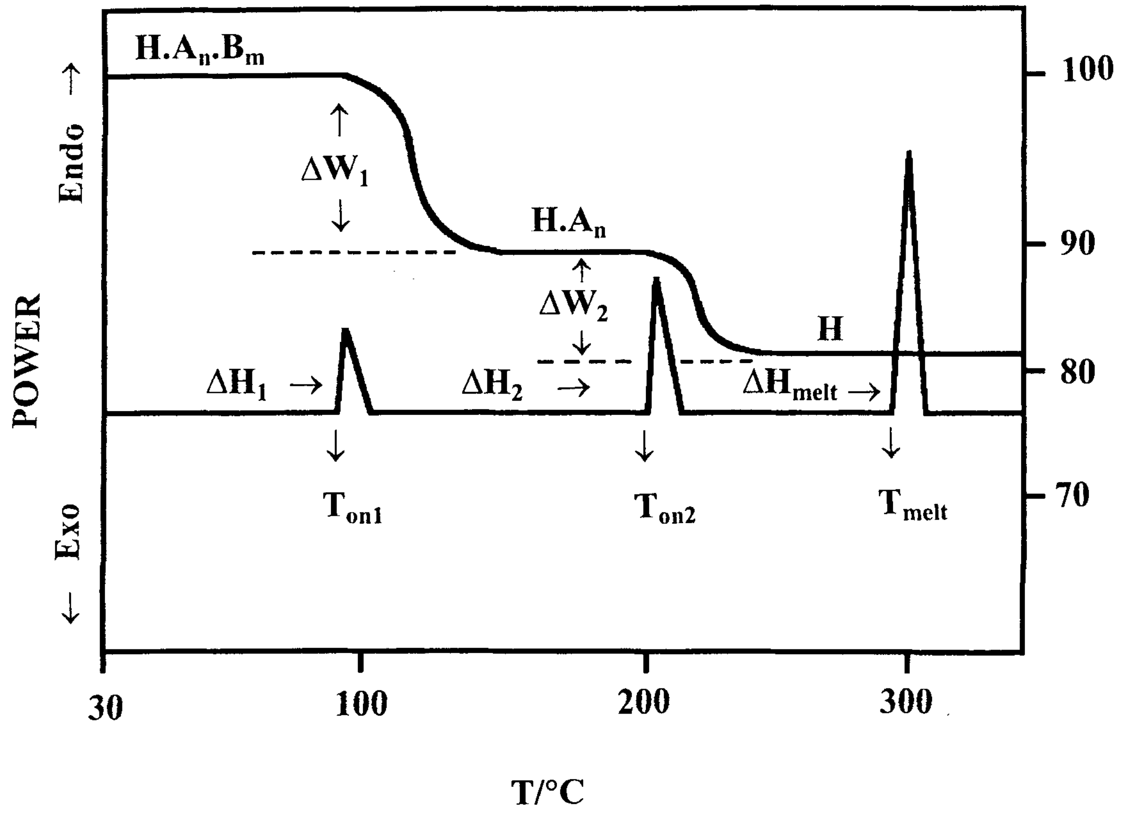

FIGURE 1 TG and DSC curves of an inclusion compound with host H and mixed guests A and B

such experiments are shown in Figure 2. The apparatus is fully automated and yields curves of P vs T. The semi-logarithmic plot of lnP vs 1/T has a slope of -ΔH/R and gives the enthalpy change to a precision of approximately 2%.

DSC methods have wide applicability, and have been used to measure the phase diagrams of binary systems, establishing eutectic points and the composition and melting temperatures of addition compounds [23]. Of particular interest to the pharmaceutical industry is the work by Giron [24] which discusses the thermal analysis and calorimetric methods used for the characterisation of polymorphs and solvates. This subject has also been recently reviewed by Caira [25]. Schröpfer [26], has described a thermal sensor which makes use of a thermopile chip that detects minute quantities of guest vapour and has shown that different host-guest systems exhibit significant differences in sensitivity of detection.

Several papers have appeared in which the authors use a combination of methodologies to study the thermodynamic behaviour in relation to the structure of inclusion compounds. Thus, Germain et al [27] have studied the hydration of β – cyclodextrin and determined the heats of solvation in water using an isoperibolic calorimeter and a MacBain thermobalance to follow the hydration as a function of water pressure. Ripmeester et al [28] have used a combination of DSC and solid state NMR measurements to investigate disorder problems in a calixarene inclusion compound. Hatta et al. [29] have

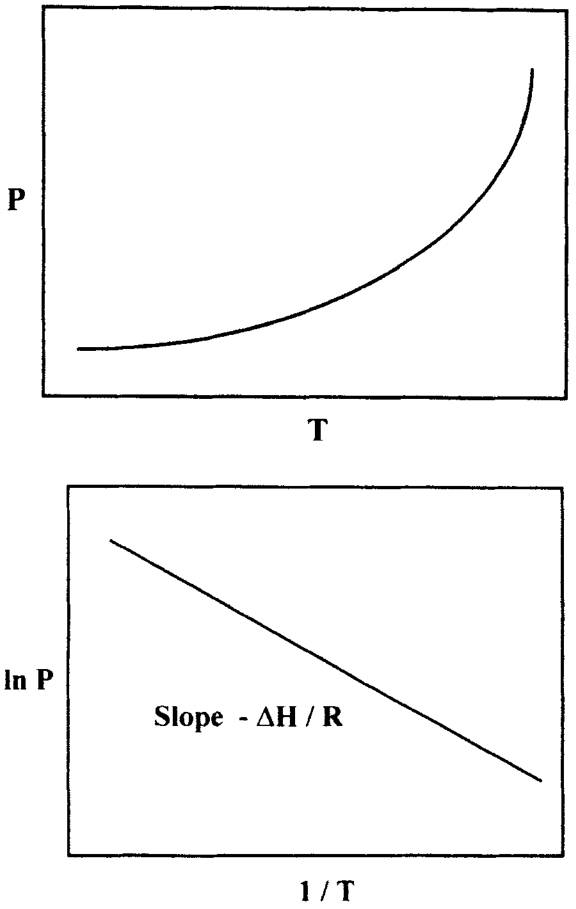

FIGURE 2 (a) Schematic curve of Pressure vs Temperature (b) Semilogarithmic plot

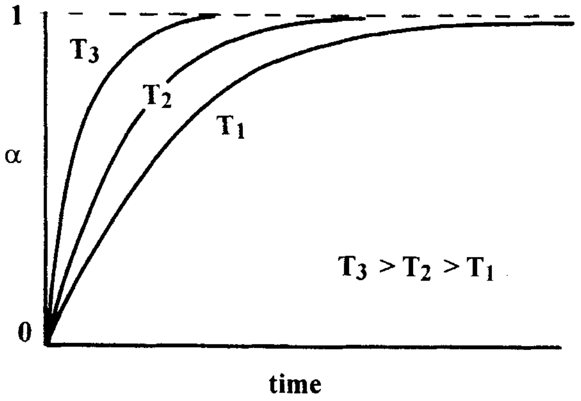

FIGURE 3 Curves of extent of reaction, α, versus time for desolvation

developed an apparatus for the simultaneous measurement of x-ray diffraction patterns and DSC, which is suitable for the study of phase transitions. Matsuo and Yamamuro [30] have carried out heat capacity measurements with adiabatic calorimeters in order to understand the low temperature properties of various clathrates and monitor their phase transitions.

KINETICS

When the non-pourous (α-phase) of a host compound, H, is exposed to the vapour of a volatile guest, G, it may form a host-guest compound, the β phase, according to the equation:

$$H\ (s, \alpha) + nG\ (g) \underset{kr}{\overset{k_f}{\rightleftharpoons}} H \cdot Gn\ (s, \beta)$$

The kinetics of the forward reaction, enclathration, is governed by the rate constant k_f, and is different from the reverse reaction, desolvation, which has the rate constant k_r.

In order to measure the velocity of the forward reaction we have constructed an automated suspension balance which allows measurement of mass change with time under controlled conditions of pressure and temperature [31]. This allowed us to measure the kinetics of enclathration of acetone vapour by the host *trans* – 9,10 – dihydroxy – 9,10 – diphenyl – 9,10 – dihydroanthracene (DDDA). We noted that, in order for reaction to take place, a threshold vapour pressure, P_o, of the guest was required, and that, for a given vapour pressure, the rate of reaction decreases with increasing temperature [32]. The balance requires a minimum of 400mg of host compound in order to yield results of acceptable precision. When such quantities of host compound are not available, apparatus of much greater sensitivity is required, and we therefore constructed a Quartz Micro Balance (QMB) suitable for this purpose, which requires less than

1mg of host compound to yield reproducible results [33].

The kinetics of desolvation is easier to monitor, and can be carried out with the suspension balance or QMB discussed above, as well as with a commercial TG apparatus. The preferred method is that of the isothermal runs at various fixed temperatures, and the measured mass losses with time are converted to extent of reaction, α, vs t curves as shown in Figure 3.

Various models can then be fitted to the curves, which correspond to particular mechanisms of the desolvation reaction [34]. We have found that the most common of these are:

$\ln(1-\alpha) = kt$	First order	F1
$1-(1-\alpha)^{1/2} = kt$	Contracting area	R2
$1-(1-\alpha)^{1/3} = kt$	Contracting volume	R3

We have also noted that the desorption of some host-guest compounds is preceded by induction periods, followed by the onset of the main reaction. This gives rise to α – time curves of the type shown in Figure 4, with the induction periods becoming shorter with rising temperatures. An example of this form of kinetic decay is that exhibited by the desolvation of DDDA with cyclohexanone guest [35]. Activation energies for both the induction period and main reaction may be derived by application of the Arrhenius equation. The application of this equation to heterogeneous reactions is controversial, but Galway and Brown [36] have given a theoretical justification for its use.

Non-isothermal methods, which are based on weight loss vs temperature at several heating rates, are more rapid than isothermal methods, but are generally less accurate. This is a somewhat controversial subject with an extensive literature, and the reader is directed to an excellent paper by Brown [37] entitled "Steps in a Minefield. Some kinetic aspects of thermal analysis", which reviews the field.

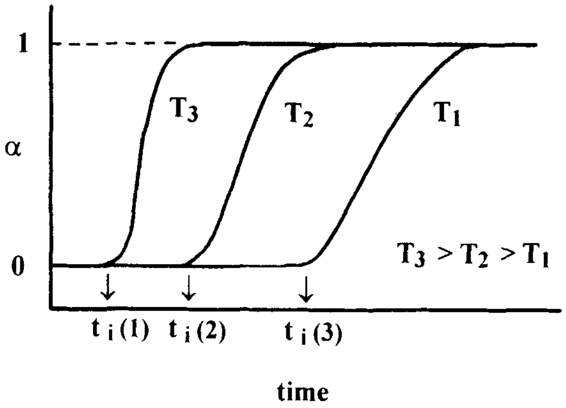

FIGURE 4 Desolvation α – time curves with periods of induction followed by decomposition

SELECTIVE ENCLATHRATION

One of the important applications of host-guest chemistry is the separation of close isomers by enclathration. This involves the choice of a suitable host compound which, when exposed to a mixture of guests, combines selectively with a particular guest to form a crystalline inclusion compound. The latter is filtered and the guest released by gentle warming, enabling the host to be recycled. The selectivity of the process depends on the efficiency of the molecular recognition between host and guest, and it may take several cycles to achieve a selectivity of > 99%.

The procedure for the competition experiment between two guests A and B is to set up 11 vials with mixtures of the two guests varying their mole fraction from 0 to 1. Care is taken to keep the guests in excess and we use a host : total guest ratio of 1 : 20 in each vial. The inclusion compounds are allowed to crystallise, filtered and both the mother liquor and guest content of the crystals are analysed, typically by gas chromatography. The process can be extended to three guests, where the composition of the mixture may be represented on an equilateral triangle.

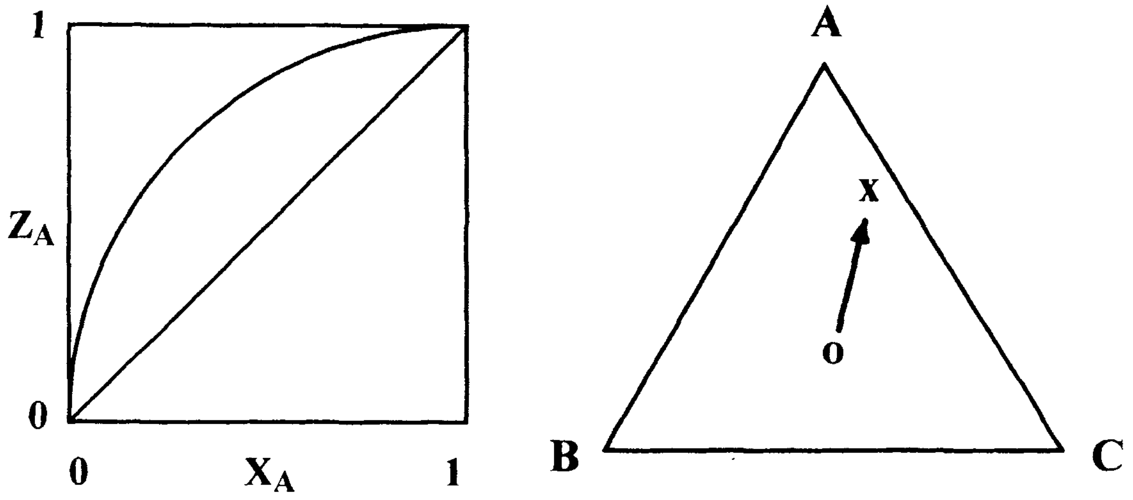

FIGURE 5 (a) Competition experiment for a two-guest system. X_A = mole fraction of guest A in starting solution. Z_A= mole fraction of guest A in the crystals. (b) Competition experiment for a three-guest system

Results are shown schematically in Figure 5a and 5b. For the two-guest competition, Figure 5a, the diagonal line represents a process which does not discriminate between A and B, while the points lying on the curve show that A is preferentially enclathrated. Figure 5b shows the result starting from an equimolar mixture of the three guests at O, resulting in a mixture at X showing strong enrichment of A after enclathration. Clearly in the latter case a proper strategy for sampling of the triangular space should be devised in order to obtain representative results.

We have analysed a number of systems in this way [38–40] and have related the selectivities to the lattice energies of the inclusion compounds.

An important aspect of the physical chemistry of host-guest systems relates to the measurement of the binding isotherms of guest vapour in solid hosts. These experiments must be carried out with great care in order to obtain meaningful results. Recently Aoyama et al. have published an excellent paper [41] which discusses the dynamics of lattice inclusion accompanied by a phase change. The study extended to using porous metalated hosts which have remarkable catalytic properties [42].

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