

Physicochemical Aspects of Host–Guest Compounds

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ABSTRACT

The macro properties of crystalline inclusion compounds depend on their structures. Their thermal stabilities are a function of the strength and the directionality of the various nonbonded interactions occurring in the host–guest assembly. Their lattice energies, as measured by the method of atom–atom potentials, correlate with the thermodynamics of the guest-release reactions and the selectivity that a given host displays for a particular guest. The kinetics of solid–host:vapor–guest reactions and of guest exchange are important in our understanding of catalytic processes. Crystal engineering, in which materials of predetermined properties may be synthesized, is still at the empirical stage.

Introduction

The field of inclusion phenomena, or host–guest chemistry, has grown dramatically in the last thirty years. As an example, the number of abstracts appearing in *Chemical Abstracts* under the term “clathrate” and “inclusion compound” was 60 in 1970, but has grown to 1025 in 2001. Most of this work has been directed at the synthesis of novel host compounds with specific properties and the elucidation of their structures. Several books and monographs are available, culminating in the authoritative eleven volume publication of *Comprehensive Supramolecular Chemistry*, which appeared in 1996.¹ Molecular recognition lies at the heart of inclusion chemistry, and for processes that occur in solution, the affinity of a host for a given guest depends on the intermolecular interactions which impinge on the host, guest, and solvent molecules under defined conditions of temperature, pressure, and concentration. These are in turn dependent on the shape, size, conformation, and surface charge distributions of the molecules making up the system. To what extent is this concept transferable to molecular and ionic solids? The answer lies in understanding the intricacies of the packing of the molecules in the solid state. The results of well defined crystal structures allow us to compute the strengths and directions of the noncovalent interactions which hold the structure together and will

ultimately help us predict the behavior of the solid under different thermodynamic conditions.

Braga² has outlined the importance of this subject and has listed a number of salient applications, which include solid-state reactivity, physical properties, polymorphism, and the construction of functional materials. The consequences of crystal symmetry and the packing of molecules is seminal to this topic, and Curtin and Paul³ have emphasized the importance of the polar axis in organic crystals and its implications in crystal growth, optical activity, and such effects as pyroelectricity, piezoelectricity, and triboluminescence. The synthesis of porous systems which can reversibly absorb and release guest molecules or act as solid-state reservoirs has received recent attention.^{4–7}

In this Account, we will discuss various macroproperties of inclusion compounds and relate them to their structures. We shall confine our analysis to small molecules in the solid state and will not deal with solid solutions, solid dispersions, and polymeric matrixes.

Classification

Host molecules may be broadly classified into two main types: (i) those that form molecular complexes by fitting convex guests into the concave cavity of the host (examples include cyclodextrins, cyclophanes, calixarenes, and various carcerands⁸) and (ii) those that form lattice inclusion compounds by packing in such a manner as to leave cavities, channels, or layers in the crystal structure so as to accommodate various guest molecules.⁹

While many of the compounds which act as hosts were discovered by chance, the last 20 years have witnessed the development of various strategies aimed at the synthesis of host molecules with specific properties, and Weber has reviewed the principles of directed host design.¹⁰ He has shown that a successful host molecule should be bulky and rigid and should preferably contain functional groups which can engage in specific host–guest interactions.

The intermolecular forces which impact on host–guest systems have been systematically reviewed.¹¹ They vary in strength from strong ionic interactions ($100\text{--}350\text{ kJ mol}^{-1}$), through hydrogen bonding, cation– π , and $\pi\text{--}\pi$ stacking, to weak van der Waals forces ($<5\text{ kJ mol}^{-1}$). Of these, hydrogen bonding is the most important, and a number of recent texts discuss various aspects of this subject.^{12,13} In a recent review entitled “Hydrogen Bridges in Crystal Engineering: Interactions without Borders”,¹⁴ Desiraju points to the great variety of hydrogen bonds observed in solids and notes the three extremes which occur: the covalent limit in $[\text{F}\cdots\text{H}\cdots\text{F}]^- \approx 167\text{ kJ mol}^{-1}$, the electrostatic limit in $\text{NH}_4^+ \cdots \text{Cl}^- \approx 60\text{ kJ mol}^{-1}$, and the van der Waals limit for weak forces $\approx 1\text{ kJ mol}^{-1}$. This allows the classification of hydrogen bonds into weak, strong and very strong. The directionality of hydrogen bonds is also important, and a number of studies describing the geometry of various hydrogen-bonding systems

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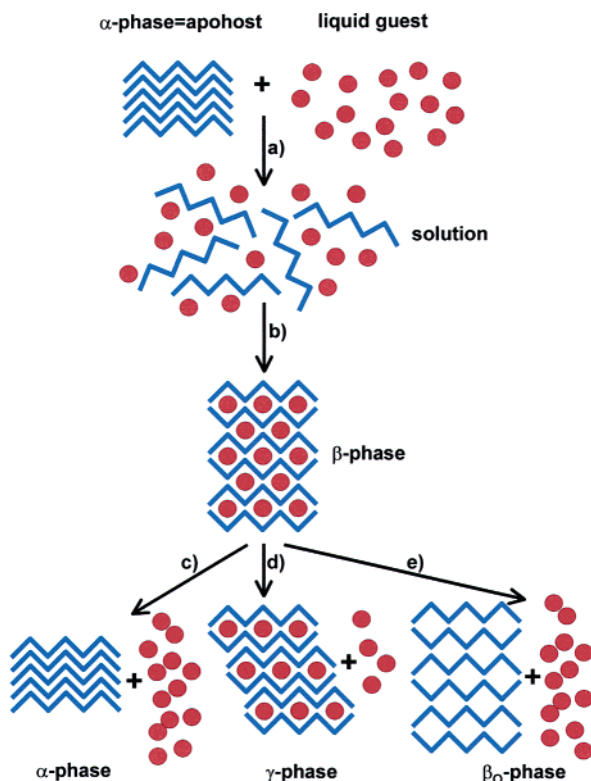
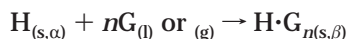


FIGURE 1. Schematics of the formation and decomposition of an inclusion compound.

have appeared.^{15–18} In this regard, Etter's contributions have particular significance, in that she has shown how hydrogen-bonding can be employed as a design element in organic solids^{19,20} and introduced the concept of graph-set analysis of hydrogen-bond patterns in organic crystals.^{21,22}

The formation of an inclusion compound may be generally formulated as



where α represents the nonporous phase of the pure host H or the apohost and β is the phase of the host–guest compound with guest:host ratio n .

The synthesis is generally carried out by dissolving the host in a liquid guest and allowing concentration of the solution. In the case of a solid guest, a noncompetitive solvent may be employed. The powdered host compound may also be exposed to vapors of the guest, and single crystals of diffraction quality may sometimes be prepared in this way.²³ The templating effect of the guest in the formation of a given inclusion compound is a topic under current debate. What, for example, is the role of a “non competitive” solvent in the crystallization of a given compound? The fact that it can give rise to a different polymorph of the host suggests a molecular recognition step involving the solvent during crystallization.²⁴

The general scheme for the formation and decomposition of an inclusion compound is shown in Figure 1. Step a shows the dissolution of the apohost in the liquid guest to give a solution. Step b displays the crystallization to the β -phase, yielding the host–guest complex. The latter

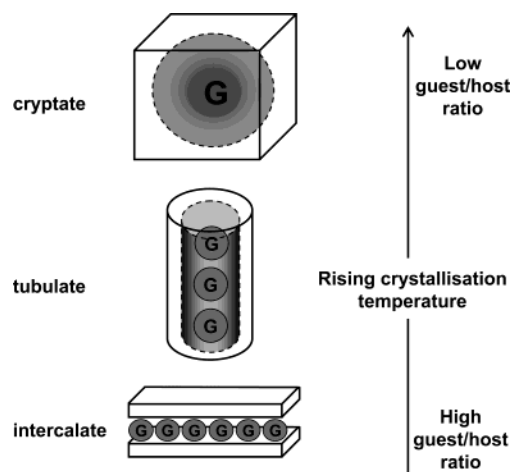
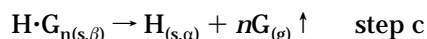
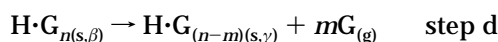


FIGURE 2. Change in host–guest topology with crystallization temperature.

may then decompose, under heating, in different ways: It may revert to the original α -phase:



It may partially decompose to yield a new γ -phase:



Finally, in step e, it may lose the guest, but the host retains its structure giving rise to an “empty” clathrate or β_0 phase. This phenomenon, in which the host behaves essentially like a zeolite, is rare, but it has been shown to occur in the gossypol–dichloromethane clathrate.²⁵

Different guests will generally give rise to dissimilar β -phase inclusion compounds, but compounds with different host–guest ratios may be prepared from the same host–guest system by changing the crystallization temperature. The general rules on how the topology is likely to change with crystallization temperature have been formulated by Ibragimov.²⁶ These may be summarized as follows:

- (i) The guest/host ratio decreases as the crystallization temperature increases.
- (ii) The topology changes from low temperature to high temperature as intercalate \rightarrow tubulate \rightarrow cryptate \rightarrow apohost.

These rules are shown schematically in Figure 2.

A number of examples illustrating this phenomenon have appeared in the recent literature.^{27–30}

Thermal Stability

Thermal analysis is an important tool for the characterization of inclusion compounds. There are several books and reviews on the subject.^{31–34}

Thermal gravimetry (TG) is employed to obtain accurate host:guest ratios. This is important because inclusion compounds are often nonstoichiometric, and the results of the TG can be employed to assign sensible site occupancy factors of the guest atoms during crystal structure refinement. Differential scanning calorimetry (DSC) yields both the onset temperatures of various

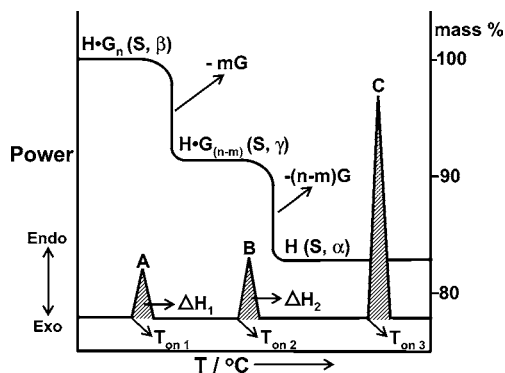


FIGURE 3. Idealized TG and DSC for the decomposition of an inclusion compound forming a stable intermediate.

thermal events such as guest release, polymorphic phase transitions, and melting, as well as the associated enthalpy changes. Accurate ΔH changes, however, are difficult to achieve by DSC, as the measurements are dependent on various experimental parameters such as crystallite size distribution and the geometry of the calorimeter.³⁵ Accurate values of the enthalpy change associated with the guest-release reaction can be obtained by measuring the vapor pressure of the guest under equilibrium conditions at variable temperature. A fully automated apparatus for this purpose has been constructed, and the ensuing graph of $\ln P$ versus $1/T$ has a slope of $-\Delta H/R$, yielding enthalpy change values to a precision of approximately 2%.³⁶

The idealized TG and DSC curves of an inclusion compound subjected to a constant heating rate are displayed in Figure 3. The compound forms a stable intermediate γ -phase. The DSC curve shows two endotherms A and B corresponding to the guest release from the β - and γ -phase respectively, followed by endotherm C, associated with the melting of the host. The areas under the curves correspond to the enthalpy change of each thermal event.

We have found that the value of the onset temperature, T_{on} , characterizing the temperature of guest release, is a reliable measure of thermal stability. For inclusion compounds of a given host with a variety of guests, the onset temperatures are clearly a function of both the host–guest interactions and the intrinsic properties of the guest itself. In particular, the normal boiling point T_b of the guest is important, and a useful measure of the relative stability of an inclusion compound is the difference ($T_{on} - T_b$). This is of interest when trying to encapsulate highly volatile guests. For example, high onset temperatures have been recorded by McAdie³⁷ for the decomposition of β -quinol clathrates with various gases such as Ar, N₂, CO, and CH₄, prepared under high pressure (45 atm) of the gaseous guest. A value of ($T_{on} - T_b$) of +324 °C was recorded for the quinol–N₂ clathrate. However recent results by Atwood and Barbour have proved even more remarkable. They have shown that various Freons can be entrapped in Calix [4] arene to well above their normal boiling points. In the case of the CF₄ inclusion compound they recorded a ($T_{on} - T_b$) value of +370 °C, a spectacular result.³⁸

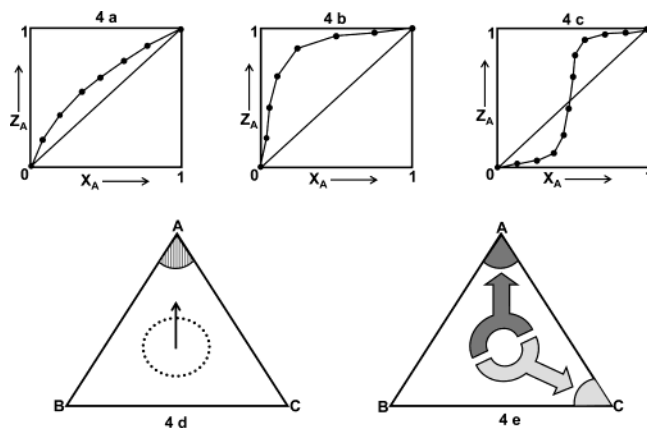


FIGURE 4. Selectivity curves obtained from competition experiments.

Selectivity

One of the important applications of host–guest chemistry is the separation of similar compounds 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 guest 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 has been described in detail³⁹ and can also be used with the host in suspension, or as a solid–solid reaction.²³

For two component systems, three kinds of selectivity curves arise, as shown in Figure 4. X_A is the mole fraction of guest A in the liquid mixture and Z_A that of guest entrapped in the crystal. Following Ward,⁴⁰ we may define a selectivity coefficient:

$$K_{A:B} = (K_{B:A})^{-1} = Z_A/Z_B * X_B/X_A \quad (X_A + X_B = 1)$$

Thus, the diagonal lines in Figure 4 represent zero selectivity and $K_{A:B} = 1$. Figure 4a represents a modest preference of A over B, with $K_{A:B} = 3$, while Figure 4b represents high selectivity with $K_{A:B} = 10$. Figure 4c results when the selectivity is concentration-dependent and is attributed to kinetic effects.

Competition experiments can be extended to analyze simultaneous competition by three guests. The results are displayed on an equilateral triangle in which each apex represents a pure guest. Starting points of the general mixtures are chosen judiciously on the inner circle of the triangle. Figure 4d displays the results in which guest A is preferentially enclathrated over B and C, while Figure 4e shows the results of a system in which guest B is rejected but guests A and C are favored, depending on their initial concentrations. A variety of systems have been analyzed by this technique, and various hosts have been employed to separate close isomers, such as picolines, lutidines xylanols, and benzenediols.^{41–44}

Interestingly, we have demonstrated that competition experiments can also be carried out with solid guests by

grinding appropriate mixtures with the solid host. This was shown by the enclathration of the isomers of aminobenzonitrile (ABN) by the host 1,1,6,6-tetraphenyl-2,4-diyne-1,6-diol. The selectivity was in the order 2ABN > 3ABN > 4ABN, and the result of the solid–solid reactions yielded an outcome that was similar to those carried out in solution using 1-butanol as a noncompetitive solvent.²³

We can reconcile the results of competition experiments with the structures of the ensuing inclusion compounds by estimating their relative stabilities. From the refined atomic positions of the crystal structures, we may compute the lattice energies of the compounds using the method of atom–atom potentials. One may employ force fields of the type

$$V(r) = a \exp(-br) - c/r^6$$

where r is the interaction distance and the coefficients a , b , and c are those given by Gavezzotti.⁴⁵ Care must be taken to incorporate a suitable hydrogen-bonding potential when required. We employ that of Vedani and Dunitz,⁴⁶ which is of the form

$$V(\text{H-bond}) = (A/R^{12} - C/R^{10}) \cos^2 \theta$$

where R is the distance between the donor hydrogen and the acceptor atom and θ is the donor–H–acceptor angle. The $\cos^2 \theta$ term is the energy penalty paid by the bond in order to take nonlinearity into account. Such lattice energy calculations often correlate well with the enthalpies of the guest-release reaction and with guest onset temperatures.^{47,48} In cases where the guest is a high boiling liquid, the DSC may yield a single endotherm corresponding to the dissolution of the host in the escaping guests. In such cases both the ΔH and the dissolution temperatures may be correlated to the lattice energies of the compounds. The importance of lattice energy calculations cannot be overemphasized. It is erroneous to consider only strong intermolecular interactions such as O–H···O and N–H···O as being solely responsible for the control of molecular packing in crystal. The C–H group can also serve as a hydrogen bond donor and makes an important contribution to the lattice energy in the form of weak hydrogen bonding of the type C–H···N, C–H···O, and C–H··· π interactions. Thus, all the intermolecular forces, weak as well as strong, must be considered. In this context it is interesting to consider methods of visualization of organic crystal structures. The Cambridge Crystallographic Data Centre has developed the program NIPMAT,⁴⁹ a pictorial matrix which defines intermolecular close contacts in terms of a gray scale. This method suffers from the fact that the result is dependent on an arbitrary method of atomic labeling. An interesting alternative has been formulated by Spackman⁵⁰ using the concept of Hirshfeld surfaces yielding a two-dimensional map, which summarizes quantitatively the nature and kind of molecular interaction experienced by a molecule in a crystal. This method, however, has yet to be used for inclusion compounds, although it would undoubtedly offer interesting insights.

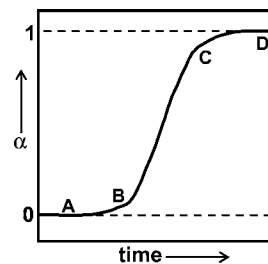


FIGURE 5. Generalized α -time curve for a decomposition reaction.

Kinetics

Both the kinetics of desorption and of enclathration are important aspects of inclusion chemistry. Both kinds of reaction may be monitored by measuring the change in mass as a function of time.

The extent of reaction, α , may be defined as

$$\alpha = (m_o - m_t)/(m_o - m_f)$$

where m_o is the initial mass, m_t is the mass at time t , and m_f is the final mass. A generalized α -time curve is shown in Figure 5, and comprises the steps of induction (A), acceleration (B), deceleration (C), and completion (D).

Various models can be fitted to the α -time curves which correspond to particular mechanisms of the reaction.^{31,34} The most common are

$$-\ln(1 - \alpha) = kt \quad \text{first order} \quad \text{F1}$$

$$1 - (1 - \alpha)^{1/2} = kt \quad \text{contracting area} \quad \text{R2}$$

$$1 - (1 - \alpha)^{1/3} = kt \quad \text{contracting volume} \quad \text{R3}$$

For the desorption reaction, α -time curves may be readily obtained on commercial thermal balances, taking due care of such experimental parameters as temperature, particle size distribution and flow rate of the purging gas. In cases of very small samples, an apparatus of high sensitivity is required, and we have constructed a quartz microbalance (QMB) suitable for this purpose, which requires less than 1 mg of host compound to yield reproducible results.⁵¹

To obtain the activation energy of desorption, the method of choice is to carry out a series of isothermal runs at selected temperatures, finding the appropriate law and deriving the corresponding rate constants which can be employed in the Arrhenius equation

$$k = A \exp(-E_a/RT)$$

Nonisothermal methods, which are based on weight loss versus 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 instructive paper by Brown⁵² which reviews the field. The application of the Arrhenius equation to heterogeneous reactions is open to question, but Galway and Brown⁵³ have given a theoretical justification for its use.

The kinetics of the formation of the inclusion compounds between a solid host and guest vapor, the enclathration reaction, has received little attention. This is

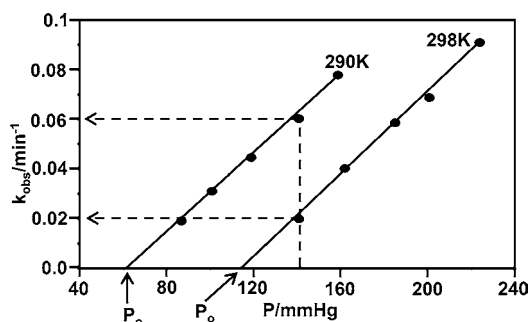
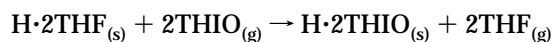


FIGURE 6. Plot of k_{obs} vs guest pressure for the enclathration of acetone vapor by *trans*-9,10-dihydroxy-9,10-bis(*p*-*tert*-butylphenyl)-9,10-dihydroanthracene. Note the existence of threshold pressures P_0 at both temperatures.

because measurements are experimentally difficult and the inclusion compounds formed are often unstable at ambient conditions. A suitable suspension balance, which allows measurement of mass change with time under controlled conditions of guest vapor pressure and temperature, has been constructed.⁵⁴ An interesting aspect of these reactions is that they give rise to anti-Arrhenius behavior in that for a given vapor pressure of the guest, the rate of the reaction decreases with increasing temperature. This arises from the fact that a threshold pressure, P_0 , is required to initiate the reactions of the gaseous guest uptake by the host. This was noted for the enclathration reaction of the host *trans*-9,10-dihydroxy-9,10-bis(*p*-*tert*-butylphenyl)-9,10-dihydroanthracene with acetone,⁵⁵ when a plot of k_{obs} versus vapor pressure of the guest at two different temperatures gives rise to two straight lines, as shown in Figure 6. When we consider the rate constant at a fixed pressure of (say) 140 Torr, we obtain a value of 0.061 min^{-1} at 290 K and 0.020 min^{-1} at 298 K.

Guest Exchange

The question of guest exchange in inclusion compounds has received little consideration despite the fact that such processes are important for sensing and catalysis based on inclusion. Microporous metal coordination compounds are currently receiving attention, and an important example is that of copper isonicotinate polymers which retain their structural integrity to above 200 °C and can reversibly absorb and desorb water molecules.⁵⁶ Guest exchange has been monitored in Werner clathrates⁵⁷ and in organic inclusion compounds. The host 1,1,6,6-tetraphenyl-2,4-diyne-1,6-diol, H, forms inclusion compounds with tetrahydrofuran, THF, and thiophene, THIO, and the dynamics of the exchange



have been followed by DSC, and the results are shown schematically in Figure 7. We have shown that the mechanism for this reaction is an initial desorption yielding the apohost, followed by adsorption of the incoming guest.⁵⁸

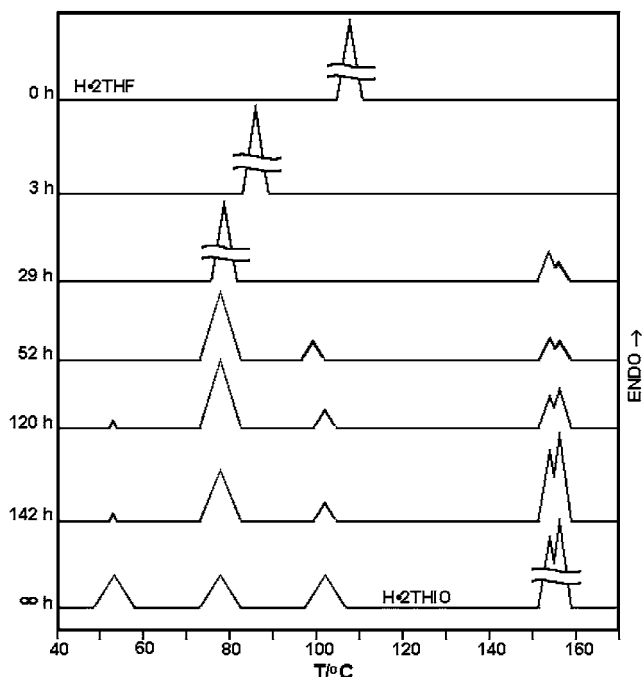


FIGURE 7. Schematic representation of the DSC curves for the guest exchange in the reaction. $\text{H}\cdot 2\text{THF}_{(\text{s})} + 2\text{THIO}_{(\text{g})} \rightarrow \text{H}\cdot 2\text{THIO}_{(\text{s})} + 2\text{THF}_{(\text{g})}$ H = 1,1,6,6-tetraphenyl-2,4-diyne-1,6-diol. (Reproduced by permission of the Royal Society of Chemistry).

Solid–Solid Reactions

“No coopora nisi fluida” (no reaction in the absence of solvent), Aristotle’s famous statement based on the observations on natural processes, is incorrect because reactions between solids do occur, and they are the subject of current interest and debate. They have many applications in metallurgy, ceramics, geochemical processes, and the manufacture of artificial gems. Significant early work was carried out by Rastogi who studied the kinetics of solid–solid reactions between various hydrocarbons and picric acid.^{59–61} They used the capillary technique, whereby the solids are placed in contact in a capillary and the advancement of the reaction is followed by the growth of the product. The mechanism is diffusion-controlled, and activation energies were evaluated. The study was extended to inorganic systems, using a variety of analytical techniques.^{62–64} The influence of microwaves in solid–solid reactions has been investigated, and the efficient synthesis of various metal chalcogenides has been achieved.^{65,66} Toda has championed their use for the efficient synthesis of novel organic compounds and has written several authoritative reviews on the subject.^{67–69} Two recent publications, however, question whether many of these reactions are indeed a solid–solid process, because they involve the formation of a liquid phase.^{70,71} It is interesting to note that Toda recently demonstrated enhanced kinetics of cocrystal formation by the addition of small quantities of appropriate solvent.⁷² We have monitored the reaction of 1,1,6,6-tetraphenylhexa-2,4-diyne-1,6 diol with benzophenone by measuring the changing infrared spectra of the hydrogen-bonding which occurs with complex formation⁷³ and have demonstrated the use of solid–solid reactions in zinc coordination

polymers with pyrazine in preparing metal–ligand compounds of differing stoichiometries.⁷⁴ The future of carrying out reactions without solvents is important, particularly from the environmental viewpoint, but the mechanisms involved remain open to question.

Crystal Engineering

Solid state inclusion compounds form a significant aspect of crystal engineering. This is a highly topical field of research. The idea is to design crystalline compounds by appropriate choice of starting molecules and to synthesize products with desired structures and concomitant macro properties. There are a number of monographs and reviews on this subject.^{75–78} The current strategy lies in understanding the patterns of nonbonded interactions that appear in crystals and to design molecules that will yield structures with similar patterns.²⁰ This approach has been summarized by Desiraju⁷⁹ and used successfully by Zaworotko^{80,81} and Aakeröy.^{82,83} However, the ultimate step in crystal engineering must be the prediction of crystal structure. This is an extremely difficult problem, and various approaches have only been partly successful. In a recent review, Sally Price states “There is still a long way to go”,⁸⁴ while Gavezzotti,⁸⁵ when asking “Are crystal structures predictable?”, bluntly answers “No”. This is currently true for crystal structures with a single molecular entity. The situation is yet more difficult for inclusion compounds in which the asymmetric unit is made up of two or more separate molecular entities.

We conclude, therefore, with Maddox’s famous statement, which he made in an editorial in *Nature* in 1988: “One of the continuing scandals in the physical sciences is that it remains in general impossible to predict the structure of even the simplest crystalline solids from a knowledge of their chemical composition.”

The statement is still valid today.

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