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Research Communication

A Simple Correlation between the Structures of Different Crystal Modifications of a Given Host–Guest Complex and their Crystallization Temperatures

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Abstract. The formation of different crystal modifications of a given host-guest complex depending on the crystallization temperature (pseudopolymorphism) is studied. It is shown that such pseudopolymorphism is a characteristic feature of versatile host compounds. A very important rule for host-guest chemistry is derived from the results of the X-ray structural investigations of pseudopolymorphs: the higher the crystallization temperature of the modification the more closed is the space occupied by guest molecules. On the basis of the formulated rule a recommendation for the topological control and solution of some central problems of supramolecular chemistry is proposed.

Key words: pseudopolymorphism, crystallization temperature, versatile hosts, gossypol, cyclotriveratrylene.

1. Introduction

Many chemical substances are represented as inclusion (host-guest, clathrate) compounds in which molecules of one component (the guest) are enclosed in an intramolecular (monomolecular inclusion) or intermolecular (lattice type inclusion) space of the other component (the host) with no covalent bonds between the two compounds [1]. A very common topological classification of the lattice type inclusion complexes depends on whether there are two-dimensional open inclusions (intercalates or layer type clathrates), one dimensional open channel inclusions (tubulates) or totally enclosed cage inclusions (cryptates) [2]. Inclusion compounds are widely used in practice. They may serve, for example, as containers for storage of toxic, hazardous, very volatile and unpleasant odor compounds [3] or they may be used as matrices for controlled (retarded) release of odorous compounds, pesticides or pheromones [4]. Obviously for purposes of the former applications the containers should be in the form of cryptates whereas host-guest compounds

used for controlled release have to be at least in the tubulate form, i.e., the *topology* of the space occupied by guest molecules is of crucial importance.

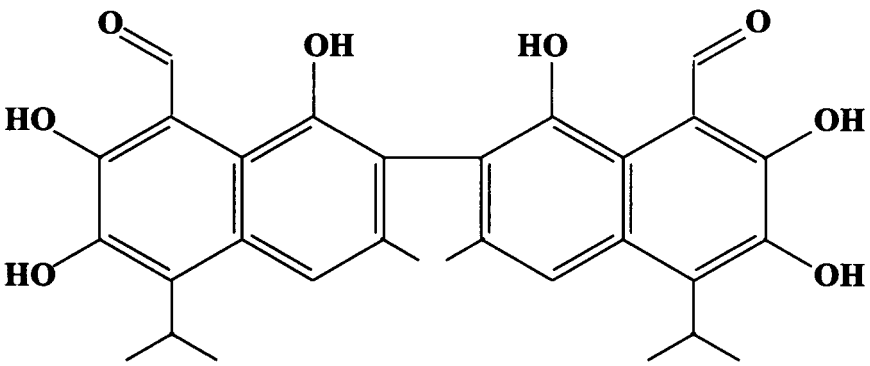
If a given inclusion complex is, say, in the tubulate form instead of the desired cryptate form, is it possible to prepare the desired modification and *vice versa*? In other words, can we control the *topology* of the space in the given inclusion compound? This would be possible if at least two crystal modifications of the same host-guest complex exist, i.e., if polymorphism (more exactly pseudopolymorphism) is a characteristic feature of the compounds formed by the given host-guest pair.

In order to obtain different polymorphs of polymorphic compounds, crystallization from solutions in various solvents, at different temperatures, pressures and concentrations is used. A similar approach should be suitable for searching for the pseudopolymorphs of host-guest compounds. However, to date, systematic investigations in this field have not been carried out apart from four studies in which pseudodimorphs were obtained at relatively high pressure and temperature [5], temperature [6], concentration [7] or by adding a third component to the crystallization solution [8]. Therefore in order to establish the presence of pseudopolymorphism for a given host-guest complex, at least in the case of versatile host compounds, and find out a correlation between the crystal structures of the modifications obtained and their formation conditions we started systematic investigations several years ago. Investigations were carried out on our traditional subject, the versatile host gossypol, its dianiline derivative and three other versatile host compounds. For simplicity a dependence on only crystallization temperature was studied keeping other parameters (pressure and concentration) constant. This communication presents a very important rule for supramolecular chemistry derived from these investigations.

2. Discussion

Gossypol (**I**), (2,2′-[1,1′,6,6′,7,7′-hexahydroxy-3,3′-dimethyl-5,5′ -diisopropyl-8,8′-diformyl]-naphthalene), is a yellow pigment of cotton seeds for which many types of bioactivity are known [9]. Its unique inclusion ability was discovered by our investigations [10]. Over 20 groups of different inclusion structures have been identified for this versatile host compound. Gossypol forms voids lined with apolar groups for inclusion of nonpolar guests and polar host cavities are prepared for the entrapment of polar guests able to form host-guest type H-bonds. Inclusion complexes of these two families never belong to the same isostructural group of crystals [10–12].

All three types of host-guest complexes with different topology are observed among gossypol inclusion complexes. For example, a very unstable 1 : 1 tubulate is formed from solutions of gossypol in dichloromethane. Its decomposition gives rise to the isostructural guest-free crystal with wide empty channels (organic zeolite) [13]. In the complex with trichloromethane the guest molecules are situated



I

in the space between host layers. This 1 : 1 intercalate slowly decomposes under ordinary conditions [14]. Tetrachloromethane forms a 1 : 1 complex with gossypol in which cages occupied by guest molecules are connected via channels [15]. However, the narrow channels restrict the movement of tetrachloromethane molecules because desolvation of this tubulato-cryptate takes place near the melting point of the crystals [16]. An authentic 1 : 0.5 cryptate formed from solutions of gossypol in benzene does not desolvate until melting [14].

An investigation of gossypol crystallization from solutions in dichloromethane at different temperatures shows that at least 3 modifications of the host-guest complex may be obtained (pseudotrimorphism) [17]. At 30 °C the 1 : 1 complex (β-phase), isostructural to that formed between gossypol and tetrachloromethane, is formed instead of the initial α-phase complex. The cryptate type 1 : 0.5 complex (γ-phase), isostructural to the complex between gossypol and benzene, is obtained at 36°C [17]. Thus instead of the wide channels of the α-phase, complex voids intermediate between channels and cages are formed in the β-phase which are replaced by well-defined cages in the γ-phase complex, i.e., the space for guest inclusion gradually becomes less open if the crystallization temperature increases. Crystallization from boiling solutions gives rise to the guest-free host identical with unsolvated gossypol obtained by desolvation of the α-phase complex.

Another low boiling solvent, diethyl ether, gives an unstable 1 : 1 tubulate with gossypol. As a result of its partial desolvation a stable 1 : 0.5 channel type complex is formed. This tubulate with half the amount of channels is also obtained by crystallization at 30 °C. In it guest molecules are situated in more closed channels and leave the crystals at 140 °C [18]. A new polymorph of unsolvated gossypol is crystallized from boiling solutions [19].

In the pyridine trisolvate of gossypol desolvating at 112 °C, the channels are wide and each of them accommodates 3 guest molecules H-bonded to host molecules [20]. At 40 °C a new 1 : 1 tubulate, isostructural to the complex of gossypol with acetone [21], is formed from solutions in pyridine. The total number of chan-

nels is halved and two pyridine molecules H-bonded to gossypol molecules are situated in relatively narrow channels. This complex does not decompose until its melting.

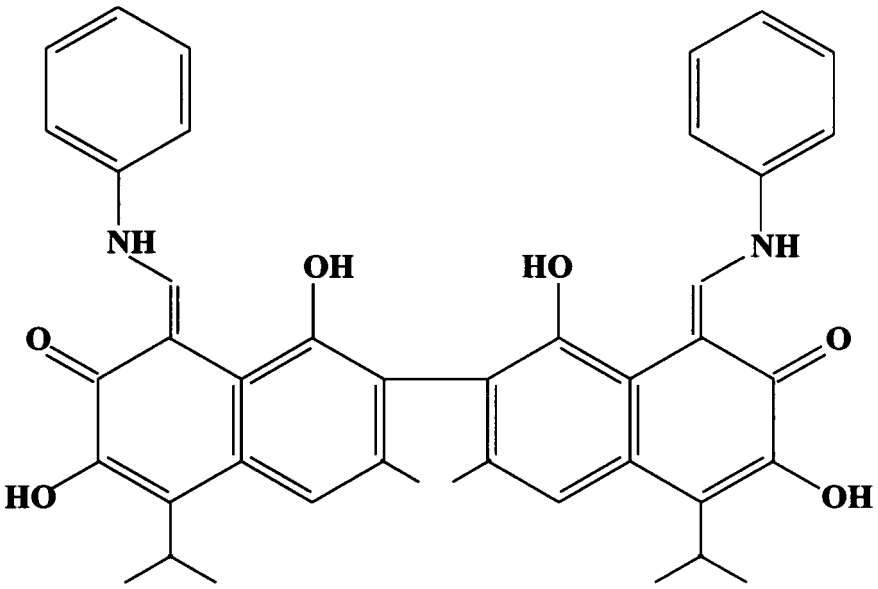
In all these 3 examples increasing the crystallization temperature leads to the formation of the inclusion complexes with “more closed” voids for guest entrapment and to a decrease of the guest component content. “More closed” entrapment has been reached here by alteration of the inclusion space topology (gossypol dichloromethane complex), reduction of the channel dimensions, reduction of the number of channels (gossypol diethyl ether complex) or simultaneous alteration of both of the last two characteristics (gossypol pyridine complex).

Gossypol is a host which easily includes any substances relating to any group of organic compounds, i.e., it is a highly versatile host compound. The observation of the pseudopolymorphism of a given host-guest complex may be connected with gossypol’s unusual versatility. Therefore it is necessary to investigate less versatile hosts with respect to pseudopolymorphism. One such compound is dianilinegossypol (**II**) because it does not include, for example, alchohols, carboxylic acids and tetrachloromethane [11]. The host-guest complexes between dianilinegossypol and acetone, DMSO and ethylacetate are 1 : 2 cryptate [22], 1 : 2 intercalate [23] and 1 : 1 tubulate [24], respectively. Only cryptates are obtained from solutions of this host in acetone, DMSO and ethylacetate at 35 °C [22], 60 °C [23] and 35 °C [25], respectively, when the initial content of the guest component remains unchanged. These cryptates are absolutely new, i.e., in contrast to the case of gossypol they are not isostructural to any known complexes prepared at ordinary conditions. Two different polymorphs of the unsolvated host are crystallized from boiling solutions in acetone and ethylacetate.

Again crystallization at higher temperatures leads to formation of inclusion complexes with more closed voids. Obviously such behaviour is a universal feature of the host-guest systems. Therefore on the basis of these results the following rule may be formulated. *A pseudopolymorphic versatile host compound responds to an increase of the crystallization temperature by entrapping of the guest component into a “more closed” space in order to withstand the higher thermal mobility of the molecules being enclathrated (it is easy to observe the phenomenon if the solvent (guest) is low boiling). Near to the boiling temperature of the guest its thermal mobility increases to such a degree that an entrapment fails and the guest-free compound is crystallized instead of an inclusion complex.*

As a consequence of this rule it may be concluded that in high temperature complexes the guest content is generally not less than that in the low temperature modifications. Indeed, in order to construct an inclusion system with more closed voids a greater amount of the host molecules per one guest molecule (or a lesser amount of the guest molecules per one host molecule) are required and it is readily observed in practice.

Following this rule it is possible to make some important recommendations in order to obtain host-guest compounds with altered topology. *If a host-guest*

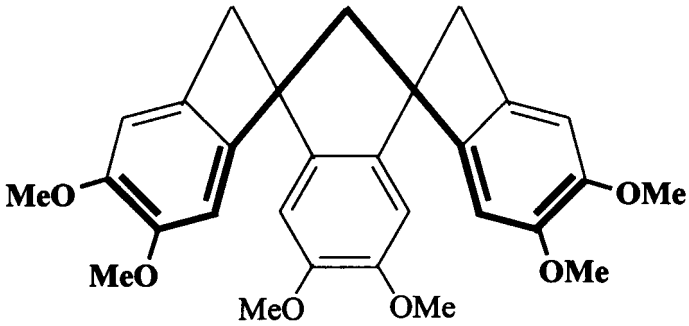


II

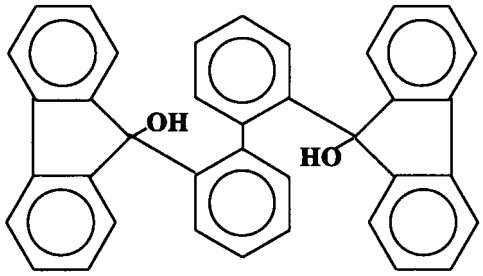
complex obtained at room temperature is tubulate, its cryptate (or another less open) modification can be prepared by increasing the crystallization temperature. If the host-guest complex is cryptate, its tubulate (or another more open) form can be prepared by decreasing the crystallization temperature.

To check the validity of the postulated rule three versatile host compounds were chosen. Cyclotriveratrylene (**III**), a well known versatile host compound with a trigonal intramolecular cavity, forms tubulates with intermolecular inclusion of solvent molecules [26]. Intracavity (endocyclic) complexes of this compound with frequently used solvents have not been obtained to date. If this type of complex, especially a modification in which solvent molecules are entrapped between two facing host molecule cups exists, it will crystallize as a clathrate with more closed space for guest inclusion. According to the proposed recommendation in order to prepare such a modification, crystallization should be carried out at higher temperatures. Carrying out the crystallization of cyclotriveratrylene from its solution in acetone at 40 °C we found an absolutely new 1 : 0.25 sandwich type endocyclic cryptate [27, 28] instead of the usual 1 : 0.5 tubulate [26].

The host-guest complex of 2,2′-bis(9-hydroxy-9-fluorenyl) biphenyl (**IV**) with acetone is a 1 : 1 cryptate [29]. If another complex with more open voids for guest inclusion is possible it must be obtained by decreasing the preparation temperature. Indeed, the anticipated modification in the form of the very unstable 1 : 2 tubulate was obtained by crystallization at 10 °C [30].



III

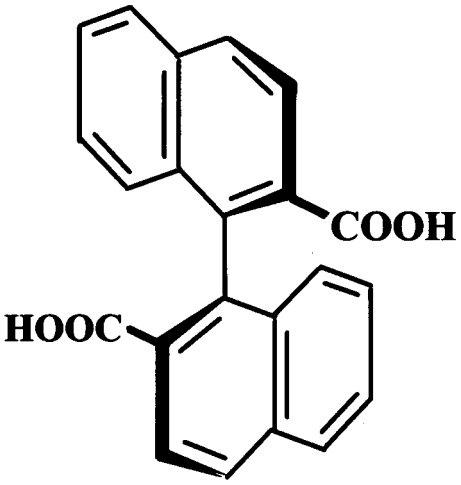


IV

Another example of the high temperature modification of the initial complex is provided by the versatile host, 1,1′-binaphthyl-2,2′-dicarboxylic acid (**V**), which forms a 1 : 2 tubulate with ethanol [31]. At 60 °C the 1 : 0.5 tubulate with half the number of channels is crystallized. The unsolvated host is obtained by crystallization at 100 °C [32]. Analysis of the crystal structures shows that the 1 : 0.5 tubulate is an intermediate phase between the initial modification and the unsolvated host.

These examples demonstrate the power and correctness of the formulated rule and the results following from its recommendations. Using this rule one may solve the following problems which are very important for practical supramolecular sciences:

- to obtain an inclusion complex with the required topology (topological control);
- to prepare pure (solvent free) substances or substances with a reduced content of solvent molecules if the compound of interest is represented by the stable inclusion complex of the versatile host compound;



V

- to introduce the new method for obtaining inclusion complexes with solid state guests (also with liquids in which the host is insoluble) according to which host and guest are dissolved in frequently used solvents and crystallization carried at temperatures slightly higher than the boiling point of the solvent;
- to prepare thermodynamically stable modifications of unstable host-guest complexes (as a rule, host-guest complexes with more closed voids for guest entrapment are more stable);
- to control the physico-chemical characteristics of the inclusion compounds and the biopharmaceutical properties (e.g., solubility, stability during storage *etc.*) of crystalline medicines (some solid state drugs are versatile host compounds);
- to explain the instability of physico-chemical (also biopharmaceutical for crystalline medicines) parameters of versatile host compounds caused by crystallization of different host-guest complex modifications under slightly different conditions (concentration, ambient temperature, pressure and humidity) for various samples;
- to explain the decomposition (desolvation) of inclusion complexes of the versatile hosts or sorption and desorption mechanisms between crystalline hosts (sensor materials) and organic vapours because these processes take place step by step passing through intermediate phases (pseudopolymorphic stages).

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