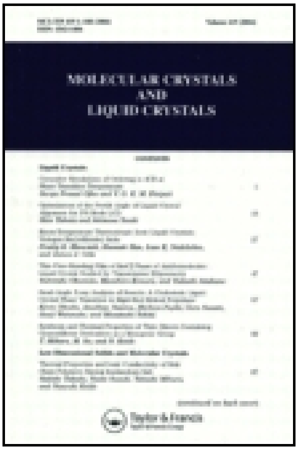

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Can Solid Clathrates be Useful for Separating Molecular Species? A Systematic Approach to the Design of Novel Coordinato-Clathrates

Harold Hart [a] , Lon-Tang W. Lin [a] & Israel Goldberg [b]
[a] Department of Chemistry, Michigan State University, East Lansing, Michigan, 48824, USA
[b] School of Chemistry, Tel-Aviv University, 69978, Ramat-Aviv, Tel-Aviv, ISRAEL

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CAN SOLID CLATHRATES BE USEFUL FOR SEPARATING MOLECULAR SPECIES? A SYSTEMATIC APPROACH TO THE DESIGN OF NOVEL COORDINATO-CLATHRATES.

HAROLD HART* AND LON-TANG W. LIN
Department of Chemistry, Michigan State University, East Lansing, Michigan 48824, USA

ISRAEL GOLDBERG*
School of Chemistry, Tel-Aviv University, 69978 Ramat-Aviv, Tel-Aviv, ISRAEL

Abstract Molecular design of a series of clathrate-forming hosts, which led to the synthesis of N,N'-ditritylurea (DTU), is discussed. DTU was found to be a versatile host, exhibiting properties of selective complexation towards guests of different functionality and molecular shape. Crystallographic analyses of several 1:1 clathrates of DTU with chiral and achiral guests revealed stable host lattices with a characteristic pattern. The results of structural and selectivity studies indicated that directional hydrogen bonding between host and guest has a major effect on the stability and formation selectivity of the clathrates.

INTRODUCTION AND CONCEPT

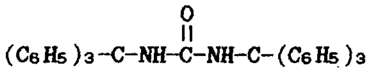
Clathrates are crystalline inclusion compounds in which guest species are completely enclosed in channels or cages that occur in a given host lattice. Formation of such multicomponent systems was first discovered in the middle of the past century.[1] Only recently, however, along with the rapid advancement of host-guest chemistry, has this class of compounds been subjected to more intensive investigations.[2] The structural aspects of inclusion compounds formed by organic host lattices have been summarized in a recent collective publication.[3]

A survey of the available literature indicates that crystal packing of molecular entities that are characterized by an irregular shape and a small number of conformational degrees of freedom frequently results in the formation of a host lattice with intermolecular voids. To achieve thermodynamic stability and dense packing, this space in the lattice must be filled by another (guest) component. Topological interactions therefore play an important role in stabilizing clathrates, particularly those composed of neutral host and guest constituents, and the ability to achieve a selective crystallization will depend significantly on the steric compatibility between the complexing partners. Suitable examples of previously studied clathrates include hosts such as Dianin's compounds[3a], perhydrotriphenylene[3b], cyclotriveratrylene[3c], triphenylmethane[3e] and tri-o-thymotide (TOT)[2a], and a variety of aliphatic and aromatic guests. Several of these hosts were found to exhibit selective clathration properties, TOT revealing also enantiomer selectivity.[2a] One of the first systematic efforts to design a clathrate host, structurally unrelated to previously known compounds (the inclusion properties of most of them were discovered accidentally), resulted in the synthesis of hexakis-(phenylthio)benzene host lattices.[3d]

As part of our continuing interest in the properties of inclusion compounds, we attempted a systematic study of the clathrate inclusion phenomena which involves molecular design of a new series of organic hosts capable of forming lattice-inclusion type structures. At the first stage of this investigation, only the basic principle of steric fit between host and guest was applied. The starting idea was that compounds with a long molecular axis and with large and relatively rigid groups at each end are expected to function as hosts since the large groups, acting as "spacers", prevent the hosts from packing efficiently in the solid. In a crystal phase, the concave sites along the molecular axis can be occupied in two different manners: either by a convex fragment of an adjacent host (with an appropriate translational shift) or by another complementarily shaped guest molecule which, during the process of crystallization, is carried from the solution into the lattice. This idea turned out to be valid, as stoichiometric clathrate-type complexes were formed between a series of *chemically different* but *similarly shaped* hosts (all compounds were characterized by thick ends and a thin center) and a variety of aromatic guests (*e.g.*, benzene, toluene, o-xylene).[4] Examples of such hosts include $R-(C\equiv C)_n-R$ (n=2,3), $R-(CH_2)_n-R$ (n=4,6), $R-CH_2-CH=CH-CH_2-R$, $R-CO-CH_2-CH_2-CO-R$, $R-CH=N-N=CH-R$ and $R'-CH=N-N=CH-R'$, where R=trityl and R'=triptycyl. The detailed structures of several clathrates have been characterized, and a certain degree of selectivity on complexation with different isomers has been observed.[4]

Further studies indicated that stable crystalline clathrates can also be formed when other functionalities with varying degrees of flexibility are included in the molecular axis of the host. Structures of the 1:1 inclusion complexes of N,N'-ditrityl-2,5-diketopiperazine with methylene chloride and of N-tritylalanine anhydride with diethyl ether provide examples.[5] All the inclusion compounds referred to above involve uncharged host and guest constituents of low polarity. The guests occupy extramolecular cavities in the lattice, interacting only weakly through dispersion forces with the surrounding molecules of the host.

At the next stage, it was anticipated that clathrate formation would be more effective in controlling guest selectivities if a functionality which could form hydrogen bonds with guest species and add this strengthening feature to that of the molecular shape were included in the host. A similar approach to the design of novel clathrates has very recently been published.[6] Successful attempts at host synthesis which utilized the above concept involved, in our study, trityl end groups as large rigid spacers and an amide moiety as a source for proton-donating and proton-accepting sites.[7] An excellent host of this type is N,N'-ditritylurea (DTU), in which the



$$(C_6H_5)_3\text{-C-NH-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-NH-C-}(C_6H_5)_3$$

amide group adds rigidity to the molecular axis, and the H-bonding feature favors complexation with polar guests. DTU was prepared from trityl isocyanate and tritylamine using a known procedure.[8]

STRUCTURAL DATA

Experimentally, DTU was found to be an excellent host for guests containing varied functionality. It formed stoichiometric complexes with a variety of amines, amides, alcohols, esters and small molecules with other functions from solutions of the components in hot ethyl acetate.[9] Most of these complexes are stable and can be heated under vacuum well above the boiling points of low-boiling guests without decomposition.

Amide derivatives are functionally compatible guests and form stable clathrates with DTU that are suitable for structural characterization. Figure 1 illustrates schematically the unique host-guest interaction pattern observed in crystals of the 1:1 DTU complexes with propanamide (space group C2/c, a=15.839, b=9.088, c=24.584 Å, β=111.05°, Z=4) and the ethyl ester of N-acetylglycine (space group P$\bar{1}$, a=9.010, b=10.800, c=19.810 Å, α=105.29, β=94.33, γ=93.03°, Z=2).[7]

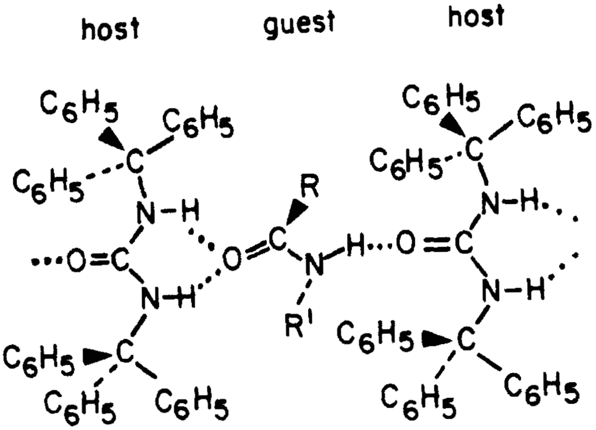


FIGURE 1. H-bonding between DTU and amide guests.

These structures contain continuous chains of alternating host and guest molecules held together by an extensive network of hydrogen bonds between the amide groups. Along each such chain the C=O and N-H groups point in opposite directions, thus providing complementary sites for an effective hydrogen-bonding association. The alkyl residue of the guest lies either above or below the nearly planar binding site.

A very similar scheme of host-guest interaction has been observed with chiral amide derivatives. The corresponding examples involve the 1:1 DTU complexes with ethyl N-acetylalaninate (space group $P2_12_12_1$, a=9.730, b=18.714, c=21.362 Å, Z=4) and with ethyl N-acetylmethioninate (space group $P2_12_12_1$, a=17.108, b=19.415, c=24.066 Å, Z=8), which formed chiral crystals.[10] In the four structures, a characteristic translation between adjacent units along the hydrogen-bonded chain is about 9Å, irrespective of the crystallographic space symmetry. The geometric parameters of the H-bonds vary within ranges NH···O 1.9-2.1Å, N···O 2.87-3.06Å, N-H···O 144-165°; *the ester residues of the amino acids are not involved in these interactions.*

In the above complexes of DTU, the host and guest components are strongly linked to each other via directional and specific interactions in a continuous manner throughout the corresponding crystal structures. They represent, therefore, *coordinato-clathrates*, an intermediate form between molecular-inclusion and lattice-inclusion type systems.[11] However, similar intermolecular arrangements with alternating host and guest moieties have also been found in crystalline complexes of DTU with other guests such as diethyl ether (space group C2/c, a=16.707, b=8.793, c=24.376 Å, β=106.94°, Z=4) and diethylamine (space group C2/c, a=16.926, b=8.740, c=24.404 Å, β-106.99°, Z=4).[9] Yet, in these two isomorphous structures, the hydrogen bonds do not form a continuous pattern but are, rather, confined to individual host-guest entities (Figure 2).

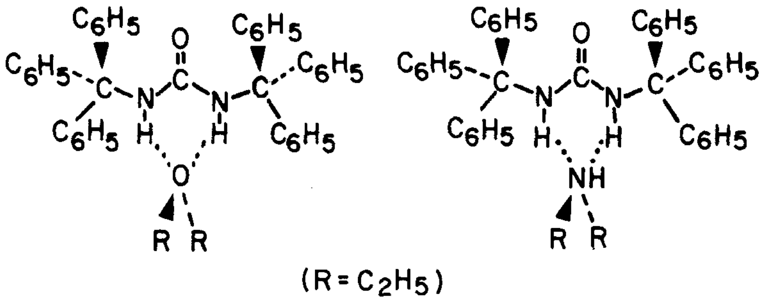


FIGURE 2. H-bonding in DTU complexes with ethers and amines.

This feature reflects on the relatively high stability of the DTU host lattice and illustrates its versatile capability to form clathrates with different guests.

Another observation relates to the complexing properties of the mono-substituted N-tritylurea (NTU). This host prefers to form clathrates with less polar guests. A structural analysis of its 2:1 complex with dimethylformamide revealed host-host self association, with the guest species occupying extramolecular cage-type voids. The crystal structure is of the lattice-inclusion type, the interaction between host and guest being mainly of a hydrophobic character.[7] Formation of this structural type (Figure 3) indicates the importance of having two large substituents on the urea to prevent host-host hydrogen bonds as in DTU, where the N-H and C=O sites are left open to attract suitable guests.

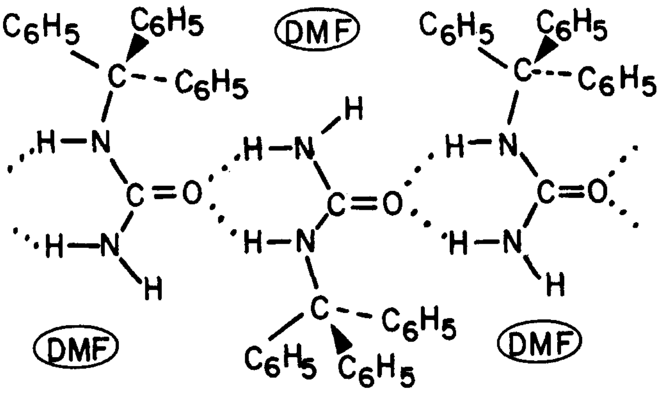


FIGURE 3. Host-host H-bonding in the NTU-DMF complex.

SELECTIVITY IN CLATHRATE FORMATION

Although DTU was found to be a versatile host for crystalline host-guest complexation, preliminary selectivity studies indicated marked discrimination in the clathrate formation. For example, DTU forms crystalline complexes with some alcohols (methanol, ethanol, propanol, 1-butanol) but not with others (2-butanol). Similarly, it complexes the ethyl esters of N-acetyl derivatives of glycine, alanine, methionine (see above) and aspartic acid, but not of proline, serine, phenylalanine and glutamic acid.[9] Moreover, a preferential guest inclusion by DTU has also been observed from solutions containing a 1:1 guest mixture in ethyl acetate. As in other clathrates, the steric factor is important in discrimination between compounds of similar functionality but different shape. This is illustrated by the following ratios of guests incorporated in the complex after one crystallization step with DTU (as determined by NMR and GC): 3.5:1.0 for diethyl ether and n-propyl methyl ether, 4.0:1.0 for 2-propanol and 1-propanol, 4.6:1.0 for diethylamine and n-propylmethylamine. The excessive inclusion of guests characterized by a higher symmetry is clearly correlated with the twofold rotational symmetry of DTU and of the host lattice it forms (in most cases). As expected, when the factor of functional complementarity is also involved, a considerably more pronounced discrimination can be obtained in complexation. A beautiful example is provided by an almost complete separation between diethyl ether and diethylamine from their 1:1 mixture.[9] The preferential enclathration of the former by a factor of over 25 (molar ratio) can clearly be attributed to the fact that the N-H(host)···OR_2(guest) hydrogen bonding is more attractive than N-H(host)···NHR_2(guest) (see above).

Similar lattice-inclusion selectivity and guest discrimination has recently been observed in coordinato-clathrates formed by 1,1'-binaphthyl-2,2'-dicarboxylic acid.[6a] The quantitative results describing the preference of guest binding by this host lattice from a two-component solvent mixture (in our study, the guest mixture was dissolved in a third solvent component) are, in fact, in excellent agreement with those described above.

CONCLUSIONS

An increasing amount of experimental evidence emerges from recent studies, indicating that both functional as well as topological complementarity between host and guest has to be considered in order to gain a better control of clathrate formation. We strongly believe, therefore, that it should be possible to make the lattice-inclusion process much more selective by adding suitable functional sensors to the host lattice. This concept appears to be a very useful one in the systematic design of novel clathrate-forming systems.

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