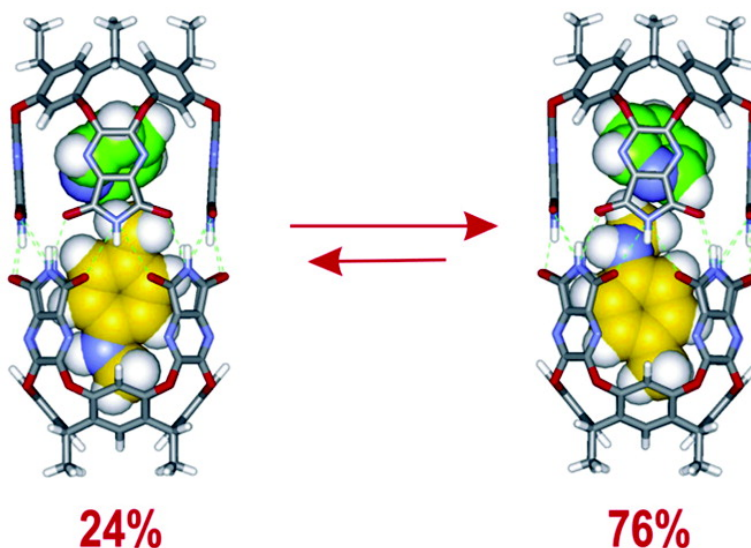


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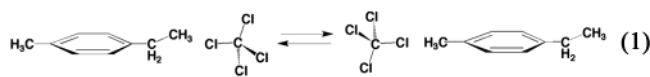
Individual Solvent/Solute Interactions through Social Isomerism

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Reversible encapsulation involves small molecule guests that are temporarily surrounded by a self-assembled host. The hosts can be held together by hydrogen bonds,¹ salt bridges,² or metal/ligand interactions,^{3,4} and the complexes reach equilibrium under mild conditions in a variety of solvents. Capsules of large size can surround two or more molecules, even two different molecules.⁵ This relatively rare event – coencapsulation – offers a snapshot of short-lived relationships between individual molecules, isolated from bulk solution. Such interactions have been observed in the gas phase at low pressures.⁶ Here, we use coencapsulation to assess recognition events between specific functional groups (eq 1) of a solute with individual molecules of solvent in the liquid phase.



The capsule **1**₂⁷ (Figure 1) takes up one of each guest, CCl₄ and *p*-ethyltoluene, when offered a solution of both in mesitylene-*d*₁₂. Two sets of resonances appear in the NMR spectrum representing the isomeric species shown. The signals are sharp and well separated, and the exchange rate between isomers is slow on the NMR time scale at 600 MHz at room temperature (see Figure 2). The size and shape of the capsule limits the mobility of the guests: they are too large to slip past each other and exchange places, and the toluene derivative is too long to tumble while within the capsule. The result is “social isomerism”,⁸ where intermolecular interactions between the guests are constrained to two contact areas. The relative stability of the isomers is reflected in the social isomer ratio and depends on the coencapsulated species.

The isomerism here is related to one discovered by Reinhoudt, in which a single molecule can adopt two different orientations in a covalently bound carcerand host.⁹ Also relevant is the “torsion balance” invented by Wilcox.¹⁰ That device revealed noncovalent forces in an intramolecular context. In the case at hand, the one-on-one encounter reports intermolecular interactions between solvent and specific portions of the solute. The assignment of roles (solvent vs solute) is, admittedly, arbitrary, but we take the solute as the larger guest.

The social isomer ratios (*K* defined below in eq 2) for three solutes are given in Table 1.

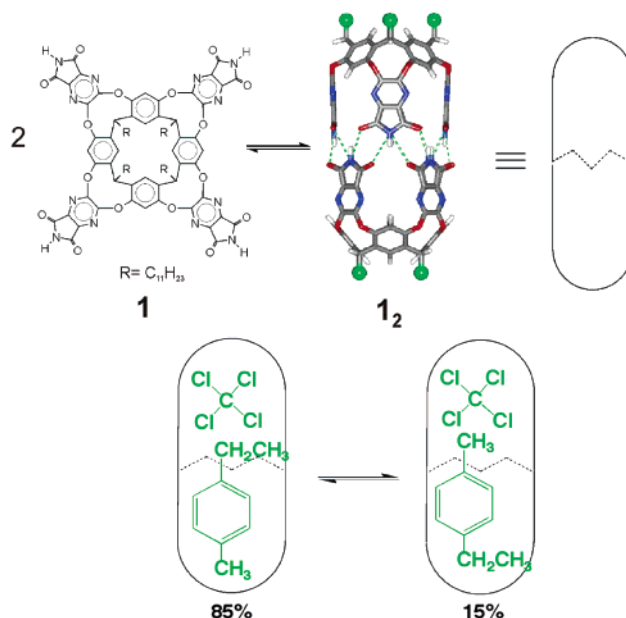
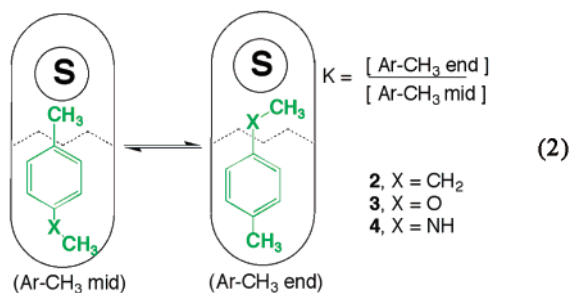


Figure 1. Top: Line drawing of the subunit and the ball-and-stick representation of the capsule **1**₂. Long peripheral pendant chains have been removed and are indicated with green balls. Cartoon representation used elsewhere is on the right. Bottom: The social isomerism shown by CCl₄ and *p*-ethyltoluene.

The interaction of the two guests is attenuated by the inner surface, the lining and shape of the capsule. The tapered ends of the cavity best accommodate smaller functions, and the belt of hydrogen bonds at the center favors polar guests. For *p*-ethyltoluene, the rotating methyl of the tolyl group sweeps out less space than the rotating ethyl group and may prefer the narrower end of the capsule; as a result, in all cases *K* > 1. Encapsulation phenomena are governed by a good fit of guest inside the host, and an optimal fit in solution means filling ~55% of the cavity.¹¹ The many guest combinations here range from 38% for CH₃CH₃ to 53% for cyclohexane and confirm that there are many ways to fill a given volume of space.

The energetic differences between social isomers are small (ΔG° varies from ~0.3 to 1.5 kcal/mol) and reflect the interactions of the solvent with the ethyl versus methyl group. The sizes of the solvents matter, with the larger cyclohexane, benzene, CCl₄, pyridine, and dichloropropane leading to larger *K* values. This may be due to attractions or repulsions: the larger ethyl group has a greater surface area for contact with these solvents, or the steric clashes can force the solute further away. There is evidence for the latter case in the form of a modest correlation between solvent size and the upfield shift of the aryl signals of the solute.¹² The smaller acetone, CH₂Cl₂, and ethane are more permissive of the Ar-methyl near the middle.

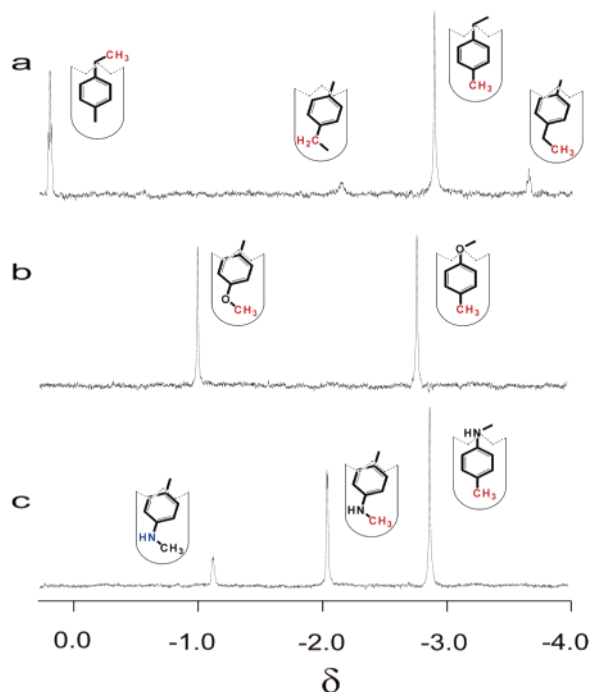


Figure 2. Upfield region of the ^1H NMR spectra (600 MHz) at 300 K of coencapsulation complexes of **12** (1 mM) in mesitylene- d_{12} (0.5 mL) and 10–30 μL of each liquid guest. (a) *p*-ethyltoluene with CCl_4 ; (b) 4-methylanisole with benzene; (c) *N*-methyl-*p*-toluidine with CCl_4 .

Table 1. Social Isomer Ratios of *p*-Ethyltoluene (**2**), 4-Methylanisole (**3**), and *N*-Methyl-*p*-toluidine (**4**) with Common Solvents and Gases

solvent	vol. ^a \AA^3	surf. \AA^2	dipole D^b	solute 2 $K^c=$	solute 3 $K^c=$	solute 4 $K^c=$
CH_2Cl_2	60	82	1.60	2.5	4.7	5.6
CHCl_3	75	98	1.01	4.4	3.1	3.5
$(\text{CH}_3)_2\text{CHCl}$	76	104	2.17	2.2	2.7	1.8
$(\text{CH}_3)_2\text{CCl}_2$	91	119	2.27	4.6	2.8	1.7
CCl_4	91	113	0	5.7	2.1	1.4
$(\text{CH}_3)_2\text{CHOH}$	66	96	1.68	4.1	4.5	4.4
$(\text{CH}_3)_2\text{CO}$	60	88	2.88	2.8	5.6	4.3
C_6H_6	77	103	0	6.0	1.2	0.7
$\text{C}_6\text{H}_5\text{N}$	72	98	2.19	4.3	4.3	3.1
$\text{C}_2\text{H}_5(\text{CH}_3)\text{CHOH}$	82	116	1.64	4.5	3.2	2.4
$\text{C}_2\text{H}_5\text{CH}_2\text{OH}$	66	96	1.68	3.5	7.1	8.9
$\text{C}_3\text{H}_7\text{CH}_2\text{OH}$	81	118	1.66	4.0	4.6	13.5
$\text{C}_2\text{H}_5\text{CH}(\text{CH}_3)_2$	91	124	0.13	5.5	2.5	1.6
<i>n</i> - C_5H_{12}	90	127	0	2.4	1.9	1.7
<i>c</i> - C_6H_{12}	97	127	0	10	1.2	0.95
$\text{CH}_3\text{CH}=\text{CH}_2$	54	78	0.37	2.9	3.2	4.6
CH_3CH_3	42	66	0	2.8	4.4	4.1

^a Volumes and surfaces were minimized with the program Hyperchem 7.0, Hypercube Inc., 2002, at semiempirical PM3 level and calculated with WebLab Viewer Pro 4.0 by Molecular Simulations Inc. ^b Dipole moments are from the *Handbook of Chemistry and Physics*. ^c The social isomeric ratios are subject to uncertainties of $\pm 10\%$, due to integration errors.

This trend contrasts with that of the anisole: the larger (and less polar) solvents cyclohexane, benzene, and CCl_4 appear to tolerate (but still not prefer) the Ar-methyl near the middle ($K = 1.2\text{--}2.1$). The smaller and more polar acetone and CH_2Cl_2 show an increased preference for the O-methyl nearby (K is 5.6 and 4.7, respectively). The smallest ethane also preferred the methoxy. The opposite trend in the ratio for **2** and **3** could be related to the repulsive interactions between the lone pairs on the oxygen of the anisole and the solvent molecules. Polar attractions to the methoxy are also apparent with pyridine and the secondary alcohols. The primary alcohol, propanol,

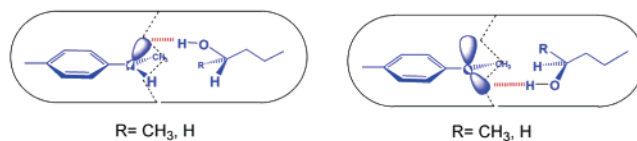


Figure 3. Idealized approaches of a hydrogen bond donor to an aniline ether (left) and an aryl ether (right).

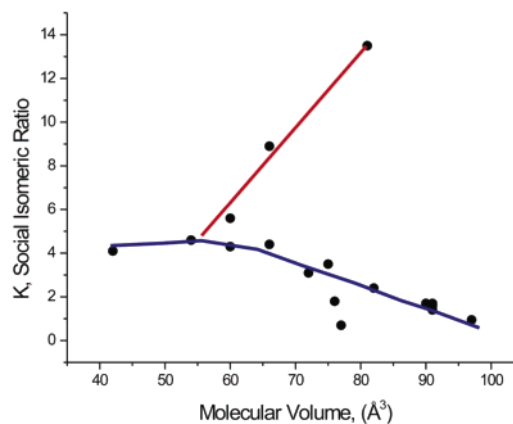


Figure 4. Plot of K , social isomeric ratio for *N*-methyl-*p*-toluidine, as a function of the molecular volume of the co-guest. The blue line is the trend due to repulsive interactions between the guests. The red line is the effect of attractive interactions due to hydrogen bonding.

shows the greatest preference for the methoxy group ($K = 7.1$) and suggests contact between the two guests.

The evidence for interguest hydrogen bonding is, at best, indirect. One would expect a larger K if the secondary alcohols were acting as donors, yet the values are comparable to acetone, which cannot donate. The dimensions of the capsule may not allow the effective approach of a secondary alcohol to the appropriate lone pair of the ethereal oxygen (Figure 3).

Like the previous case, the shape of *N*-methyltoluidine prejudices its orientation in the capsule, but the range is now broader and nearly a factor of 20 separates the highest and lowest isomer ratios. Cyclohexane and benzene now prefer the Ar-methyl, while the alkanes and CCl_4 show a slight preference for the polar N-methyl end of the solute, and the smallest CH_2Cl_2 , acetone, and ethane favor the N-methyl group nearby. Secondary alcohols showed little evidence of hydrogen bonding, but the effects of primary alcohols were dramatic. The expected interactions between the best donor (alcohol) and acceptor (nitrogen) involve a geometry different from that of the anisole case (Figure 3).

Another piece of evidence on the hydrogen bonding issue is presented in Figure 4. There is a general trend relating solvent volume to the social isomer ratio, K . The larger solvents lower the K as observed for **2** (blue line). The primary alcohols, however, reverse this trend (red line), as would be expected from interguest hydrogen bonding.

Energy minimized structures for typical coencapsulation complexes are shown in Figure 5.

Ad hoc explanations abound because it is not possible to change a single feature at a time. Every change in shape comes with changes in size, surface, polarity, volume, etc. The restricted geometries for interactions between solvent and solute do not guarantee that either social isomer is the universal energy minimum; instead, their relative energies are established. Accordingly, interpretations may – and are likely to – change with time, but data must not. In the meantime, two features of coencapsulation conspire to make the events here unique: First, concentrations are amplified – the volume of the capsule ($\sim 4 \times 10^{-25}$ L) translates into ~ 4 M

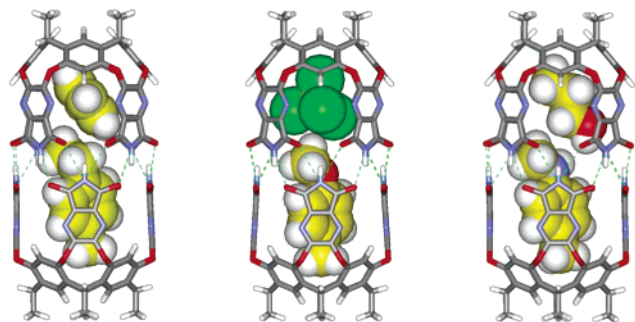


Figure 5. Energy optimized structures (MM⁺ force field¹³) of the favored social isomers of *p*-ethyltoluene with benzene (left), 4-methylanisole with CCl₄ (middle), and *N*-methyl-*p*-toluidine with 1-propanol (right).

concentration of each guest inside. Second, the lifetime of the coencapsulation complex is on the order of 1 s, an interval some billion times longer than that of an encounter complex between solvent and solute, free in solution. The coencapsulated state is an intermediate phase, somewhere between conditions in bulk solution and the intramolecular solvation of reactants in the gas phase.¹⁴

Supramolecular stereochemistry assumes many forms,¹⁵ as the mechanical barriers impose both obvious and subtle limitations on mobility. These limitations create new forms of isomerism dealing with arrangements in space, rather than covalent connectedness.¹⁶ Translational and rotational freedom can be curtailed,¹⁷ and even the internal dynamics of the guest – rotation around amide bonds¹⁸ or ring inversions^{19,20} – can be affected. The case at hand provides well-defined contacts between two molecules temporarily frozen in space and time, yet in the liquid phase and at ambient temperatures. It expands the scope of physical organic chemistry.

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