Communications to the Editor

Carceplex Formation: Scope of a Remarkably Efficient Encapsulation Reaction†

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Carceplexes are closed surface compounds that contain permanently entrapped molecules within their shells, akin to a ship in a bottle.[1,2] Molecular entrapment in materials with a high degree of crystallinity augers well for the use of carceplexes in nanotechnological applications where intermolecular organization is paramount to success.[3] Sherman and Cram synthesized carceplexes **1**·guest (where guest is one solvent molecule) by joining six molecules and forming eight new bonds in over 60% yield.[1] The reaction appeared to require templation by a guest molecule such as dimethyl sulfoxide. Here, we explore the scope of the carceplex reaction and probe the driving force for incarceration. We report a method that expands the range of possible guest molecules well beyond that of dipolar aprotic solvents. We also show that the efficiency of the carceplex-forming reaction is extraordinarily sensitive to the guest molecule; thus, incarceration represents a dramatic example of a templation effect.

Previously, the carceplex reaction (Scheme I) proceeded in 49, 54, and 61% yields when the reaction was run in the solvents dimethylformamide, dimethylacetamide (DMA), and dimethyl sulfoxide, respectively. No carceplex was isolated when the reaction was run in *N*-formylpiperidine, a solvent too large for the carceplex interior. Furthermore, a 10% yield of **1**·DMA was isolated when *N*-formylpiperidine was doped with 0.5% DMA.[1] We decided to exploit this last observation by using a bulky, polar[4] reaction solvent that is a poor guest/template to probe a wide range of nonsolvent molecules as potential guests/templates. Table I lists guests that successfully effected carceplex formation[5] in the solvent 1-methylpyrrolidin-2-one (NMP)[4] along with their yields[6] and the relative preference for incarceration based upon competition experiments.[7] We chose NMP, the poorest guest/template to date, as a reference point for the preferential ratios.[7] The 87% yield for pyrazine is the only optimized yield. To probe the templating power of pyrazine, we also ran the carceplex reaction using *only 1 equiv* of pyrazine per two tetrol **2** molecules (0.01 mol % based on solvent NMP) and obtained a 75% yield of **1**·pyrazine. Unsuccessful guests include *N*,*N*-dimethylpro-

Scheme I. Carceplex Formation.

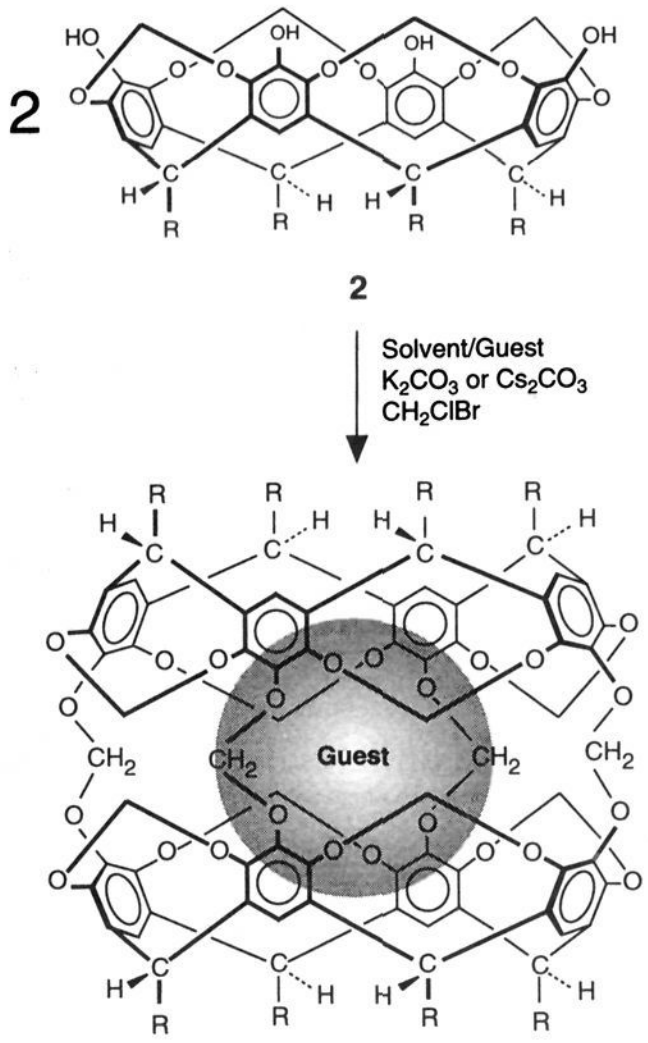

Table I. Carceplex Yields and Competition Experiments

guest	yield (%)[a]	ratio[b]	conditions[b]
pyrazine	87	1 000 000	A
1,4-dioxane	68	290 000	A
dimethyl sulfide	52	180 000	A
dimethyl sulfoxide	63	70 000	A
1,3-dioxolane	64	38 000	A
2-butanone	75	37 000	A
pyridine	46	34 000	A
dimethyl sulfone	60	19 000	A
furan	54	12 000	A
tetrahydrofuran	50	12 000	A
acetone	51	6700	A
thiophene	23	5800	A
benzene	43	2400	A
2-propanol	74	1500	A
pyrrole	73	1000	B
tetrahydrothiophene	34	410	B
1,3-dioxane	45	200	B
acetamide	26	160	B
trioxane	24	100	B
acetonitrile	35	73	B
ethanol	38	61	B
dimethylacetamide	15	20	B
dimethylformamide	4	7	B
NMP	5[c]	1	B

[a] Yield refers to the reaction run with one guest only (see note 5). [b] A: 1 mol % guests. B: 5 mol % guests, 1 day at 25 °C, 2 days at 60 °C (see note 7). [c] Reaction was run in 100% NMP.

† Dedicated to Prof. D. J. Cram on the occasion of his 75th birthday.

(1) Sherman, J. C.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 2194–2204.

(2) (a) Bryant, J. A.; Blanda, M. T.; Vincenti, M.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 2167–2172. (b) Cram, D. J. *Nature* **1992**, *356*, 29–36. (c) Müller, A.; Diemann, D.; Krickemeyer, E. *Naturwissenschaften* **1993**, *80*, 77–78.

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(4) The phenoxide salts of **2** are most soluble in highly polar solvents. We chose 1-methylpyrrolidin-2-one (NMP) as the solvent because it is less expensive than *N*-formylpiperidine.

(5) A modification of the literature procedure[1] was used. Typical conditions were as follows: 0.1 mmol of tetrol **2**, 50 mmol of guest (5% v/v based on NMP), 1 mmol of bromochloromethane, and 10 mmol of potassium carbonate were added to 100 mL of NMP. The reaction mixture was stirred at 60 °C for 2 days. High dilution is unnecessary, and K_2CO_3 works as well as Cs_2CO_3. The workup was as reported earlier.[1] Carceplexes **1**·acetamide through **1**·ethanol in Table I were initially obtained as mixtures of **1**·guest and **1**·NMP. These carceplexes were separated by chromatography using 3:1 chloroform:hexanes on silica gel.

(6) All new carceplexes in Table I gave C and H analyses within 0.4% of theory and the expected ^{1}H NMR and desorption chemical ionization mass spectra.

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pionamide, *N*,*N*-diethylacetamide, *N*,*N*-diethylformamide, *N*-formylpiperidine, dimethoxyethane, chloroform, norbornadiene, α-pyrone, cyclohexanone, 3-pentanone, fluorobenzene, chlorobenzene, bromobenzene, hexafluorobenzene, cyclohexane, cyclopentane, *n*-hexane, pyrrolidine, piperidine, diethylamine, morpholine, *N*,*N*-dimethylcyanamide, water, and ethylene glycol.

We suggest that the ratios in Table I represent the relative rates of the guest-determining step, which is the step that renders the guest permanently entrapped under the reaction conditions. The rate of this step is enhanced by a factor of 10^6 by the use of a good template molecule.[8] From Table I and the list of unsuccessful guests, we can make the following conclusions. (1) Size selectivity: the failure to entrap large amides and substituted benzenes suggests a limit of about seven non-hydrogen atoms, NMP being the largest (and poorest) successful guest. (2) Polarity: neither highly polar (e.g., water) nor highly apolar molecules (e.g., cyclopentane) are entrapped; good guests range in polarity from dimethyl sulfoxide to benzene. (3) Symmetry: 1,4-dioxane is over 1400 times better at templating the carceplex reaction than 1,3-dioxane. (4) Secondary amines are not entrapped.[9] (5) Cyclic molecules are better templates than acyclic. Overall, the templation of the carceplex reaction is driven by an optimum of van der Waals interactions and a minimum of steric interactions between the guest/template molecule and the interior of the forming shell. We have observed no correlation between our ratios and solvent parameters (e.g., acceptor number,[10] dielectric constant,[11] dipole moment,[11] E_T,[11] or Hildebrand's δ[12]), which suggests that solvophobic effects are not a major driving force for templation. We have observed no correlation between our template ratios and MM2 calculations[13] on the final carceplex molecules (data not shown) to model size/shape effects. This suggests that the final carceplex molecule is a poor model for the intermediate involved in the guest-determing step. We are currently analyzing reaction intermediates so we can delineate and explore the guest-determining step of incarceration.

In summary, we have described a method that dramatically expands the types of guest molecules that can be entrapped in carceplexes; thus, nanotechnological applications are now even more viable. We have demonstrated an extraordinary templation effect in which the size and shape of guest molecules yield a 10^6-fold range in entrapment selectivity.

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(7) Competition experiments were performed by running the reaction as described[5] except with the addition of 1 or 5 mol % (conditions A or B, respectively) of each pair of guests that are adjacent in Table I. For condition B, the reaction was run at room temperature (RT) for 1 day and then at 60 °C for 2 days. The guest ratios were determined by integration of the host and guest signals in the ^{1}H NMR spectra of the mixtures. Errors are estimated to be <20% based on integration. Crosschecks were run to check the validity of tabulating the guest ratios based on adjacent competition experiments. A pyrazine:2-propanol competition was run starting with a 1:500 ratio of pyrazine:2-propanol and gave, after adjusting for the starting ratio, an 850:1 ratio for pyrazine:2-propanol. This is in good agreement with the 670:1 ratio derived from our table. Likewise, a 2-propanol:NMP crosscheck gave a 1000:1 2-propanol:NMP ratio, which agrees with the 1500:1 ratio derived from the table. Overall, the two crosschecks yield an 850 000:1 ratio for pyrazine:NMP, which compares well with the 1 000 000:1 from the table, considering a possible 20% error for each adjacent pair of guests. Over 30 other crosschecks were run; all agree to within a factor of 2 with the numbers from the table. Lastly, competition reactions starting with ratios of guests varying from 1:1 to 9:1 guest A:guest B gave the same relative preferences of A:B to within 20% error. Thus, competition between guests is linearly dependent on their concentrations.

(8) Note that yields are not strictly indicative of a guest's templating ability. For example, pyrrole gives a higher yield than thiophene, which is higher on the table. Lower yields may be caused by a small fraction of the guest (e.g., thiophene) slowly reacting with CH_2BrCl and thus degrading the bridging reagent. This would not affect the ratios. Lower yields may also be due to slow reactions subsequent to the guest-determining step. This problem is particularly true with the larger guests (e.g., benzene), which may distort the shell and thus misalign the phenoxides involved with the formation of the final bridge. Slower formation of the final bridge could allow polymerization to increase and thus diminish carceplex yields. For the worst case, benzene, the 30% lower yield compared to 2-propanol might manifest itself in a lower apparent ratio by as much as 30% since 30% of the benzene carceplex intermediates may polymerize. This is only slightly outside of our 20% error.

(9) Experiments with 1 mol % of pyrazine and 1 mol % of the four secondary amines gave 1·pyrazine. Thus, the inability of secondary amines to effect carceplex formation is due to their unsuitability as guests and not due to degradation of CH_2BrCl.

(10) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: New York, 1988; p 23.

(11) Reference 10, pp 407–410.

(12) Hildebrand, J. H.; Prausnitz, J. M.; Scott, R. L. *Regular and Related Solutions*; Van Nostrand Reinhold Company: New York, 1970; pp 27, 213–215.

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