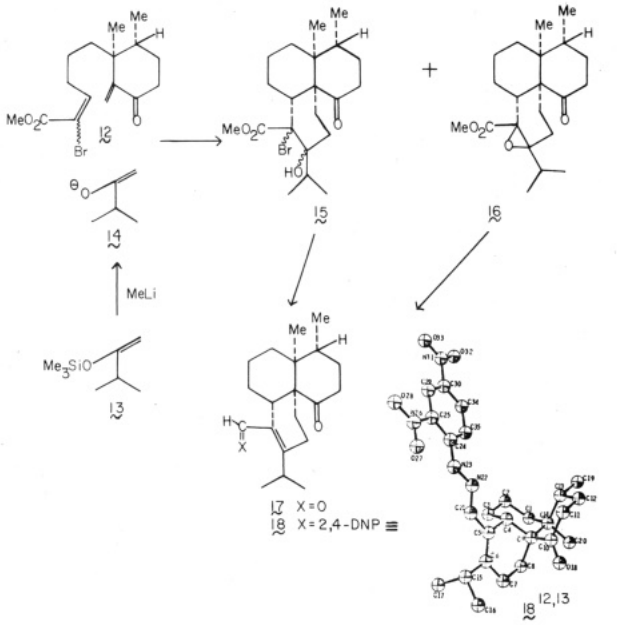
Scheme I



ture) from **9**, reacts with the sodium salt of methyl (dimethylphosphinyl)bromoacetate[9] in 1,2-dimethoxyethane to afford **11**. Treatment of **11** with *m*-chloroperoxybenzoic acid gives rise to **12** as a 2:3 mixture of *E* and *Z* isomers.

Reaction of silyl enol ether **13** (3.5 equiv) at −78 °C in 1,2-dimethoxyethane with methyllithium (2.5 equiv) generates, presumably, enolate **14**, which reacts with the esters **12** (−78 °C (30 min) → room temperature (1 h)). Chromatography on silica gel afforded three products (Scheme I). The least polar product (25%) corresponds to a bromohydrin,[5] formulated as structure **15**.[10] The other two products (15% combined, in a 4:1 ratio) are the epoxides **16**.[11] The major less polar epoxide melts from 138 to 139 °C, while the minor isomer melts from 142 to 143 °C.

That the bromohydrin **15** and the epoxides **16** contain the cis–cis stereochemistry (required for aflavinine) was demonstrated by their conversion to the same keto enal **17**. For **15**, this transformation was accomplished (44%) by reaction with lithium aluminum hydride in ether followed by oxidation with bis(pyridinium) dichromate in methylene chloride. Compound **17** was also obtained (51%) from the major epoxide **16** by the following sequence: (i) Red-Al–THF (Aldrich); (ii) pyridinium chlorochromate; (iii) Me_3SiI–carbon tetrachloride.

The structure of **17** was confirmed by X-ray crystallographic analysis[12,13] of its derived 2,4-dinitrophenylhydrazone, mp 243–244 °C dec.

Enlargements upon this theme and applications to the solution of various problems in total synthesis are receiving continuing attention in our laboratory.

Acknowledgment. This work was supported by PHS Grant HL 25848. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210.

Registry No. **4**, 1119-51-3; **5**, 10463-42-0; **6**, 82343-62-2; **7**, 82343-65-5; **8**, 87011-65-2; **9**, 87011-66-3; **10**, 87011-67-4; **11**, 87011-68-5; (*E*)-**12**, 87011-69-6; (*Z*)-**12**, 87068-06-2; **13**, 17510-45-1; **15**, 87011-70-9; **16** (isomer 1), 87011-71-0; **16** (isomer 2), 87068-07-3; **17**, 87011-72-1; **18**, 87011-73-2.

Supplementary Material Available: Tables containing fractional coordinates, temperature factors, bond distances, and bond angles are compound **18** (5 pages). Ordering information is given on any current masthead page.

(9) Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

(10) The stereochemistry of the hydroxyl and bromine and functions of the bromohydrin are unassigned.

(11) The sterochemistry of the oxirane ring is unassigned.

(12) Suitable crystals for X-ray diffraction formed from a methylene chloride/methanol mixture with symmetry $P2_1/c$. Preliminary experiments gave cell parameters of a = 12.860 (1) Å, b = 10.574 (3) Å, c = 19.108 (2) Å, and β = 106.91 (1)° for Z = 4. An automatic four-circle diffractometer equipped with a sealed-tube Cu X-ray source (λ = 1.5418 Å) and graphite monochromator was used for data collection. Of the 3573 reflections measured with $2\theta \leq 114°$, 2447 were observed ($I \geq 3\sigma I$). A multisolution tangent formula approach[13] to the phase solution gave an initial model, which was subsequently refined by using full-matrix least-squares techniques. Hydrogens were added with fixed isotropic temperature factors. The function minimized was $\sum\omega(|F_o| - |F_c|)^2$ with $\omega = (1/\sigma F_0)^2$ to give a final unweighted residual of 0.040. All intramolecular bond distances and angles are within normal ranges, and there are no abnormally short intermolecular contacts. Figure **18** is a perspective drawing showing the relative configuration of **18**. Tables I–III containing the final X-ray parameters, bond distances, and bond angles are provided as supplementary material.

(13) The following library of crystallographic programs was used: MULTAN 80, University of York, York, England, 1980; Structure Determination Package V17.0, Enraf-Nonius Corporation, Delft, Holland, 1981; ORTEP-II, Oak Ridge National Laboratory, Oak Ridge, TN, 1970.

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Phosphine- and Phosphite-Mediated Difluorocarbene Exchange Reactions of (Bromodifluoromethyl)phosphonium Salts.[1] Evidence for Facile Dissociation of (Difluoromethylene)triphenylphosphorane

Summary: (Bromodifluoromethyl)triphenylphosphonium bromide undergoes facile exchange of the bromodifluoromethyl group with tertiary phosphine and trialkyl phosphite. A mechanism that involves formation of the difluoromethylene ylide and dissociation of the ylide into difluorocarbene and triphenylphosphine is proposed to account for the observed exchange processes.

Sir: Phosphonium ylide formation by capture of electrophilic carbenes with nucleophilic tertiary phosphines is a well-established synthetic method[2] and has been recently shown to be a symmetry-breaking allowed pathway to ylides.[3] To our knowledge, however, no evidence has been presented to demonstrate the reverse process, namely, dissociation of a phosphonium ylide into carbene and tertiary phosphine.

We now report that (difluoromethylene)triphenylphosphorane (**3**), generated by the reaction of (bromodifluoromethyl)triphenylphosphonium bromide (**1**) with

(1) Presented in part at the 10th International Symposium on Fluorine Chemistry, Vancouver, Canada, August 1982, Abstract O-5.

(2) Speziale, A. J.; Marco, G. T.; Ratts, K. W. *J. Am. Chem. Soc.* **1960**, *82*, 1260. Speziale, A. J.; Ratts, K. W. *Ibid.* **1962**, *84*, 854. Burton, D. J.; Naae, D. G. *Synth. Commun.* **1973**, *3*, 197. Naae, D. G.; Kesling, H. S.; Burton, D. J. *Tetrahedron Lett.* **1975**, 3789. Tyuleneva, V. V.; Rokhlin, E. M.; Knunyants, I. L. *Russ. Chem. Rev.* (*Engl. Transl.*) **1981**, *50*, 280.

(3) Trinquier, G.; Malrieu, J. P. *J. Am. Chem. Soc.* **1979**, *101*, 7169.

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Scheme I

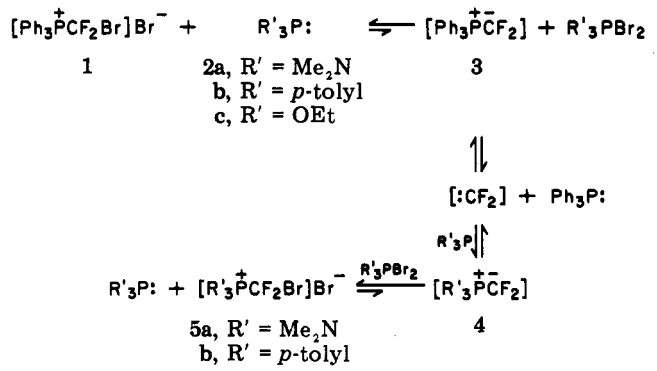


Table I. Reactions of 1 and 2a in Proton-Donor Solvents

reactants (equiv)	solvent	fluorinated products,[a] % 1	2a	6	7
1 (1) + 2a (5.5)	CH_2Cl_2			100	
1 (1) + 2a (5.5)	CH_3CN			100	
1 (4) + 2a (1)	CH_2Cl_2	73			27
1 (2) + 2a (1)	CH_3CN	57		4	38

[a] Product distribution determined by ^{19}F NMR.

tertiary phosphine or trialkyl phosphite, readily dissociates into difluorocarbene and triphenylphosphine, cf. Scheme I. Evidence consistent with this mechanistic proposal follows.

Tertiary phosphines other than triphenylphosphine react with 1 to give new (bromodifluoromethyl)phosphonium salts 5. The rate and extent of bromodifluoromethyl exchange depends upon the phosphine, solvent, and temperature. For example, 1 and 2a react in 1,2-dimethoxyethane at 50 °C after 64 h to give only 5a and triphenylphosphine. In triglyme, the exchange between 1 and 2a is complete within 5 h.[4-7]

As expected, 1 and 2b also exchange, but at a slower rate. Thus, in 1,2-dimethoxyethane, a 1:1 mixture of 1 and 5b is observed after 120 h at room temperature. In triglyme at 70 °C, the ratio of 1/5b is 94:6 after 6 h, 32:68 after 24 h, and 7:93 after 48 h.[8]

The concentration dependence of product formation is also consistent with the dissociation–exchange mechanism (Scheme I). In proton-donating solvents such as CH_2Cl_2 or CH_3CN, 1 and an excess of 2a react rapidly and exothermically to give 6 as the *only* fluorinated product (eq 1). By contrast, 7 is the major product from 2a and an

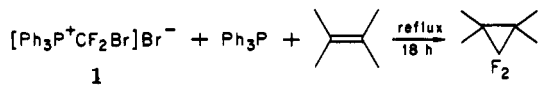
$$1 + \text{excess } \mathbf{2a} \xrightarrow[CH_3CN,\ 25\ °C]{CH_2Cl_2\ or} \underset{\mathbf{6}}{[(Me_2N)_3P^+CF_2H]X^-} \quad (1)$$

excess of 1 in these solvents[9] (Table I) (eq 2).

$$\text{excess 1 and } \mathbf{2a} \xrightarrow[CH_3CN,\ 25\ °C]{CH_2Cl_2\ or} \underset{\mathbf{7}\ \text{(major)}}{[Ph_3P^+CF_2H]X^-} + \mathbf{6}\ \text{(minor)} \quad (2)$$

This concentration dependence suggests that protonation and exchange involve a common intermediate, ylide 3. Since direct attack of phosphine on 3 is improbable, the equilibrium $3 \rightleftharpoons :CF_2 + Ph_3P$ is implicated, and exchange proceeds via phosphine capture of difluorocarbene.[10]

Further evidence for the dissociation of 3 into $:CF_2$ and Ph_3P is provided by carbene-trapping experiments with 2,3-dimethyl-2-butene (TME). 1,1-Difluoro-2,2,3,3-tetramethylcyclopropane (8) is formed in 35% yield if an equimolar mixture of 1 and Ph_3P is heated in an excess of TME (21 mol) (eq 3). If 1 is heated in TME under the



1 8 (3)

same conditions in the absence of Ph_3P, 8 is not detected by GLPC or ^{19}F NMR.[11]

Additional corroborative evidence for dissociation of 3 is provided by the facile exchange between 1 and triethyl phosphite (2c). Thus, 1 and 2c in CH_2Cl_2 react to give a 92% yield of diethyl (bromodifluoromethyl)phosphonate (9)[12] after 10 min at room temperature (eq 4). The for-

$$3 \rightleftharpoons Ph_3P + [:CF_2] \xrightleftharpoons{(EtO)_3P} [(EtO)_3P^+C^-F_2] \xrightleftharpoons{(EtO)_3PBr_2} [(EtO)_3P^+CF_2Br]Br^- + (EtO)_3P \rightarrow \underset{\mathbf{9}}{(EtO)_2P(O)CF_2Br} + EtBr \quad (4)$$

mation of 9 is best explained by the ylide–carbene equilibrium outlined in Scheme I. The irreversible Michaelis–Arbuzov reaction in the last step shifts all the equilibria toward 9.[14]

In summary, the ready exchange reactions of 1 with tertiary phosphines and trialkyl phosphites, the concentration dependence of the reactions of 1 with tertiary

(4) These exchange reactions are easily monitored by ^{31}P and ^{19}F NMR spectroscopy; cf.: Van Hamme, M. J.; Burton, D. J.; Greenlimb, P. E. *Org. Magn. Reson.* **1978**, *6*, 275 for typical chemical shifts and coupling constants. The product 5a was isolated, and its melting point and ^{31}P and ^{19}F NMR spectra were identical with those of an authentic sample.

(5) The exchange between 1 and 2a is irreversible within the NMR detection limits (all 1 is converted to 5a). However, triphenylphosphine apparently can abstract positive bromine from 5a. This is corroborated by the reaction between 5a and triphenylphosphine in $CHCl_3$/EtOH, which gives only $[(Me_2N)_3P^+CF_2H]Br^-$ after 6 h at room temperature.

(6) The exchange between 1 and 2a is rapid even at low temperatures. In THF at −53 °C, the ratio of 1/5a was 87:13 after 1 h, 42:58 after 3.5 h, and 16:84 after 4.5 h.

(7) Since 1 and 5 have limited solubilities in most solvents and the reactions reported here are heterogeneous, no special significance should be placed on the rate or extent of exchange.

(8) Addition of trifluoroacetophenone to the triglyme reaction after 56 h resulted in a 53% yield of $C_6H_5C(CF_3)=CF_2$, in agreement with the equilibrium reaction proposed in Scheme I.

(9) Cf. ref 4 for NMR data of 6 and 7.

(10) Alternative possibilities might include reaction between 3 and R'_3PBr_2 or the direct attack of phosphine on 1 to produce a bisphosphonium salt, which then selectively cleaves to give 4 or 5. However, related phosphonium salts such as $[Et_3P^+CF_2P^+Bu_3]\,2Br^-$ have been prepared in our laboratory and do not undergo cleavage by bromide ion to either (bromodifluoromethyl)phosphonium salts or difluoromethylene ylides; unpublished work of H. S. Kesling, University of Iowa.

(11) An alternative explanation for the formation of 8 could be a [2 + 2] cycloaddition between 3 and TME, followed by the extrusion of Ph_3P and 8. However, such a rationale seems unduly speculative and it is not consistent with the observed concentration dependence results. A reviewer has suggested that a competition experiment might provide additional supportive evidence for the carbene intermediate. Consequently, we have heated (95 °C) 1 with excess TME, triphenylphosphine, and 2-methyl-2-butene. A mixture of 8 and the analogous difluorocyclopropane derivative from 2-methyl-2-butene was obtained in a ratio of ~4:1. This ratio compares favorably with that expected (3:1) from previous work of Mitsch [Mitsch, R. A.; Rogers, A. S. *Int. J. Chem. Kinet.* **1969**, *1*, 439].

(12) Product 9 was isolated and identified by comparison of its boiling point and ^{19}F NMR spectrum with an authentic sample.[13] Ethyl bromide was identified by its ^1H NMR spectrum and enhancement of the NMR signals on addition of EtBr. Triphenylphosphine was isolated in 65% yield and identified by mixture melting point with authentic material.

(13) Burton, D. J.; Flynn, R. M. *J. Fluorine Chem.* **1977**, *10*, 329.

(14) Alternative routes that involve intermediates such as $[Ph_3P^+CF_2P(O)(OEt)_2]Br^-$ are improbable since $[Bu_3P^+CF_2P(O)(OEt)_2]Br^-$ has been prepared and is stable; unpublished work of H. S. Kesling, University of Iowa. It does not cleave to 9, and there is no reason to expect that the triphenyl analogue would behave differently.

(15) Contribution No. 3236 from the Central Research and Development Department.

phosphines, and the cyclopropanation of TME by 1 and triphenylphosphine can best be explained by formation and dissociation of the difluoromethylene ylide. Whether the driving force for this facile dissociation is the stability of difluorocarbene or whether this behavior is general for ylides cannot be ascertained without additional work. However, caution should be excercised when one writes these types of ylide reactions as irreversible processes without any experimental justification.

Acknowledgment. The work at UI was generously supported by the National Science Foundation and the Air Force Office of Scientific Research. D.J.B. thanks Professors Chambers and Koch for helpful discussions and NATO for a travel grant.

Registry No. 1, 58201-66-4; **2a**, 1608-26-0; **2b**, 1038-95-5; **2c**, 122-52-1; **5a**, 58310-30-8; **5a** (phosphorane), 58310-29-5; **5b**, 87137-21-1; **6**, 87145-05-9; **6** (phosphorane), 87137-22-2; **7**, 58310-28-4; **8**, 823-25-6; **9**, 65094-22-6; TME, 563-79-1.

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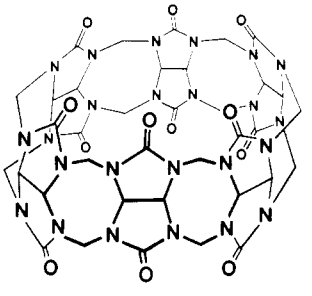
Host–Guest Binding Capacity of Cucurbituril

Summary: The novel cage substance cucurbituril encapsulates and tightly binds substituted ammonium ions having dimensions smaller than a para-disubstituted benzene ring.

Sir: Cucurbituril (1, $C_{36}H_{36}N_{24}O_{12}$) is a recently rediscovered nonadecacyclic cage structure of hexagonal symmetry, which is readily assembled from urea, glyoxal, and formaldehyde.[1,2] It has a relatively rigid structure, with



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a hollow core of several angstroms diameter, which is accessible from the exterior. The substance dissolves readily in acidic aqueous solutions. According to the following evidence, it forms a novel series of host–guest complexes with alkylammonium ions. For example, gradual addition of 1 to a dilute formic acid solution of isobutylamine [$(CH_3)_2CHCH_2NH_2$] results in diminution of the proton NMR methyl signal for the isobutyl group and concurrent emergence of a new doublet approximately 1 ppm to higher field. This is attributed to encapsulation of the aliphatic residue within the cavity of 1. The complexation is stoichiometric (1:1, by NMR integration), and quite evidently exchange between external and internal environments is slow, since there is no averaging of NMR signals at 40 °C when excess isobutylammonium ion is present.

Table I. Dissociation Constants for Representative Alkylammonium and Alkyldiammonium Ions in 1:1 Aqueous Formic Acid (v/v)[a]

guest (RNH_3^+)	K_d, M
$CH_3CH_2CH_2NH_3^+$	8.2×10^{-5}
$CH_3CH_2CH_2CH_2NH_3^+$	1.0×10^{-5}
$CH_3CH_2CH_2CH_2CH_2NH_3^+$	4.2×10^{-5}
$(CH_3)_2CHCH_2CH_2NH_3^+$	2.8×10^{-5}
$(CH_3)_3CCH_2CH_2NH_3^+$	5.7×10^{-2}
$(CH_2)_2CHCH_2NH_3^+$ (cyclopropanemethyl)	6.8×10^{-5}
$(CH_2)_3CHCH_2NH_3^+$ (cyclobutanemethyl)	2.7×10^{-6}
$(CH_2)_4CHCH_2NH_3^+$ (cyclopentanemethyl)	3.0×10^{-6}
$(CH_2)_5CHCH_2NH_3^+$ (cyclohexanemethyl)	not bound[a]
$C_6H_5CH_2NH_3^+$	3.7×10^{-3}
p-$CH_3C_6H_4CH_2NH_3^+$	3.1×10^{-3}
m-$CH_3C_6H_4CH_2NH_3^+$	not bound[b]
o-$CH_3C_6H_4CH_2NH_3^+$	not bound[b]
2-$C_4H_3SCH_2NH_3^+$ (thiophenemethyl)	4.3×10^{-6}
$NH_3^+(CH_2)_4NH_3^+$	6.5×10^{-6}
$NH_3^+(CH_2)_5NH_3^+$	4.1×10^{-7}
$NH_3^+(CH_2)_6NH_3^+$	3.6×10^{-7}
$NH_3^+(CH_2)_7NH_3^+$	2.3×10^{-5}
$NH_3^+(CH_2)_8NH_3^+$	1.1×10^{-4}

[a] $K_d = (RNH_3^+)(1)/(RNH_3^+ \cdot 1)$. [b] Unmeasurable by present technique, estimate $K_d > 5 \times 10^{-2}$.

The latter feature permits measurement of relative binding constants by the simple expedient of allowing two different alkylammonium ions to compete for a limited amount of 1. NMR integration of the pertinent signals gives an affinity ratio directly (in favorable cases). By application of this technique we have accumulated extensive data on the host–guest specificity of 1. By spectral perturbations (UV) of the reference guest species, (4-methylbenzyl)ammonium ion, these measurements have been put on an absolute scale. Table I contains a sampling of our data (expressed as dissociation constants).

Among the straight-chain aliphatic monoamines, the *n*-butylammonium ion seems to be bound most tightly, with the measured K_d values increasing (weaker binding) for its higher or lower *n*-alkyl homologues. The isopentylammonium ion is bound about as well as the *n*-butyl ammonium ion, but the neohexylammonium ion is held relatively weakly and does not show the characteristic NMR shift, suggesting that the *tert*-butyl group is too large to be encapsulated by 1. The capacity of 1 is further defined by the cycloaliphatic series, in which (cyclopentanemethyl)ammonium ion seems to have the maximum size accommodated. For the (methylbenzyl)ammonium ions, affinity toward 1 is low, with only the *p*-methyl derivative able to adapt to the cavity. Evidently aromatic substituents must be oriented to the carbonyl-fringed portals of 1, and the ortho and meta substitution pattern cannot fit.[3] The comparatively stronger binding of (thiophenemethyl)ammonium ion further suggests that the larger, six-membered aromatics may not be ensconced within 1 without some distortion, resulting in higher K_d values.[4] Therefore, a para-disubstituted benzene ring

(1) Freeman, W. A.; Mock, W. L.; Shih, N.-Y. *J. Am. Chem. Soc.* **1981**, *103*, 7367.
(2) Compounds such as 1 have been given the class name cavitand: Moran J. R.; Karbach, S.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 5826.
(3) This specificity stands in contrast to the cyclodextrin complexes, in which arene substituent pattern has only a minor effect upon strength of binding: VanEtten, R. L.; Sebastian, J. F.; Clowes, G. A.; Bender, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 3242.

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