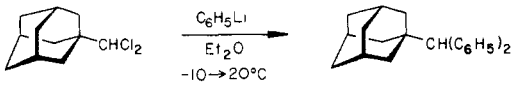
conformation is likely adopted to minimize steric interactions between the aromatic ring and dodecahedrane framework hydrogens. As a consequence, the noncrystallographic point symmetry of **4b** is C_s within experimental error.

While the three-membered ring is strikingly undistorted, those dodecahedrane bonds in the immediate vicinity of the C1–C11 fusion are extensively perturbed.[19] Thus, atoms C1 and C11 are involved in short C–C bonds ranging from 1.503 to 1.515 Å.[20] To compensate, the other C–C bonds within the two pentagonal rings which contain the C1–C11 bond are meaningfully lengthened (1.555–1.560 Å).[21] Furthermore, the interior C–C–C angles of these rings range from 106.0° to 109.8°. For the two pentagonal rings which contain either C1 or C11, but not both of these carbons, the range of internal angles is even greater: 104.5–113.7°. All the other cyclopentane rings have internal angles much closer to the ideal 108° (107.2–108.6°).

Finally, it remains to point out that the success of the intramolecular carbenoid insertion process described herein rests on the ability of the reaction center to eclipse a neighboring C–H bond. When this is not possible as in **8**,[11a] where the constrained molecular architecture forces the carbenoid carbon to bisect the H–C–H angle in all three directions, only substitution (and reduction) products are formed.[22]



8 (62%)

Acknowledgment. We are grateful to the National Institutes of Health for their generous financial support of this research program (Grant AI-11490).

(19) For a theoretical assessment of the energy costs associated with distorting the dodecahedrane framework, consult Ermer (Ermer, O. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 411).

(20) As a means of comparison, dodecahedrane itself has two types of framework bonds [1.541 (2) and 1.535 (5) Å] and three types of C–C–C bond angles [108.1 (1), 107.7 (2), and 107.9 (4)°]. See ref 8.

(21) All of the remaining C–C bonds lie in the range 1.536–1.552 Å and cannot be considered significantly different from the cyclopentane value of 1.546 Å (Adams, W. J.; Geise, H. J.; Bartell, L. S. *J. Am. Chem. Soc.* **1970**, *92*, 5013). Although no reduction to (chloromethyl)adamantane is seen with phenyllithium, this product does arise when methyllithium is utilized.

(22) Although no reduction to (chloromethyl)adamantane is seen with phenyllithium, this product does arise when methyllithium is utilized.

Selective Binding of Imidazoles and Related Organic Molecules in an Organic Solvent

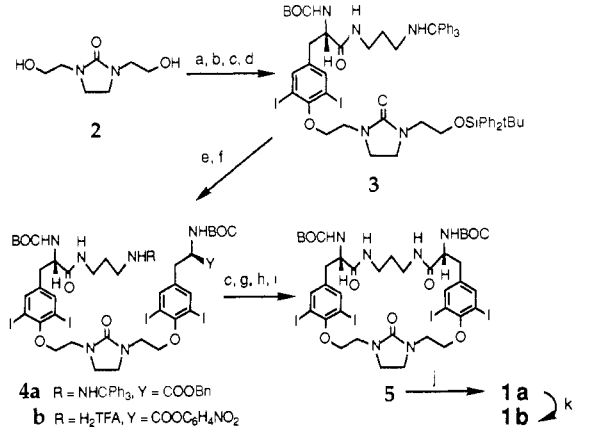
Jeremy D. Kilburn, A. Roderick MacKenzie, and W. Clark Still*

Department of Chemistry, Columbia University New York, New York 10027

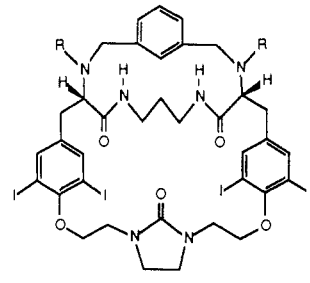
Received September 28, 1987

To form molecular complexes between neutral molecules, a driving force is needed which is compatible with the medium in which the complexation is to operate. In water, removing lipid surfaces from contact with solvent is an effective way to stabilize a molecule or complex. In organic solvents, specific electrostatic effects become more important and may not only drive complexation but also orient a substrate within a ligand. Previous reports of binding in organic solvents have described several systems capable of the oriented binding of neutral substrates although a few of the ligands incorporate well-defined three-dimensional cavities possessing functionality actively involved in the substrate complexation.[1] We believe that such geometrical features are important for selective binding and have prepared a new ligand (**1**) incorporating an enforced cavity lined with convergent but spatially separated hydrogen bond donor and acceptor functionalities. These acidic and basic sites cannot easily associate with one another either inter- or intramolecularly but should bind to organic substrates having complementary functionality and size. Here we describe the synthesis and structure of **1** and summarize the highly selective binding of **1a** to certain organic molecules having appropriately oriented hydrogen bond donor and acceptor functionalities.

Scheme I.



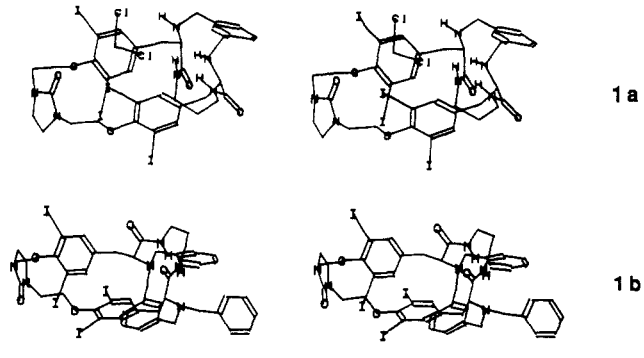
[a] a. *t*-BuPh$_2$SiCl (1 equiv), imidazole (45%); b. N-BOC O-Bn L-diiodotyrosine, Ph$_3$P, (*i*-PrO$_2$CN)$_2$ (90%); c. LiOH, H$_2$O, dioxane; d. Ph$_3$CNH(CH$_2$)$_3$NH$_2$, DCC, HOBT (c. + d. 70%); e. Bu$_4$NF, THF; f. N-BOC O-Bn D-diiodotyrosine, Ph$_3$P, (*i*-PrO$_2$CN)$_2$ (e. + f. 70%); g. *p*-NO$_2$C$_6$H$_4$OH, DCC, HOBT; h. 0.7% TFA, CH$_2$Cl$_2$ (c. + g. + h. 62%); i. high dilution, *i*-Pr$_2$NEt, CH$_3$CN (35–45%); j. (a) 35% TFA, (b) high dilution, *m*-C$_6$H$_4$(CH$_2$Br)$_2$, *i*-Pr$_2$NEt, CH$_3$CN (25–35%); k. excess BnBr, *i*-Pr$_2$NEt (70%).



1a R = H
1b R = CH$_2$Ph

The synthesis of **1** is outlined in Scheme I and begins with cyclic urea **2**.[2] The transformations were generally straightforward, and we note only that the macrocyclization steps proceeded in <50% yield. The mediocre yields for these steps probably reflect the size and flexibility of the ring (28 members, 16 low barrier rotatable bonds) in the monocyclization of **4** to **5** (35–45%) and the requirement of both inter- and intramolecular steps in the cyclization of **5** to **1a** (25–35%).

Ligand **1a** was recrystallized from CH$_2$Cl$_2$, and its structure was determined by X-ray crystallography. As shown below, the



1a

1b

(1) Previous examples of oriented binding in organic solvents: Rebek, J.; Askew, B.; Islam, N.; Killoran, M.; Nemeth, D.; Wolak, R. *J. Am. Chem. Soc.* **1985**, *107*, 6736. Rebek, J.; Nemeth, D. *J. Am. Chem. Soc.* **1985**, *107*, 6738. Rebek, J.; Nemeth, D. *J. Am. Chem. Soc.* **1986**, *108*, 5637. Sheridan, R. E.; Whitlock, H. W. *J. Am. Chem. Soc.* **1986**, *108*, 7120. Rebek, J.; Askew, B.; Ballester, P.; Buhr, C.; Jones, S.; Nemeth, D.; Williams, K. *J. Am. Chem Soc.* **1987**, *109*, 5033. Hamilton, A. D.; Van Engen, D. *J. Am. Chem. Soc.* **1987**, *109*, 5035. Kelly, T. R.; Maguire, M. P. *J. Am. Chem. Soc.* **1987**, *109*, 6549.

(2) Steele, A. B. U.S. Patent no. 2847418, 1958; *Chem. Abstr.* **1959**, *53*, 1382i.

0002-7863/88/1510-1307$01.50/0

Table I. NMR Binding Data for Ligand **1a** in Deuteriochloroform

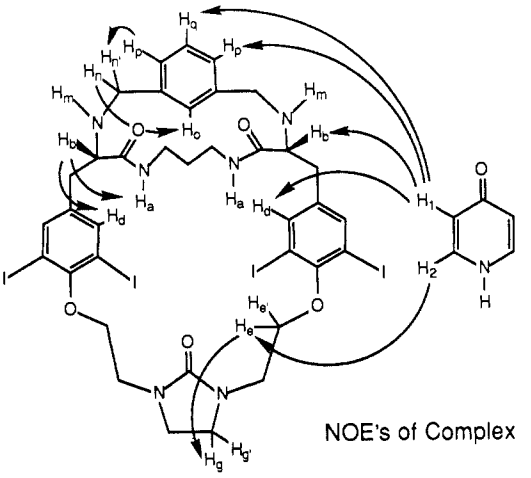
substrate	saturation achieved (%)	association energy[a] saturation[b]	Scatchard[c]	stoichiometry[d]
imidazole	89	-4.3 (0.4)	-4.7 (0.4)	0.90
1-Me imidazole		0.0[e]	0.0[e]	
2-Me imidazole	67	-3.4 (0.3)	-3.5 (0.2)	0.95
4-Me imidazole	85	-4.1 (0.4)	-4.4 (0.4)	0.89
N-Ac Me L-histidine	37	-1.9 (0.4)	-1.7 (0.4)	1.19
N-Ac Me L-phenylalanine		0.0[e]	0.0[e]	
benzimidazole	88	-4.3 (0.5)	-4.9 (0.4)	0.86
2-Me benzimidazole	30	-2.7 (0.2)	-2.6 (0.2)	1.20
benztriazole	58	-3.9 (0.1)	-4.5 (0.2)	0.67
pyrazole		0.0[e]	0.0[e]	
pyrrole		0.0[e]	0.0[e]	
pyridine		0.0[e]	0.0[e]	
2-pyridone	70	-3.7 (0.3)	-3.7 (0.3)	0.99
4-pyridone	95	-5.0 (1.0)	-4.7 (0.7)	1.10
3-hydroxypyridine	74	-3.9 (0.6)	-3.9 (0.6)	0.95
4-aminopyridine	55	-3.0 (0.3)	-3.0 (0.2)	0.99
4-Me_2N pyridine		0.0[e]	0.0[e]	
aniline		0.0[e]	0.0[e]	

[a] Association energies in kcal/mol (error limit). [b] By least-squares nonlinear fit assuming an equilibrium of the type A + B ⇌ AB. [c] By Scatchard which assumes the saturation value determined by the nonlinear fit. [d] Stoichiometry of complex obtained from Scatchard data treatment. [e] No binding of **1a** (5 mM) could be detected.

molecule possesses a deep cleft between the tyrosine phenyls which is occupied in the crystal by solvent.[3] Hydrogen positions were not determined, but the amide and amine hydrogens could be defined by molecular mechanics[4] to create strong hydrogen bonds from the amide hydrogens to the nearby amines. The X-ray of the benzylated **1b** shows this interaction explicitly and further demonstrates that **1** is capable of existing in several distinct conformations having large, well-defined cavities.

The X-ray structures above suggest that certain small heterocycles could indeed fill the cavity of **1** and donate a hydrogen bond to the urea at one end of the binding site and accept a hydrogen bond from an amide at the other. As shown in Table I, **1a** does in fact bind imidazole and a variety of related molecules in $CDCl_3$ with 1:1 stoichiometry according to NMR titrations. Association energies as high as 5 kcal/mol were found and represent minimum values since most of the substrates associate in chloroform.[5] The main feature, which distinguishes substrates which form complexes from those which do not, is their ability to both accept and donate hydrogen bonds to the ligand. Thus binding was found with all imidazoles tested except those having substitution on nitrogen. No binding was observed in DMSO or acetonitrile. The binding site accommodates considerable changes in the distance between the substrate's hydrogen bond donors and acceptors since the H/N distance in imidazole and the H/O distance in 4-pyridone is 3.2 and 5.0 Å, respectively.

While none of the complexes could be crystallized and facile protoisomerism made study of the imidazole complexes problematic, the structure of the 4-pyridone/**1a** complex could be elucidated by COSY-aided assignments and NOESY experiments. Important NOE's are shown in the figure below and interestingly are not consistent with a complex of 4-pyridone and the X-ray conformation of **1a**. They are however compatible with a complex having **1a** in a conformation similar to that of the X-ray of **1b**. Molecular mechanics suggests that the two conformations are similar in energy and shows internuclear distances of <4.0 Å in the energy minimized complex for all NOE-related hydrogens.



These results demonstrate the use of specific hydrogen bonding within an enforced cavity to provide well-defined complexes of donor/acceptor substrates and underscore the importance of considering conformational alternatives to X-ray structures when three-dimensional geometry is important.[6]

(6) This work was supported by National Science Foundation Grant CHE-8605891.

(3) Chang, M., to be published elsewhere.

(4) Weiner, S. J.; Kollman, P. A.; Case, D. A.; Singh, U. C.; Chio, C.; Alagona, G.; Profeta, S.; Weiner, P. *J. Am. Chem. Soc.* **1984**, *106*, 765. Additional parameters necessary for modeling **1** will be reported in the future.

(5) Imidazole for example: Wang, S.-M.; Lee, L.-Y.; Chen, J.-T. *Spectrochim. Acta* **1979**, *35A*, 765.

Isolation and Structure Determination of the Didemnenones, Novel Cytotoxic Metabolites from Tunicates

Niels Lindquist and William Fenical*

Scripps Institution of Oceanography
University of California, San Diego
La Jolla, California 92093

David F. Sesin and Chris M. Ireland*

Department of Medicinal Chemistry
University of Utah, Salt Lake City, Utah 84112

Gregory D. Van Duyne, Craig J. Forsyth, and Jon Clardy*

Department of Chemistry—Baker Laboratory
Cornell University, Ithaca, New York 14853-1301

Received June 26, 1987

The didemnid tunicates have been a rich source of cytotoxic amino acid derived metabolites.[1-3] We recently investigated the didemnid tunicates *Didemnum voeltzkowi* and *Tridemnum* cf. *cyanophorum* and wish to report the isolation and structure determination of a series of biologically active C_{11} cyclopentenone metabolites **1-4**. These are the first nonnitrogenous metabolites reported from a didemnid tunicate.

The tunicates were collected in widely separated parts of the world. *Didemnum voeltzkowi* is an encrusting tunicate on coral and coralline algae found in the high tidal zone of the fringing reef at Suva Harbor, Fiji. *Tridemnum* cf. *cyanophorum* was collected on the seagrass beds off Shroud Cay, Bahama Islands. Didemnenones A (**1**) and B (**2**) were isolated (0.7% combined dry weight) from the ethyl acetate extracts of *T. cyanophorum*. The extracts were subjected to flash chromatography with iso-

(1) Ireland, C.; Scheuer, P. J. *J. Am. Chem. Soc.* **1980**, *102*, 5688-91.
(2) Rinehart, K. L.; Gloer, J. B.; Cook, J. C., Jr.; Mizsak, S. A.; Scahill, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 1857-9.
(3) Sesin, D. F.; Gaskell, S. J.; Ireland, C. M. *Bull. Soc. Chim. Belg.* **1986**, *95*, 853-67.

0002-7863/88/1510-1308$01.50/0