X-ray structure of **3d**. We also thank Central Glass and Tosoh Akzo Co. for gifts of hexafluorocumyl alcohol and alkyllithiums, respectively.

Supplementary Material Available: Physical and spectral data of **3a-e** and **6** and X-ray crystallographic data with tables of thermal and positional parameters, bond lengths, and bond angles for **3d** (18 pages). Ordering information is given on any current masthead page.

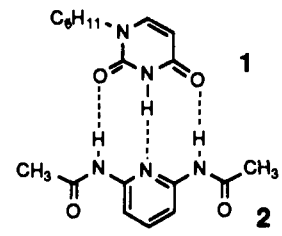
New Triply Hydrogen Bonded Complexes with Highly Variable Stabilities

Thomas J. Murray and Steven C. Zimmerman*

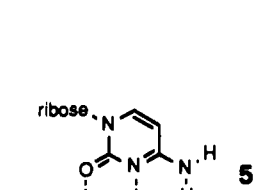
Department of Chemistry, University of Illinois Urbana, Illinois 61801

Received November 27, 1991

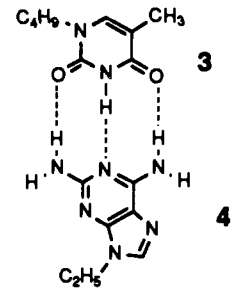
The use of hydrogen bonds to confer binding strength and selectivity has become a dominant theme in host-guest complexation studies.[1] As the number of reports on hydrogen-bonded complexes grows, so will the opportunities to discern patterns and, in turn, formulate rules for predicting the properties of unknown systems.[2] A case in point is the insightful analysis of triply hydrogen bonded systems recently reported by Jorgensen.[3] It notes that two complexes in which hydrogen bond donor (D) and acceptor (A) groups alternate (ADA·DAD; **1·2**, **3·4**) have $K_{assoc} \approx 10^2$ M^{-1},[4,5] while two DDA·AAD complexes (**5·6**, **7·8**) are significantly stronger with $K_{assoc} \approx 10^4$ M^{-1}.[6,7] Since the primary hydrogen bonds were similar in each system, the discrepancy was proposed to result from the different arrangement of the hydrogen-bonding sites and, in turn, different secondary electrostatic interactions. To test the generality of this analysis, we have experimentally examined four new triply hydrogen bonded complexes (**9·10**, **9·11**, **12·13**, **14·15**), of which one included the previously unknown DDD·AAA hydrogen-bonding motif (**12·13**). This latter arrangement contained four attractive secondary interactions and was predicted computationally to lead to the strongest complex.[3]



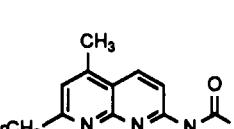
1



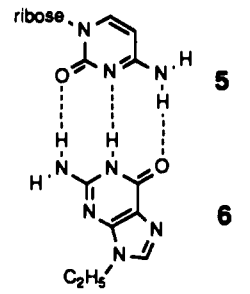
2



3



4

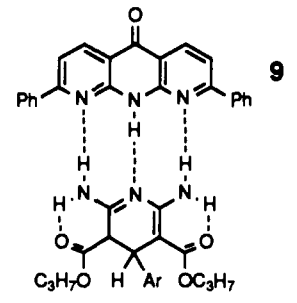


5

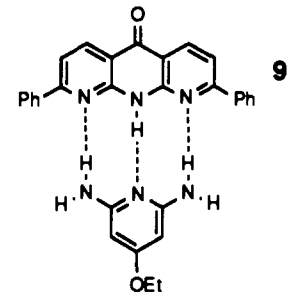
6

7

8



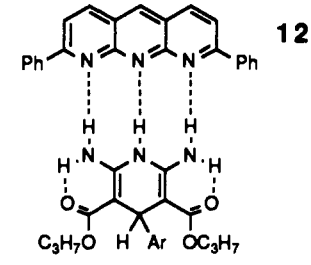
9



9

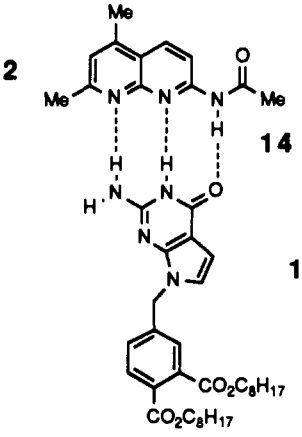
10 : Ar = 2-nitrophenyl

11



12

13 : Ar = 3-nitrophenyl



14

15

Most of the compounds used in this study were commercially available or were readily prepared using known procedures.[8-11]

* Address correspondence to Professor Steven C. Zimmerman, Department of Chemistry, 1209 West California St., University of Illinois, Urbana, IL 61801.

(1) Representative examples: Rebek, J., Jr.; Nemeth, D. *J. Am. Chem. Soc.* **1985**, *107*, 6738-6739. Aarts, V. M. L. J.; van Staveren, C. J.; Grootenhuis, P. D. J.; van Eerden, J.; Kruise, L.; Harkema, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1986**, *108*, 5035-5036. Pirkle, W. H.; Pochapsky, T. C. *J. Am. Chem. Soc.* **1986**, *108*, 5627-5628. Sheridan, R. E.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7120-7121. Kelly, T. R.; Maguire, M. P. *J. Am. Chem. Soc.* **1987**, *109*, 6549-6551. Kilburn, J. D.; Mackenzie, A. R.; Still, W. C. *J. Am. Chem. Soc.* **1988**, *110*, 1307-1308. Chang, S.-K.; Hamilton, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 1318-1319. Bell, T. W.; Liu, J. *J. Am. Chem. Soc.* **1988**, *110*, 3673-3674. Ebmeyer, F.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 79-81. Schmidtchen, F. P.; Gleich, A.; Schummer, A. *Pure Appl. Chem.* **1989**, *61*, 1535-1547. Echavarren, A.; Galán, A.; Lehn, J.-M.; de Mendoza, J. *J. Am. Chem. Soc.* **1989**, *111*, 4994-4995. Zimmerman, S. C.; Wu, W. *J. Am. Chem. Soc.* **1989**, *111*, 8054-8055. Adrian, J. C., Jr.; Wilcox, C. S. *J. Am. Chem. Soc.* **1989**, *111*, 8055-8057. Tanaka, Y.; Kato, Y.; Aoyama, Y. *J. Am. Chem. Soc.* **1990**, *112*, 2807-2808. Bonar-Law, R. P.; Davis, A. P.; Murray, B. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1407-1408. Hegde, V.; Madhukar, P.; Madura, J. D.; Thummel, R. P. *J. Am. Chem. Soc.* **1990**, *112*, 4549-4550. Medina, J. C.; Li, C.; Bott, S. G.; Atwood, J. L.; Gokel, G. W. *J. Am. Chem. Soc.* **1991**, *113*, 366-367. Furuta, H.; Magda, D.; Sessler, J. L. *J. Am. Chem. Soc.* **1991**, *113*, 978-985. Sijbesma, R. P.; Kentgens, A. P. M.; Nolte, R. J. M. *J. Org. Chem.* **1991**, *56*, 3199-3201. Ikeura, Y.; Kurihara, K.; Kunitake, T. *J. Am. Chem. Soc.* **1991**, *113*, 7342-7350. Ogoshi, H.; Hatakeyama, H.; Kotani, J.; Kawashima, A.; Kuroda, Y. *J. Am. Chem. Soc.* **1991**, *113*, 8181-8183. Kelly-Rowley, A. M.; Cabell, L. A.; Anslyn, E. V. *J. Am. Chem. Soc.* **1991**, *113*, 9687-9688.

(2) Etter, M. C.; Reutzel, S. M. *J. Am. Chem. Soc.* **1991**, *113*, 2586-2598. Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120-126. Schneider, H.-J.; Juneva, R. K.; Simova, S. *Chem. Ber.* **1989**, *122*, 1211-1213.

(3) Jorgensen, W. L.; Pranata, J. *J. Am. Chem. Soc.* **1990**, *112*, 2008-2010. Pranata, J.; Wierschke, S. G.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1991**, *113*, 2810-2819.

(4) Hamilton, A. D.; Van Engen, D. *J. Am. Chem. Soc.* **1987**, *109*, 5035-5036.

(5) Kyogoku, Y.; Lord, R. C.; Rich, A. *Proc. Natl. Acad. Sci. U.S.A.* **1967**, *57*, 250-257.

(6) Kyogoku, Y.; Lord, R. C.; Rich, A. *Biochim. Biophys. Acta* **1969**, *179*, 10-17.

(7) Kelly, T. R.; Zhao, C.; Bridger, G. J. *J. Am. Chem. Soc.* **1989**, *111*, 3744-3745.

(8) Compounds **10** and **13** were prepared according to ref 10. Compounds **9** and **12** were prepared according to ref 9. Compound **11** was prepared according to ref 11. Compound **14** is available from the Aldrich Chemical Co. as the amine. All compounds used in this study gave correct elemental analyses and had spectral data in full accord with the assigned structures.

(9) Caluwe, P.; Majewicz, T. G. *J. Org. Chem.* **1977**, *42*, 3410-3413.

(10) Meyer, H.; Bossert, F.; Horstmann, H. *Liebigs Ann. Chem.* **1978**, 1476-1482.

(11) Markes, D. G.; Dewey, V. C.; Kidder, G. W. *J. Med. Chem.* **1968**, *11*, 126-129.

0002-7863/92/1514-4010$03.00/0

Table I. Association Constants and Complexation Shifts for Various Triply Hydrogen Bonded Complexes in Chloroform-d^a

complex	type	method used	proton(s) monitored	$\Delta\delta_{max}$ (ppm)	K_{assoc} (M^{-1})	$-\Delta G°_{298}$ (kcal mol^{-1})	ref
1·2	DAD·ADA				90	2.7	5
3·4	DAD·ADA				140	2.9	6
9·10	DAD·ADA	A	N9-H (**9**)	3.98	78	2.6	this work
9·11	DAD·ADA	A	N9-H (**9**)	4.10	70	2.5	this work
7·8	DDA·AAD				1.7×10^4	5.8	7
16·17 (5·6)	DDA·AAD	B			1×10^4	5.5	this work
14·15	DDA·AAD	B	N1-H (**15**)	1.63	9.3×10^3	5.4	this work
12·13[b]	DDD·AAA	B	NH_2 (**13**)	1.80	$\geq 10^5$	≥ 7	this work

[a] At 298 K. Duplicate runs gave K_{assoc} values that agreed within 5%. Method A: Titration with **9** at fixed concentration. Method B: Dilution of 1:1 complex. [b] Carried out in the presence of 2 molar equiv of 1,8-bis(dimethylamino)naphthalene (see ref 18).

Compound **15** was prepared by alkylating 9-deazaguanosine[12] with dioctyl 4-(bromomethyl)phthalate,[13] the long-chain ester groups providing high solubility in chloroform. Only an approximate association constant was reported[6] for the GC base pair (**5·6**) in chloroform, so a more accurate determination was made using 2′,3′,5′-tripentanoylguanosine (**16**)[14] and 4-ethylcytosine (**17**).[15]

The 4-aryl group in dihydropyridines **10** and **13** serves as a convenient tautomeric "switch". Thus, in dimethylformamide-d_7, **13** exists exclusively in the 1,4-dihydro form, while **10** is entirely in the 3,4-dihydro form, presumably due to a steric effect.[10] In chloroform-*d*, the ^1H NMR spectrum of **10** showed it to be in the 3,4-dihydro form, while that for **13** indicated a solvent-induced shift in the equilibrium to a ca. 67:33 mixture of 1,4-dihydro and 3,4-dihydro forms.[16] Interestingly, 10 equiv of **12** converted **10** (ca. 1 mM, $CDCl_3$) entirely into the 1,4-dihydro form. Likewise, 4 equiv of **9** converted **13** (ca. 5 mM, $CDCl_3$) from a 67:33 mixture to a 44:56 mixture of 1,4-dihydro and 3,4-dihydro forms.

Complexation studies were performed by ^1H NMR spectroscopy in chloroform-*d* under conditions where self-association of **9–17** was negligible. The association constants were determined using standard methods;[17] they are compiled in Table I. The alternating hydrogen-bonding motif (DAD·ADA) in **9·10** and **9·11** was weak with K_{assoc} values of 78 and 70 M^{-1}, respectively. The DDA·AAD complexes of **14·15** and the GC base pair (**16·17**) were significantly more stable with K_{assoc} values of 9.3×10^3 and 1×10^4 M^{-1}, respectively. The **12·13** (DDD·AAA) complex was by far the tightest examined. Indeed, only ca. 15% of uncomplexed **13** was observed when the concentration of the 1:1 complex was ca. 2×10^{-4} M. By accounting for the tautomeric equilibrium constant, the association constant can be estimated to be larger than or equal to 10^5 M^{-1}.[18] The difference in stability between complexes **9·10** and **12·13** is striking. Despite their structural similarity and identical number of hydrogen bonds, the latter complex is more stable by over 4 kcal mol^{-1}.

These results are consistent with Jorgensen's proposal that the variable stabilities of triply hydrogen bonded complexes originate in the arrangement of the hydrogen-bonding sites.[3,19] Combined with previous results,[3-7] the variations in K_{assoc} seen in Table I, and in particular the large difference in stability of complexes **9·10** and **12·13**, indicate that the number of hydrogen bonds alone will be a poor predictor of complex stability. For triply hydrogen bonded complexes the arrangement of donor and acceptor groups appears to correlate well with K_{assoc}, although not all triply hydrogen bonded complex stabilities are expected to fall in the narrow ranges found for the complexes in Table I.[19-21] Efforts are underway to incorporate some of these new complexes into supramolecular assemblies.

Acknowledgment. Funding from the NSF-PYI program (CHE 58202), the Searle Company, and a Camille and Henry Dreyfus Teacher-Scholar Award to S.C.Z. is gratefully acknowledged. T.J.M. acknowledges support from the Du Pont Company in the form of a graduate fellowship. The authors thank Professor W. L. Jorgensen for useful discussions and for sharing results prior to publication.

(12) Seela, F.; Kehne, A.; Winkeler, H.-D. *Liebigs Ann. Chem.* **1983**, 137–146.
(13) Anzalone, L.; Hirsch, J. A. *J. Org. Chem.* **1985**, *50*, 2128–2133.
(14) Zimmerman, S. C.; Wu, W.; Zeng, Z. *J. Am. Chem. Soc.* **1991**, *113*, 196–201.
(15) 9-Ethylcytosine was a generous gift of Prof. Nelson J. Leonard.
(16) The tautomers were in slow exchange at 300 MHz. The ester resonances in the ^1H NMR spectrum of **10** are doubled, with δ_{H-3} = 3.61 ppm and δ_{H-4} = 4.99 ppm ($J \approx 0$ Hz). Compound **10** appears to be a single diastereomer, which we tentatively assign as the cis isomer. The ^1H NMR spectrum of **13** is highly symmetrical, with δ_{H-4} = 4.88 ppm.
(17) For an excellent overview, see: Wilcox, C. S. In *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H. J., Durr, H., Eds.; VCH: New York, 1991; pp 123–143.
(18) In the presence of acid this complex is unstable, undergoing clean hydride transfer from C-4 of **13** to C-10 of **12**. The binding constants were determined in the presence of 1,8-bis(dimethylamino)naphthalene.
(19) The present results do not indicate the origin of the variable stabilities, and other possibilities such as changes in the strength of the primary hydrogen bonds, differential solvation, alignment of molecular dipole moments, etc. cannot be ruled out.
(20) Recently, several new ADA·DAD complexes have been reported with K_{assoc} values somewhat higher than those in Table I: (a) Park, T. K.; Schroeder, J.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 5125–5127 (K_{assoc} = 670 M^{-1}, $\Delta G°_{298}$ = 3.9 kcal mol^{-1} and K_{assoc} = 960 M^{-1}, $\Delta G°_{298}$ = 4.1 kcal mol^{-1}). (b) Kelly, T. R.; Bridger, G. J.; Zhao, C. *J. Am. Chem. Soc.* **1990**, *112*, 8024–8034 (K_{assoc} = 440 M^{-1}, $\Delta G°_{298}$ = 3.6 kcal mol^{-1}).
(21) A complex of type DDA·AAD (very similar to **14·15**) has been reported to have an association constant of 126 M^{-1} ($\Delta G°_{298}$ = 2.9 kcal mol^{-1}): Hamilton, A. D.; Pant, N. *J. Chem. Soc., Chem. Commun.* **1988**, 765–766. This exception will be discussed in a full paper.

Molecular Harpoons: Membrane-Disrupting Surfactants That Recognize Osmotic Stress[1]

Kensuke Naka, Andrzej Sadownik, and Steven L. Regen*

Department of Chemistry and Zettlemoyer Center for Surface Studies, Lehigh University Bethlehem, Pennsylvania 18015

Received January 22, 1992

In this paper we introduce a class of membrane-disrupting surfactants that has been designed to recognize osmotic stress in lipid bilayers. On the basis of their molecular shape and their pressure-sensitivity, we term such amphiphiles *molecular harpoons*. Results presented herein show that the ability of a harpoon to recognize a stressed bilayer is a function of its structure, its oligomeric state, and the strength of the osmotic gradient. The relevance of these findings to the creation of novel antimicrobial agents is briefly discussed.

When large unilamellar vesicles are first prepared via freeze–thawing and extrusion, the concentration of ionic solute within their aqueous interior equals that of the external phase.[2,3] The membrane is thus formed under isotonic conditions, and its compactness is maximized through hydrophobic interactions.[4]

(1) Supported by PHS Grant AI28220 awarded by the National Institutes of Health (NIAID).
(2) Hope, M. J.; Bally, M. B.; Webb, G.; Cullis, P. R. *Biochim. Biophys. Acta* **1985**, *812*, 55.
(3) Mayer, L. D.; Hope, M. J.; Cullis, P. R.; Janoff, A. S. *Biochim. Biophys. Acta* **1985**, *817*, 193.

0002-7863/92/1514-4011$03.00/0