with silica gel. The solvent was removed, and the slurry was applied to the top of a silica gel column packed in 5% MeOH/95% $CHCl_3$ solvent. The column was eluted with a $CHCl_3$–MeOH gradient (5–12% MeOH) to give **30** as a colorless solid (434 mg, 75%). An analytical sample was obtained by recrystallization of **30** from EtOH/H_2O as white crystals: mp 179–80 °C; UV (MeOH) λ_{max} 253 (12001), 270 (sh, 9120) nm; ^{31}P NMR (DMSO-d_6) δ 31.99; ^1H NMR (DMSO-d_6) δ 10.53 (bs, 1 H, NH), 7.62 (s, 1 H, H8), 7.23–7.31 (m, 5 H, C_6H_5), 6.42 (bs, 2 H, NH_2), 3.88 (t, 2 H, J = 6.9 Hz, H1′), 3.56 (d, 3 H, J_{HP} = 10.5 Hz, OCH_3), 3.39 (d, 3 H, J_{HP} = 10.5 Hz, OCH_3), 3.25 (ddd, 1 H, J_{HP} = 22.2 Hz, J = 10.2, 4.8 Hz, H4′), 1.70–1.90 (m, 2 H, H3′), 1.46–1.60 (m, 2 H, H2′); ^{13}C NMR (DMSO-d_6) δ (J_{PC}) 157.28 (C6), 153.53 (C2), 151.47 (C4), 138.20 (C8), 135.87 (d, J = 6.8 Hz, C1″), 129.31 (d, J = 6.6 Hz, C2″), 128.87 (d, J = 2.2 Hz, C3″), 127.58 (d, J = 2.9 Hz, C4″), 116.58 (C5), 53.37 (d, J = 6.7 Hz, OCH_3), 53.06 (d, J = 6.7 Hz, OCH_3), 42.48 (C1′), 41.91 (d, J = 134.7 Hz, C4′), 27.77 (d, J = 15.2 Hz, C3′), 26.49 (d, J = 2.4 Hz, C2′); MS (FAB) m/z 392 (M + 1, 98.4). Anal. Calcd for $C_{17}H_{22}N_5O_4P\cdot0.5H_2O$: C, 51.00; H, 5.79; N, 17.49; P, 7.74. Found: C, 51.07; H, 5.71; N, 17.72; P, 7.70.

9-(4-Phenyl-4-phosphonobut-1-yl)guanine (31). Compound **31** was obtained by deprotection of **30** as described for **24**. Product **31** was purified by crystallization from EtOH/H_2O as a white solid (200 mg, 77%): mp 220–22 °C. UV (MeOH) λ_{max} 254 (12100), 270 (11646) nm; ^{31}P NMR (DMSO-d_6) δ 24.36; ^1H NMR (DMSO-d_6) δ 10.52 (bs, 1 H, NH), 7.61 (s, 1 H, H8), 7.15–7.30 (m, 5 H, C_6H_5), 6.41 (bs, 2 H, NH_2), 3.87 (t, 2 H, J = 6.9 Hz, H1′), 2.81 (ddd, 1 H, J_{HP} = 21.9 Hz, J = 10.8, 4.2 Hz, H4′), 1.90 (m, 1 H, H3′), 1.70 (m, 1 H, H3′), 1.52 (m, 2 H, H2′); ^{13}C NMR (DMSO-d_6) δ (J_{PC}) 156.75 (C6), 153.44 (C2), 151.04 (C4), 138.35 (d, J = 6.5 Hz, C1″), 137.39 (C8), 129.01 (d, J = 6.3 Hz, C2″), 127.98 (d, J = 1.9 Hz, C3″), 126.17 (d, J = 2.6 Hz, C4″), 116.42 (C5), 44.69 (d, J = 133.2 Hz, C4′), 42.31 (C1′), 28.00 (d, J = 14.4 Hz, C3′), 26.96 (bs, J = ~1.5 Hz, C2′); MS (FAB$^+$) m/z 364 (M + 1, 27). Anal. Calcd for $C_{15}H_{18}N_5O_4P\cdot H_2O$: C, 47.24; H, 5.28; N, 18.36; P, 8.12. Found: C, 47.02; H, 5.12; N, 18.15; P, 8.42.

2,6-Diamino-9-(4-phenyl-4-phosphonobut-1-yl)purine (32). Compound **29** (280 mg) was dissolved in 10 mL of methanolic ammonia and heated in a bomb at 80 °C for 24 h. The solution was concentrated, and H_2O (5 mL) was added, followed by a few drops of NH_4HCO_3. The solution was applied to a DEAE-cellulose column and eluted first with H_2O (200 mL) and then with a NH_4HCO_3 gradient (0–0.3 M). Evaporation gave the monoammonium salt of **32**. The sodium salt of **32** was prepared on a Dowex (Na^+ form) column. Crystallization from H_2O/EtOH gave **32** as a white solid (196 mg, 66%): UV (H_2O) λ_{max} 255 (7308), 280 (9338) nm; ^{31}P NMR (D_2O) δ 21.02; ^1H NMR (D_2O) δ 7.56 (s, 1 H, H8), 7.02–7.20 (m, 5 H, C_6H_5), 3.86 (m, 2 H, H1′), 2.62 (ddd, 1 H, J_{HP} = 20.7 Hz, J = 11.4, 3.0 Hz, H4′), 2.0–2.15 (m, 1 H, H3′), 1.15–1.18 (m, 3 H, H2′, H3′); ^{13}C NMR (D_2O) δ (J_{PC}) 160.82 (C2), 157.12 (C6), 151.96 (C4), 142.96 (d, J = 5.9 Hz, C1″), 141.56 (C8), 130.43 (d, J = 5.6 Hz, C2″), 129.22 (d, J = 1.8 Hz, C3″), 126.89 (d, J = 2.4 Hz, C4″), 114.46 (C5), 48.79 (d, J = 125.1 Hz, C4′), 45.21 (C1′), 29.22 (C2′), 29.01 (d, J = 15.2 Hz, C3′); MS (FAB$^+$) m/z 363 (M + 1, 4). Anal. Calcd for $C_{15}H_{17}N_6O_3PNa_2\cdot2H_2O$: C, 40.73; H, 4.78; N, 18.99; P, 7.26. Found: C, 41.04; H, 4.89; N, 18.76; P, 7.10.

Acknowledgment. Support of this research by Grant CA 11045 from the National Cancer Institute of the Public Health Service and by a grant from the National Science Foundation is gratefully acknowledged.

Registry No. **7**, 4850-50-4; **8**, 137333-75-6; **9**, 137333-76-7; **10**, 137333-77-8; **11**, 137333-78-9; **12**, 137333-79-0; **13**, 137333-80-3; **14**, 71009-09-1; **15**, 137333-81-4; **16**, 137333-82-5; **17**, 137333-83-6; **18**, 137333-84-7; **19**, 137333-85-8; **20**, 137333-86-9; **21**, 137333-87-0; **22** (isomer 1), 137333-88-1; **22** (isomer 2), 137334-00-0; **23** (isomer 1), 137333-89-2; **23** (isomer 2), 137334-01-1; **24**, 137333-90-5; **25**, 137333-91-6; **25**·2Na, 137334-02-2; **26**, 137333-92-7; **27**, 137333-93-8; **28**, 137333-94-9; **29**·2Na, 137333-95-0; **30**, 137333-96-1; **31**, 137333-97-2; **32**·2Na, 137333-98-3; $PhCH_2OP(NEt_2)OMe$, 137333-99-4; adenine, 73-24-5; cytosine, 71-30-7; 2-amino-6-chloropurine, 10310-21-1; 3-benzoylpropionic acid, 2051-95-8; 5-chloro-1-pentanol, 5259-98-3; glycidol, 556-52-5.

Accumulation of Hydrogen-Bonding and Electrostatic Binding Sites: Stabilization of Salts in Hydroxylic Media via Intramolecular Hydrogen Bonding[1]

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Pyridyl–bisresorcinol derivative **1a** and dodecyl phosphate (**5**) form a pyridinium–phosphate salt which is stabilized via hydrogen-bonding interaction between the bisresorcinol moiety and bound phosphate anion. The salt-formation constants (K) are relatively insensitive to solvent polarities; $K_{1a}(5)$ = 1.2 × 10^3 (water–methanol (2:1)), 1.2 × 10^3 (methanol), 1.1 × 10^3 (ethanol), and 6.9 × 10^2 M^{-1} (2-propanol). On the other hand, the salt formation with 2-picoline (**3**) as a less crowded reference host takes place with much difficulty and is highly solvent dependent; $K_3(5)$ = 2.1 × 10^2 (water–methanol (2:1)), 3.2 × 10 (methanol), 1.6 × 10 (ethanol), and 9.2 (2-propanol). The selectivities $K_{1a}(5)/K_3(5)$ thus increase with respect to change in solvents in the order, water–methanol (2:1) (6) < methanol (37) < ethanol (72) < 2-propanol (75). The role of a pair of hydroxyl groups in the bisresorcinol moiety is discussed in terms of intramolecular microsolvation.

Multipoint hydrogen bonding is a general guiding principle for the molecular recognition of complicated biorelevant molecules such as amino acids,[2] dicarboxylic acids,[3] diols,[4] sugars,[5] quinones,[6] and nucleobases and related nitrogen heterocycles[7] in apolar organic media. Biorelevant anions as guests, especially phosphates, can also be solubilized in organic solvents upon formation of salts with lipophilic cations as hosts.[8] The resulting salts

(1) Molecular Recognition. 11. Part 16 of this series: Aoyama, Y.; Asakawa, M.; Matsui, Y.; Ogoshi, H. *J. Am. Chem. Soc.* **1991**, *113*, 6233. Part 10: Tanaka, Y.; Sutarto, S.; Aoyama, Y., manuscript in preparation.

(2) Rebek, J., Jr.; Askew, B.; Nemeth, D.; Parris, K. *J. Am. Chem. Soc.* **1987**, *109*, 2432. (b) Aoyama, Y.; Asakawa, M.; Yamagishi, A.; Toi, H.; Ogoshi, H. *Ibid.* **1990**, *112*, 3145.

(3) (a) Tanaka, Y.; Kato, Y.; Aoyama, Y. *J. Am. Chem. Soc.* **1990**, *112*, 2807. (b) G.-Tellado, F.; Goswami, S.; Chang, S.-K.; Geib, S. J.; Hamilton, A. D. *Ibid.* **1990**, *112*, 7393.

(4) Kikuchi, Y.; Kato, Y.; Tanaka, Y.; Toi, H.; Aoyama, Y. *J. Am. Chem. Soc.* **1991**, *113*, 1349.

(5) (a) Aoyama, Y.; Tanaka, Y.; Toi, H.; Ogoshi, H. *J. Am. Chem. Soc.* **1988**, *110*, 634. (b) Aoyama, Y.; Tanaka, Y.; Sugahara, S. *Ibid.* **1989**, *111*, 5397. (c) Tanaka, Y.; Ubukata, Y.; Aoyama, Y. *Chem. Lett.* **1989**, 1905.

(6) Aoyama, Y.; Asakawa, M.; Matsui, Y.; Ogoshi, H., the paper cited in note 1.

(7) Rebek, J., Jr. *Angew. Chem.* **1990**, *102*, 261; *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245 and references cited therein.

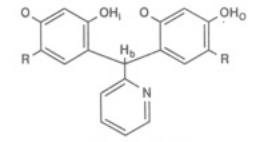
0022-3263/91/1956-7224$02.50/0

can be further stabilized by additional host–guest hydrogen-bonding interactions.[9]

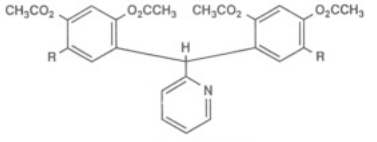
We have prepared a pyridyl compound **1a** having a bisresorcinol moiety. The latter group constitutes the unit-binding sites of resorcinol–aldehyde cyclotetramer which is capable of multipoint hydrogen-bonding fixation of dicarboxylic acids,[3] diols,[4] and sugars.[5] In the present work, we investigated the salt formation of compound **1a** with a phosphoric acid in *hydroxylic* media. We report here that the bisresorcinol moiety gives rise to a significant stabilization of salts.

Results and Discussion

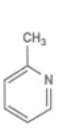
Pyridyl–Bisresorcinol Bifunctional Host. Acid-catalyzed condensation of pyridine-2-carboxaldehyde and 4-ethyl- or 4-hexylresorcinol in methanol under essentially the same conditions as for the preparation of resorcinol–aldehyde cyclotetramer[5b] gave a 2-pyridyl compound **1a** or **1b** having a bisresorcinol moiety as a hydrogen-bonding site. Acetylation of compounds **1a** and **1b** gave tetraacetates **2a** and **2b**, respectively, which, together with 2-picoline (**3**), served as references having no hydrogen-bonding site. Condensation with benzaldehyde afforded phenyl-substituted bisresorcinol references **4a** and **4b** having no site for salt-formation.



1a ; R = C_2H_5
1b ; R = C_6H_{13}



2a ; R = C_2H_5
2b ; R = C_6H_{13}



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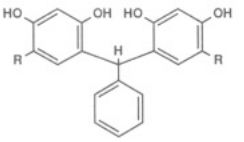
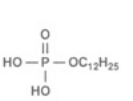


4a ; R = C_2H_5
4b ; R = C_6H_{13}



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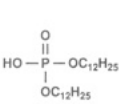


6

The pK_a value for the pyridyl moiety ($NH^+ \rightleftharpoons N + H^+$) of compound **1a** in D_2O–CD_3OD (8:2 by volume) was determined by pH titration of the buildup of pyridinium ion, as monitored by ^1H NMR chemical shift of 4-H of the pyridyl ring at 25 °C (Figure 1); p$K_a(NH^+)$ = 5.6. This was identical with the corresponding pK_a = 5.6 for reference **3** under similar conditions. The pK_a value for the first ionization of the OH groups of **1a** in H_2O–CH_3CN (9:1 by volume) at 25 °C was determined by pH titration of the buildup of phenolate ion, as monitored by UV absorbance at 300 nm (Figure 1) at 25 °C; pK_a(OH) = 9.5. This was identical with the corresponding pK_a(OH) = 9.5 determined for reference **4a**. These results indicate that there is neither intermolecular nor intramolecular interaction between N(H^+) and OH groups in **1a**. This is also supported by an examination of CPK molecular models. Compound **1a** as well as **4a** can take a propeller-like conformation with a pair of hydrogen-bonded OH groups

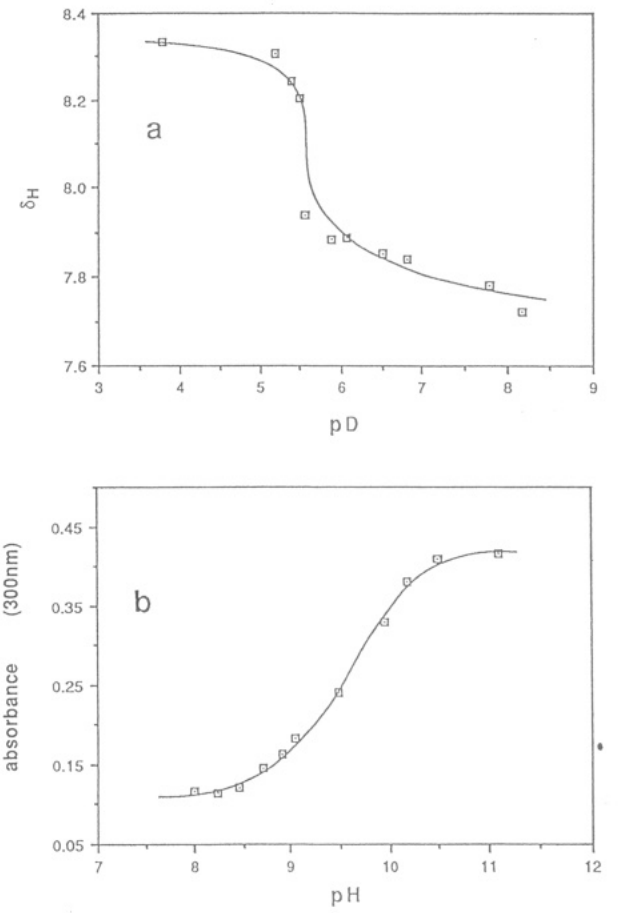


Figure 1. pH titrations of (a) the ^1H NMR chemical shift of the 4-H of the pyridyl ring of **1a** (3.58×10^{-2} M) in D_2O–CD_3OD (8:2 by volume) at 25 °C and (b) UV absorbance at 300 nm of **1a** (4.32×10^{-4} M) in H_2O–CH_3CN (9:1 by volume) at 25 °C.

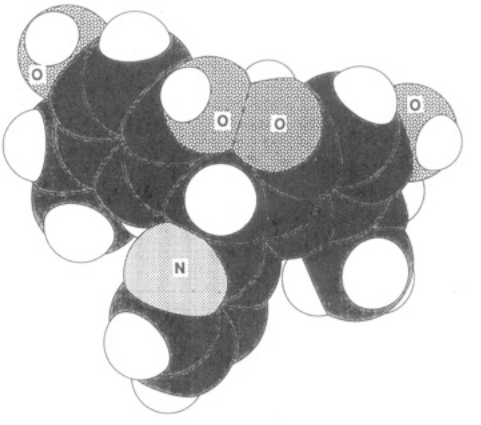


Figure 2. CPK molecular model for host **1a**.

(Figure 2). For this conformation, the pyridyl nitrogen and a hydroxyl group in **1a** are kept in proximity (approximately 4.5 Å) but not so close as to allow direct interaction of OH···N or NH^+···OH.

Salt Formation and Intramolecular Hydrogen Bonding. Compound **1a** in methanol is monomeric as revealed by vapor pressure osmometry (VPO). It reversibly forms a pyridinium–phosphate salt with dodecyl phosphate (**5**) as a phosphoric acid (eq 1, where R–Py represents a 2-pyridyl compound). Upon salt formation,

$$\text{R–Py} + \mathbf{5} \rightleftharpoons \text{(R–Py)}\cdot\mathbf{5} \qquad (1)$$

the pyridyl moiety of **1a** underwent shift of the ^1H and ^{13}C NMR resonances which were characteristic of a pyridinium ion. In Figure 3 are shown the upfield shifts ($\Delta\delta_C = \delta_C$-

(8) (a) Tabushi, I.; Imuta, J.; Seko, N.; Kobuke, Y. *J. Am. Chem. Soc.* **1978**, *100*, 6287. (b) Dietrich, B.; Fyles, T. M.; Lehn, J.-M.; Pease, L. G.; Fyles, D. L. *J. Chem. Soc., Chem. Commun.* **1978**, 934. (c) Echavarren, A.; Galan, A.; Lehn, J.-M.; de Mendoza, J. *J. Am. Chem. Soc.* **1989**, *111*, 4994.

(9) (a) Pant, N.; Hamilton, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 2002. (b) Müller, G.; Riede, J.; Schmidtchen, F. P. *Angew. Chem.* **1988**, *100*, 1574; *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1516. (c) Aoyama, Y.; Mizokami, K.; Toi, H. *Chem. Lett.* **1990**, 651. (d) Furuta, H.; Magda, D.; Sessler, J. L. *J. Am. Chem. Soc.* **1991**, *113*, 978.

Table I. Formation Constants (K) at 25 °C and ^{13}C NMR Saturation Shifts ($\Delta\delta_C^{sat}$)[a] for Salts 1a•5 and 3•5

	salt			
	1a•5		3•5	
medium	K (M^{-1})	$\Delta\delta_C^{sat}$ (ppm)	K (M^{-1})	$\Delta\delta_C^{sat}$ (ppm)
D_2O–CD_3OD (2:1)	$(1.2 \pm 0.1) \times 10^3$	−3.27	$(2.1 \pm 0.3) \times 10^2$	−4.01
CD_3OD	$(1.2 \pm 0.1) \times 10^3$	−3.05	$(3.2 \pm 0.5) \times 10$	−3.81
CD_3CD_2OD	$(1.1 \pm 0.1) \times 10^3$	−2.67	$(1.6 \pm 0.1) \times 10$	−3.21
$(CD_3)_2CDOD$	$(6.9 \pm 0.4) \times 10^2$	−1.89	9.2 ± 2.5	−2.83

[a] $\Delta\delta_C^{sat} = \delta_C$(1a•5) − δ_C(1a) or δ_C(3•5) − δ_C(3); δ_C is the chemical shifts for 2-C of the pyridyl rings.

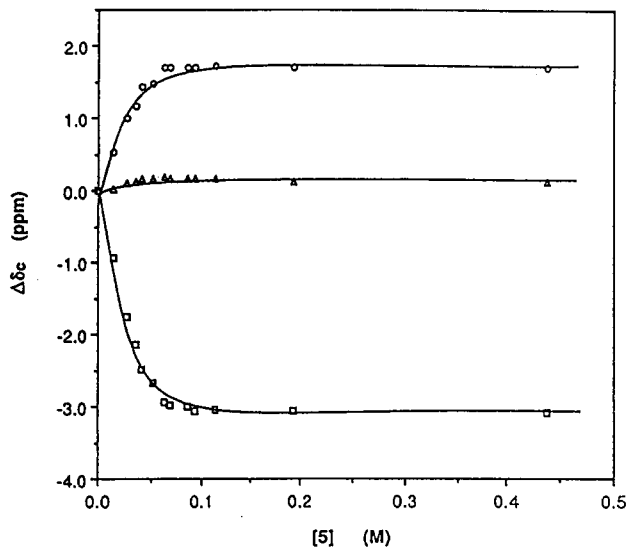


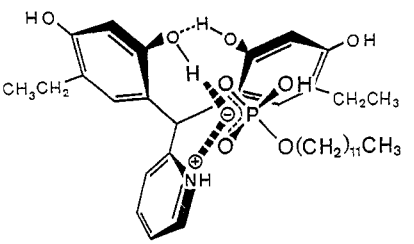
Figure 3. Correlations between [5] and shifts ($\Delta\delta_C = \delta_C$(obsd) − δ_C(1a)) in ^{13}C NMR resonances for 2-C of the pyridyl ring (□) and C–OH_i (○) and C–OH_o (△) of the phenyl rings of host 1a (4.54×10^{-2} M) in CD_3OD at 25 °C.

(obsd) − δ_C(1a)) for 2-C of the pyridyl ring of 1a (4.54×10^{-2} M) with increasing amounts of guest 5. The 5-induced shifts for other ring carbons as well as all the ring-proton resonances showed the same dependence on [5] as that for 2-C (Figure 3). Both the ^1H and ^{13}C NMR spectra at saturation were almost identical with those for the hydrochloride salt of 1a. The Job plots of [1a•5] vs mole fractions of 1a (f_{1a}) for the complexation of 1a and 5 under conditions where $[1a]_t + [5]_t$ (t = total) was kept constant at 8.6×10^{-2} M had the maximum at $f_{1a} = 0.5$ ($[1a•5]/10^{-2}$ M = 1.2, 1.7, 3.7, 1.5, and 1.1 at $f_{1a} = 0.25$, 0.33, 0.5, 0.67, and 0.75, respectively). This result, coupled with the above VPO result, confirms a 1:1 complexation. The formation constant (K, eq 1, R–Py = 1a) for salt 1a•5 was evaluated by an analysis of the titration data in Figure 3; $K_{1a}(5) = (1.2 \pm 0.1) \times 10^3$ M^{-1} at 25 °C (Table I). Titration of hexyl-substituted host 1b gave a similar salt-formation constant $K_{1b}(5) = (1.1 \pm 0.1) \times 10^3$ M^{-1}. Compound 1a also forms a salt with didodecyl phosphate (6) with $K_{1a}(6) = (1.2 \pm 0.2) \times 10^3$ M^{-1} at 25 °C. The titration data are shown in Figure 4 (supplementary material).

It was interesting to note that the formation of salt 1a•5 also affected the ^1H and ^{13}C resonances for the bisresorcinol moiety of host 1a. The ^1H NMR spectrum of 1a (2.35×10^{-2} M) in CD_3OH–DMSO-d_6 (1:1) at −30 °C showed two sharp OH proton resonances at δ_H 9.06 and 8.90, the former being assigned to the inner OH protons (H_i, referring to structure 1a) and the latter to the outer ones (H_o) on the basis of NOE experiments (details are shown in the supplementary material). In the presence of guest 5, the OH-proton resonances, especially that for OH_i, underwent significant line broadening. At [5] = 7.06×10^{-2} (i.e., 3 equiv of 1a), the OH_i resonance was too broad to be observed. The ^{13}C NMR spectrum of 1a (4.54×10^{-2} M) in CD_3OD at room temperature gave a pair of OH-carrying carbon resonances at δ_C 155.05 and 154.72 respectively for C–OH_i and C–OH_o, as assigned by long-range selective decupling (details are shown in the supplementary material). These resonances underwent characteristic downfield shifts ($\Delta\delta_C$) upon addition of guest 5, as also shown in Figure 3. The shifts are significant for C–OH_i, but only slight for C–OH_o. Furthermore, $\Delta\delta_C$ for C–OH_i shows the same dependence on [5] as $\Delta\delta_C$ for 2-C of the pyridyl ring. This result indicates that the pyridinium–phosphate salt formation is responsible for the shifts in ^{13}C resonance for C–OH_i.

The effects of added guest 5 on the ^1H (CD_3OH–DMSO-d_6 (1:1), −30 °C) and ^{13}C NMR (CD_3OD, room temperature) spectra of phenyl-substituted references 4a and 4b were far less pronounced as compared with those for 1a: for 4b, δ_H 8.90 and 8.84 (OH) and δ_C 155.35 and 154.92 (C–OH) in the absence of 5 and δ_H 8.91 and 8.84 with some line broadening and δ_C 155.39 and 154.95 in the presence of 3 equiv of 5; for 4a, δ_C 154.43 and 154.19 (C-OH) in the absence of 5 and δ_C 154.43 and 154.17 in the presence of 3 equiv of 5.

All the NMR results, coupled with CPK-model-building studies, suggest that salt 1a•5 contains an additional intramolecular hydrogen-bonding interaction between the inner OH pairs of the bisresorcinol moiety and bound phosphate anion, as schematically shown in structure 7.



7

The effectiveness of this hydrogen bonding should be ascribed to the prior pyridinium–phosphate salt formation or electrostatic interaction, since *intermolecular* hydrogen bonding between reference host 4 and guest 5 is far less effective.[10]

Stabilization of Salts via Intramolecular Hydrogen Bonding. In marked contrast to parent hosts 1a and 1b, their tetraacetyl derivatives 2a and 2b showed almost no tendency of salt formation with guest 5. The high selectivity of 5 for 1a over 2a was also confirmed by competition; a 1:1:1 mixture of 1a, 2a, and 5 afforded salt 1a•5 almost exclusively ($K_{1a}(5)/K_{2a}(5) \geq 250$). The dramatic reduction in K's on going from 1a to 2a might be due to increase in steric hindrance upon acetylation of the bulky bisresorcinol moiety at the ortho position of pyridyl nitrogen. However, even 2-picoline (3) showed the corre-

(10) For a similar selectivity in the two-point fixation of nucleotides, see ref 9c. For a general discussion on the selectivities arising from two-point interactions, see refs 4 and 6.

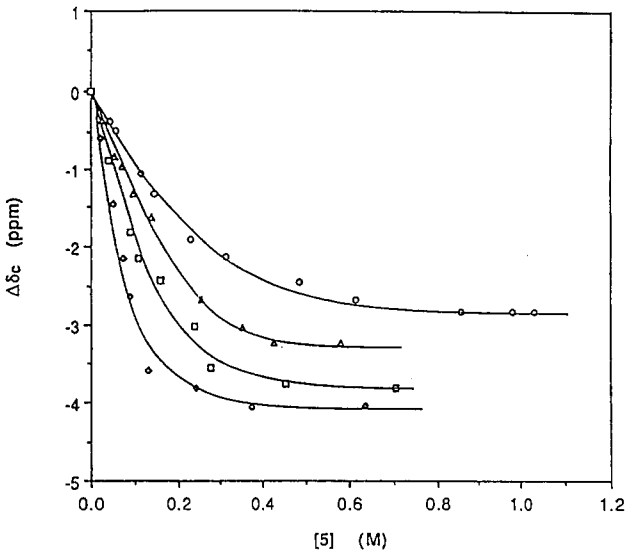


Figure 5. Correlations between [5] and shifts ($\Delta\delta_C = \delta_C$(obsd) $- \delta_C$(**3**)) in ^{13}C NMR resonances for 2-C of host **3** (1.27×10^{-1} M) in D_2O–CD_3OD (2:1 by volume) (◇), CD_3OD (□), CD_3CD_2OD (△), and $(CD_3)_2CDOD$ (○) at 25 °C.

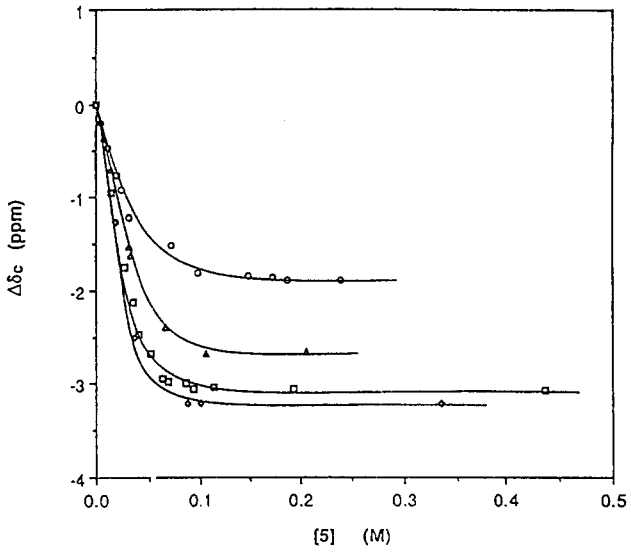


Figure 6. Correlations between [5] and shifts ($\Delta\delta_C = \delta_C$(obsd) $- \delta_C$(**1a**)) in ^{13}C NMR resonances for 2-C of the pyridyl ring of host **1a** (4.54×10^{-2} M) in D_2O–CD_3OD (2:1 by volume) (◇), CD_3OD (□), CD_3CD_2OD (△), and $(CD_3)_2CDOD$ (○) at 25 °C.

sponding salt-formation constant of $K_3(\mathbf{5}) = (3.2 \pm 0.5) \times 10$ M^{-1} (eq 1, R–Py is **3**), which still was significantly smaller than $K_{1a}(\mathbf{5}) = 1.2 \times 10^3$ M^{-1} (vide supra). The titration data for host **3** are shown in Figure 5. Competitive salt formation using a 1:1:1 mixture of **1a**, **3**, and **5** allowed direct evaluation of $K_{1a}(\mathbf{5})/K_3(\mathbf{5}) = 34$, which was in agreement with the ratio of independently determined salt-formation constants ($K_{1a}(\mathbf{5})/K_3(\mathbf{5}) = (1.2 \times 10^3)/(3.2 \times 10) = 37$).[11] The extra stabilization in adduct **1a·5** is most reasonably ascribed to the bisresorcinol–phosphate hydrogen bonding (structure **7**). The free OH group in bound **5** is not important since $K_{1a}(\mathbf{5}) \cong K_{1a}(\mathbf{6})$.

The salt formation between hosts **1a** and **3** with guest **5** was examined also for solutions in water–methanol (2:1 by volume), ethanol, and 2-propanol. The [**5**]-dependent changes in $\Delta\delta_C$ for 2-C of the pyridyl rings of **1a** and **3** are shown in Figures 6 and 5, respectively. In Table I are summarized the salt-formation constants (K) evaluated from the titration data and the saturation shifts observed ($\Delta\delta_C^{sat} = \delta_C$(**1a·5**) $- \delta_C$(**1a**) or δ_C(**3·5**) $- \delta_C$(**3**)). The saturation shifts for both **1a** and **3** decrease with respect to change in solvents in the order water–methanol > methanol > ethanol > 2-propanol. For a given solvent, reference host **3** exhibits a larger (0.5–0.9 ppm) saturation shift than bifunctional host **1a**.

Salts in solutions exist as ion pairs, either intimate or solvent-separated.[13] In a more polar solvent, the constituent cation and anion are more effectively solvated by solvent molecules; they are more solvent-separated and hence more independent of each other. In a less polar solvent, on the other hand, they form a more intimate ion pair, where the respective positive and negative charges are partially neutralized. The solvent effects on the saturation shifts ($\Delta\delta_C^{sat}$) are understandable along these lines; $\Delta\delta_C^{sat}$ reflect the extents to which the pyridinium moiety is like a free pyridinium ion.

The effects of solvent polarity (and hence solvation ability) on the stabilities of salts are reflected in the K's for host **3**, which decrease sharply on going from water–methanol as solvent through methanol and ethanol to 2-propanol (Table I). In marked contrast, the K's for host **1a** remain practically the same for the water–methanol, methanol, and ethanol systems, although formation of salt **1a·5** is somewhat depressed in 2-propanol. Evidently, *intermolecular* solvation of salt **1a·5** with solvent molecules is not so important as in the case of salt **3·5**. This fact reveals an essential role of the bisresorcinol moiety in host **1a**. It is to stabilize the pyridinium–phosphate salt via what may be called *intramolecular microsolvation*. The selectivities $K_{1a}(\mathbf{5})/K_3(\mathbf{5})$ increase with respect to solvent change in the order water–methanol (2:1) (6) < methanol (37) < ethanol (72) < 2-propanol (75). It is significant that the present microsolvation by a pair of phenolic hydroxyl groups is thus more effective than the intermolecular solvation by water–methanol.

Conclusions

Steric restraint in host **1a** prevents intramolecular phenol–pyridine acid–base neutralization[14] and allows a multiple interaction with an phosphoric acid. A pair of hydroxyl groups of the bisresorcinol moiety of **1a** act as intramolecular microsolvents. The microsolvation effect promotes salt formation more effectively in less polar and bulkier solvents and, although to a lesser extent, even in aqueous media. Further work is now under way (1) to shed more light on the host–guest hydrogen-bond network and (2) to achieve discrimination of anions based on their multifunctionalities. Fixation and activation of biological phosphates, e.g., nucleotides and nucleic acids,[8,9,15] is also

(11) Similar competition of **1a** and **3** for such acids as DCl, CF_3CO_2H, and CH_3CO_2H showed that $K_{1a}(DCl)/K_3(DCl) = 2.0$, $K_{1a}(CF_3CO_2H)/K_3(CF_3CO_2H) = 10$, and $K_{1a}(CH_3CO_2H)/K_3(CH_3CO_2H) = 41$. Thus, the enhanced salt-formation ability of **1a** over **3** is also true for carboxylic acids. In addition, heteronuclear ^{1}H–^{13}C NOE measurements[12] on the CF_3CO_2H salts revealed another interesting point. Irradiation of the benzylic proton H_b (referring to structure **1a**) for salt **1a**·CF_3CO_2H in CF_3CO_2H at room temperature resulted in an NOE (approximately 1.3%) on the ^{13}C resonance of the carbonyl group, indicating a close proximity of H_b and the C=O group. On the other hand, irradiation of the methyl protons for salt **3**·CF_3CO_2H gave no NOE on the substrate.

(12) (a) Ford, J. J.; Gibbons, W. A.; Niccorai, N. *J. Magn. Reson.* **1982**, *47*, 522. (b) Khaled, M. A.; Watkins, C. L. *J. Am. Chem. Soc.* **1983**, *105*, 3363. (c) Gajewski, J. J.; Emrani, J. *Ibid.* **1984**, *106*, 5733.

(13) Sykes, P. *A Guide Book to Mechanism in Organic Chemistry*, 5th ed.; Longman Group Ltd.: London, 1981.

(14) (a) Breslow, R.; Doherty, J. B.; Guillot, G.; Lipsey, C. *J. Am. Chem. Soc.* **1978**, *100*, 3227. (b) Aoyama, Y.; Yamagishi, A.; Tanaka, Y.; Toi, H.; Ogoshi, H. *Ibid.* **1987**, *109*, 4735. (c) Wolfe, J.; Nemeth, D.; Costero, A.; Rebek, J., Jr. *Ibid.* **1988**, *110*, 983. (d) Wolfe, J.; Mueldorf, A. M.; Rebek, J., Jr. *Ibid.* **1991**, *113*, 1453.

an interesting application of this work.

Experimental Section

General Procedures. The ^1H (at 270 MHz) and ^{13}C (at 68.7 MHz) NMR, IR, UV–visible, and EI-MS spectra were obtained with a JEOL JNM-GX 270 spectrometer, a JASCO IR-810 infrared spectrophotometer, a Hitachi 320 spectrophotometer, and a Shimadzu GCMS 6020 spectrometer, respectively. Vapor pressure osmometry (VPO) was carried out using a Corona 114 molecular weight apparatus. Dodecyl phosphate (**5**) and didodecyl phosphate (**6**) (purity, 99%; Kao Corporation) were further recrystallized from *n*-hexane. Water was distilled and deionized. The pH's of solutions were varied by using HCl, phosphate, borate–cabonate, and NaOH buffers. The pD's were measured at 25 °C using a Toko TPX 90*i* pH meter equipped with a calibrated glass electrode with a temperature compensation probe; pD = pH meter reading +0.4.

Bis(2,4-dihydroxy-5-ethyl-1-phenyl)(2-pyridyl)methane (1a) and Bis(2,4-dihydroxy-5-hexyl-1-phenyl)(2-pyridyl)methane (1b). A solution of 4-ethylresorcinol (2.00 g, 14.5 mmol) and pyridine-2-carboxaldehyde (0.77 g, 7.2 mmol) in methanol (50 mL) containing concd hydrochloric acid (1 mL) was stirred at 40 °C under nitrogen for 24 h. The solvent was removed in vacuo. To the residue was added an aqueous solution (20 mL) of $NaHCO_3$ (calculated amount), and the mixture was extracted with three portions of ether (30 mL). The combined ether extracts were washed with aqueous $NaHCO_3$ and then with water. The ether was removed and the residue recrystallized from benzene–*n*-hexane to give **1a** (1.90 g, 73%): mp 158–159 °C; ^1H NMR (DMSO-d_6) δ_H 9.16 and 8.88 (each s, each 2 H, OH), 8.41 (d), 7.64 (t), 7.13 (t), and 7.06 (d) (each 1 H, pyridyl-H), 6.52 and 6.28 (each s, each 2 H, phenyl-H), 5.75 (s, 1 H, CH), 2.30 (q, 4 H, CH_2), 0.97 (t, 6 H, CH_3); ^{13}C NMR (DMSO-d_6) δ_C 164.77, 148.02, 136.31, 123.14, and 120.79 (pyridyl-C), 153.57, 153.33, 130.10, 119.60, and 102.55 (phenyl-C), 46.08 (CH), 22.29 (CH_2), 14.68 (CH_3); IR (KBr) 3200 cm^{-1} (ν_{OH}); EI-MS *m/e* 365 (M^+); molecular weight (VPO) for a CH_3OH solution 360 (calcd 365). Anal. Calcd for $C_{22}H_{23}O_4N$: H, 6.34, C, 72.31; N, 3.83. Found; H, 6.36; C, 72.16; N, 3.89.

Compound **1b** (2.66 g, 72%) was obtained similarly form 4-hexylresorcinol (3.00 g, 15.5 mmol) and pyridine-2-carboxaldehyde (0.83 g, 7.76 mmol): mp 157–158 °C. Anal. Calcd for $C_{30}H_{38}O_4N$: C, 75.59; H, 8.04; N, 2.94. Found: C, 75.71; H, 8.04; N, 2.98.

Bis(2,4-diacetoxy-5-ethyl-1-phenyl)(2-pyridyl)methane (2a) and Bis(2,4-diacetoxy-5-hexyl-1-phenyl)(2-pyridyl)methane (2b). A solution of compound **1a** (1.00 g, 2.74 mmol) in acetic anhydride (10 mL) containing pyridine (0.20 g, 2.56 mmol) was stirred at room temperature under nitrogen for 6 h. Acetic anhydride and pyridine were removed in vacuo to give **2a** (0.97 g, ~100%): mp 135–137 °C; ^1H NMR (DMSO-d_6) δ_H 8.52 (d), 7.76 (t), 7.25 (t), and 7.18 (d) (each 1 H, pyridyl-H), 6.93 and 6.88 (each s, each 2 H, phenyl-H), 5.68 (s, 1 H, CH), 2.40 (q, 4 H, CH_2), 0.99 (t, 6 H, CH_3); IR (KBr) 1760 cm^{-1} ($\nu_{C=O}$); EI-MS *m/e* 533 (M^+). Anal. Calcd for $C_{30}H_{31}O_8N$: H, 5.86; C, 67.52; N, 2.63. Found: H, 5.80; C, 67.29; N, 2.64. Compound **2b** was obtained similarly.

Bis(2,4-dihydroxy-5-ethyl-1-phenyl)phenylmethane (4a) and Bis(2,4-dihydroxy-5-hexyl-1-phenyl)phenylmethane (4b). Condensation of 4-ethylresorcinol (2.00 g, 14.5 mmol) and benzaldehyde (0.80 g, 7.55 mmol) under the same conditions as those for the preparation of **1a** gave **4a** (1.92 g, 70%): mp 110–111 °C; ^1H NMR (DMSO-d_6) δ_H 8.80 and 8.73 (each s, each 2 H, OH), 7.18 (t, 2 H), 7.09 (t, 1 H), and 6.92 (d, 2 H) (phenyl-H), 6.39 and 6.29 (each s, each 2 H, phenyl-H for the resorcinol moieties), 5.79 (s, 1 H, CH), 2.31 (q, 4 H, CH_2), 0.97 (t, 6 H, CH_3); ^{13}C NMR (DMSO-d_6) δ_C 153.22, 153.06, 145.96, 129.96, 128.83, 127.62, 125,08, 121.00, 119.39, 102.36 (phenyl-C), 41.28 (CH), 22.34 (CH_2), 14.76 (CH_3); IR (KBr) 3200 cm^{-1} (ν_{OH}); EI-MS *m/e* 364 (M^+). Anal. Calcd for $C_{23}H_{24}O_4$: H, 6.64; C, 75.80. Found: H, 6.57; C, 75.11.

Compound **4b** (2.46 g, 68%) was obtained similarly from 4-hexylresorcinol (3.00 g, 15.5 mmol) and benzaldehyde (0.81 g, 7.64 mmol): mp 116–116.5 °C. Anal. Calcd for $C_{31}H_{39}O_4$: C, 78.27; H, 8.27. Found: C, 78.31; H, 8.01.

Salt-Formation Constants. ^{13}C NMR titration of host **1a** (4.54×10^{-2} M) with varying amounts of guest **5** was carried out at 25 °C, monitoring [**5**]-dependent chemical shifts for 2-C of the pyridyl ring. The salt-formation constants (K) were evaluated by $K = [\mathbf{1a}\cdot\mathbf{5}]/[\mathbf{1a}][\mathbf{5}]$; $[\mathbf{1a}\cdot\mathbf{5}] = [\mathbf{1a}]_t\cdot(\delta_{1a} - \delta_{obs})/(\delta_{1a} - \delta_{sat})$, $[\mathbf{1a}] = [\mathbf{1a}]_t\cdot(\delta_{obsd} - \delta_{sat})/(\delta_{1a} - \delta_{sat})$, and $[\mathbf{5}] = [\mathbf{5}]_t - [\mathbf{1a}\cdot\mathbf{5}]$ (t = total), where δ_{1a} and δ_{sat} are the chemical shifts of **1a** and **1a·5**, respectively, and δ_{obsd} are the observed chemical shifts in the intermediate concentration ranges of **5**. The salt-formation constants for host **3** were similarly obtained. In all the cases, the saturation shifts ($\delta_{1a\cdot5} - \delta_{1a}$ or $\delta_{3\cdot5} - \delta_3$) could be experimentally determined (Figures 3, 4, and 5). The K values listed in Table I are averages of those obtained at three or four different concentrations of **5**, which covered 20–90% binding.

Competitive salt formation was carried out by using a 1:1:1 mixture of **1a**, **3** or **2a**, and **5**. The relative binding constants were evaluated directly from the respective shifts in ^{13}C NMR resonances; e.g.,

$$K_{1a}/K_3 = [(\delta_{1a} - \delta_{obsd})/(\delta_{obsd} - \delta_{sat})]_{1a}/[(\delta_3 - \delta_{obsd})/(\delta_{obsd} - \delta_{sat})]_3$$

Since δ_{sat} for tetraacetate host **2a** could not be experimentally accesible, it was assumed to be the same as that for parent host **1a**.

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Registry No. **1a**, 134785-33-4; **1a·5**, 137300-40-4; **1a·6**, 137300-43-7; **1b**, 137300-41-5; **1b·5**, 137300-42-6; **2a**, 137300-48-2; **2b**, 137300-45-9; **3·5**, 137300-44-8; **4a**, 137300-46-0; **4b**, 137300-47-1; 4-ethylresorcinol, 2896-60-8; pyridine-2-carboxaldehyde, 1121-60-4.

Supplementary Material Available: Figure of correlations between [**6**] and shifts in ^{13}C NMR resonances and assignments of NMR spectra (2 pages). Ordering information is given on any current masthead page.

(15) (a) Dietrich, B.; Fyles, T. M.; Lehn, J.-M.; Pease, L. G.; Fyles, D. L. *J. Chem. Soc., Chem. Commun.* **1978**, 937. (b) Boger, J.; Knowles, J. R. *J. Am. Chem. Soc.* **1981**, *103*, 6152. (c) Tabushi, I.; Kobuke, Y.; Imuta, J. *Ibid.* **1979**, *101*, 7631. (d) Dietrich, B.; Hosseini, M. W.; Lehn, J.-M.; Sessions, R. B. *Ibid.* **1981**, *103*, 1282. (e) Kimura, E.; Kodama, M.; Yatsunami, T. *Ibid.* **1982**, *104*, 3182. (f) Hosseini, M. W.; Lehn, J.-M.; Jones, J. C.; Plute, K. E.; Mertes, K. W.; Mertes, M. P. *Ibid.* **1989**, *111*, 6330 and references cited therein. (g) Basile, L. A.; Raphael, A. L.; Barton, J. K. *Ibid.* **1987**, *109*, 7550. (h) Lehn, J.-M. *Angew. Chem.* **1989**, *100*, 91; *Angew. Chem., Int. Ed. Engl.* **1989**, *27*, 89.