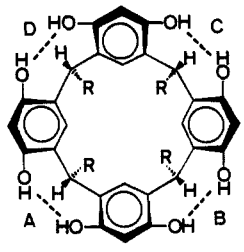
Two-Point Hydrogen-Bonding Interaction: A Remarkable Chain-Length Selectivity in the Binding of Dicarboxylic Acids with Resorcinol–Aldehyde Cyclotetramer as a Multidentate Host[1]

Yasutaka Tanaka, Yasushi Kato, and Yasuhiro Aoyama*,[2]

Department of Chemistry
Nagaoka University of Technology
Kamitomioka, Nagaoka, Niigata 940-21, Japan
Received August 10, 1989

Multipoint hydrogen bonding plays an essential role for the selectivities in biological systems. We have recently reported on the selective sugar binding with resorcinol–aldehyde cyclotetramer **1**;[3] a striking feature of **1** is that it is a *multidentate* host having four independent binding sites (A, B, C, and D). We wish to report here that **1** in fact allows a two-point hydrogen-bonding fixation of dicarboxylic acids in a remarkably selective manner.[4-7]



1a ; R = $(CH_2)_{10}CH_3$
1b ; R = $(CH_2)_3CH_3$

$X(CH_2)_nCOOH$
2; n = 1, X = COOH
3; n = 3, X = COOH
4; n = 5, X = COOH
5; n = 3, X = CH_3
6; n = 3, X = $COOCH_3$

Glutaric acid (**3**) is slightly soluble in $CHCl_3$ but is readily solubilized in the presence of **1a** or **1b**. The ^1H NMR spectrum of a $CDCl_3$ solution of **1a** after being stirred with an excess amount of solid **3** showed highly upfield shifted CH proton resonances for bound **3** at δ_H 0.70 (H_a, 2 H), 0.10 (H_b, 2 H), and −1.33 (H_c, 2 H) as well as those with marks for **3** free from complexation (Figure 1),[8] The ^{13}C NMR spectrum of complex **1b–3** in $CDCl_3$ showed a single resonance for each carbon of bound **3**, δ_C 178.07 (CO), 29.11 (C_α), and 15.43 (C_β), referring to structure **7**. Two-dimensional ^1H–^{13}C and ^1H–^1H COSY and ^1H–^1H NOESY spectra of bound **3** indicated that (1) both H_a and H_b (refer to Figure 1) couple with C_α, while H_c couples with C_β, (2) H_a and H_b strongly couple with each other (J = 18 Hz) as H_a and H_c and H_b and H_c do, and (3) H_a and H_b are strongly NOE correlated. These results indicate that H_a and H_b are nonequivalent geminal protons on equivalent C_α's, as shown in **7**. The stoichiometry of $\mathbf{1}:\mathbf{3}_{bound}$ = 1:1 is established by ^1H NMR integration, and the appearance of distinct signals for $\mathbf{3}_{bound}$ and $\mathbf{3}_{free}$ suggests

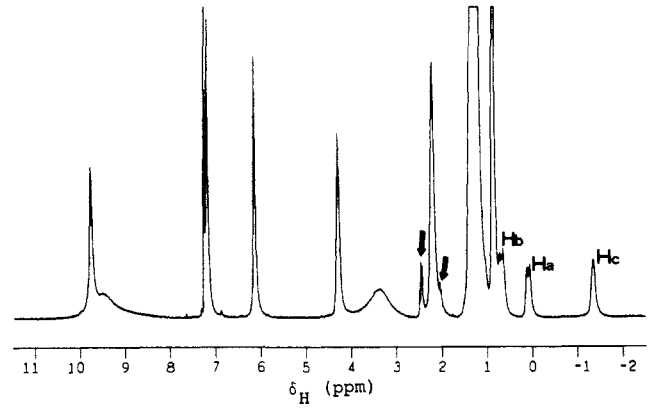
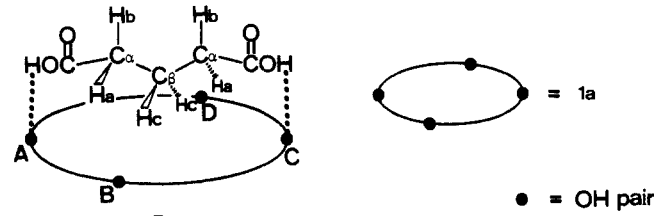


Figure 1. ^1H NMR spectrum of **1a** in $CDCl_3$ at room temperature after being stirred with excess **3**. Absorptions H_a, H_b, and H_c are for **3** bound with **1a**; see structure **7** for the assignments. Absorptions with marks are for **3** free from complexation, which is present owing to its intrinsic solubility.

that the exchange between these (refer to eq 1, guest is **3**) is slow at room temperature compared with NMR time scale.

$$\mathbf{1} + \text{guest} \overset{K}{\rightleftharpoons} \mathbf{1}\text{-guest} \qquad (1)$$

The 1:1 adduct **1a–3** isolated was shown to be monomeric as such in CCl_4 by vapor pressure osmometry, and its IR spectrum for a CCl_4 solution gave a single ν_{CO} at 1725 cm^{-1} indicative of hydrogen-bonded CO_2H groups. Complexation was observed neither between **1a** and dimethyl glutarate nor between **3** and the octaacetate derivative of **1a**,[3] and no evidence was obtained for the complexation of **3** in such hydrogen bond-breaking polar solvents as acetone-d_6 and $CDCl_3$–CD_3OD (9:1). These results, coupled with spectroscopic evidence (vide supra) for the equivalency of the two CO_2H groups and two H_2C moieties of bound **3**, leave little doubt that **3** is bound with **1** via two-point hydrogen bonding involving both terminal CO_2H groups, as illustrated in **7** (in a schematic representation).



7

Pimelic acid (**4**) forms an adduct with **1** likely via a similar two-point interaction.[9] There is, however, a remarkable difference in the affinities of **3** and **4** to **1**. Analysis of exactly equimolar and completely homogeneous solutions of **1a** and **3** in $CDCl_3$ at 25 °C ([**1a**] = [**3**] = 10 and 0.50 mM) indicated that approximately 97 and 87% complexations, respectively, were taking place as directly evaluated by ^1H NMR integration of the distinct signals for $\mathbf{3}_{bound}$ and $\mathbf{3}_{free}$; the binding constant K (eq 1) must be very large ($K_3 \cong 10^5$ M^{-1})[10,11] as compared with $K_4 = 1.1 \times 10^3$ M^{-1} ($\Delta G°_4 = -4.1$ kcal/mol) obtained by a similar ^1H NMR analysis.[12] The affinities of valeric acid (**5**) and glutaric acid monomethyl ester (**6**) as monoacid references of **3** are even lower, $K_5 = 7.0 \times 10$ and $K_6 = 3.1 \times 10$ M^{-1} ($\Delta G°_5 = -2.5$ and $\Delta G°_6 = -2.0$

(1) Molecular Recognition. 8. Part 7 of this series: Tanaka, Y.; Ubukata, Y.; Aoyama, Y. *Chem. Lett.* **1989**, 1905.
(2) Section of Bioorganic Chemistry, Department of Bioengineering, Nagaoka University of Technology.
(3) (a) Aoyama, Y.; Tanaka, Y.; Toi, H.; Ogoshi, H. *J. Am. Chem. Soc.* **1988**, *110*, 634. (b) Aoyama, Y.; Tanaka, Y.; Sugahara, *Ibid.* **1989**, *111*, 5397.
(4) For a study on the binding of dicarboxylic acids via two-point hydrogen-bonding interaction in apolar media, see: Rebek, J., Jr.; Nemeth, D.; Ballester, P.; Lin, F.-T. *J. Am. Chem. Soc.* **1987**, *109*, 3474.
(5) For the binding of dicarboxylic acids in aqueous media, see: (a) Breslow, R.; Rajagopalan, R.; Schwarz, J. *J. Am. Chem. Soc.* **1981**, *103*, 2905. (b) Kimura, E.; Sakonaka, A.; Yatsunami, T.; Kodama, M. *Ibid.* **1981**, *103*, 3041. (c) Hosseini, M. W.; Lehn, J. M. *Ibid.* **1982**, *104*, 3525.
(6) For examples of multipoint interactions involving hydrogen bonding, see: (a) Rebek, J., Jr.; Askew, B.; Nemeth, D.; Parris, K. *J. Am. Chem. Soc.* **1987**, *109*, 2432. (b) Askew, B.; Ballester, P.; Buhr, C.; Jeong, K. S.; Jones, S.; Parris, K.; Williams, K.; Rebek, J., Jr. *Ibid.* **1989**, *111*, 1982. (c) Williams, K.; Askew, B.; Ballester, P.; Buhr, C.; Jeong, K. S.; Jones, S.; Rebek, J., Jr. *Ibid.* **1989**, *111*, 1090. (d) Goswani, S.; Hamilton, A. D.; Van Engen, D. *Ibid.* **1989**, *111*, 3425. (e) Kelly, T. R.; Zhao, C.; Bridger, G. J. *Ibid.* **1989**, *111*, 3744.
(7) For examples of electrostatic–electrostatic or hydrophobic–electrostatic two-point interactions, see: (a) Tabushi, I.; Kobuke, Y.; Imuta, J. *J. Am. Chem. Soc.* **1981**, *103*, 6152. (b) Hamilton, A.; Lehn, J.-M.; Sessler, J. L. *Ibid.* **1986**, *108*, 5158. (c) Tabushi, I.; Shimizu, N.; Sugimoto, T.; Shiozuka, M.; Yamamura, K. *Ibid.* **1979**, *99*, 7100.
(8) The CO_2H proton resonance appeared at δ_H 12.06 at −60 °C.
(9) In a similar manner as adduct **1a–3**, adduct **1a–4** shows highly upfield shifted ^1H resonances at δ_H −0.1 to −0.8 (approximately 4 H) and a single ^{13}C resonance for the CO group at δ_C 181.04.
(10) Calculation of $K_3 = [\mathbf{1a}\text{–}\mathbf{3}]/[\mathbf{1a}]_{free}[\mathbf{3}]_{free} = [\mathbf{1a}\text{–}\mathbf{3}]/[\mathbf{3}]^2_{free}$ based on percent complexation data gives $K_3 = 1.4 \times 10^5$ or 1.2×10^5 M^{-1} and 1.1×10^5 M^{-1} at $[\mathbf{1a}]_{total} = [\mathbf{3}]_{total} = 10$ and 0.50 mM, respectively (see Supplementary Material). These values must be regarded as only approximate, since $[\mathbf{3}]_{free}$ and $[\mathbf{1a}]_{free}$ are too small to assure accurate determination of K_3.
(11) The methyl-substituted derivatives of **3** also form adducts with **1**, although less effectively than with parent **3**. On the other hand, the solubilities of 3-ketoglutaric, diglycolic, and iminodiacetic acids in $CDCl_3$ are too poor to allow complexation with **1**.

0002-7863/90/1512-2807$02.50/0

kcal/mol).[12] A more reliable value of K_3 was obtained by competition. Analysis of a 1:1:1 mixture of **1a**, **3**, and **4** (10 mM) in $CDCl_3$ gave $K_3/K_4 = ([\mathbf{1a}\text{-}3]/[\mathbf{1a}\text{-}4])([4]_{free}/[3]_{free}) = 105$,[13] and hence $K_3 = 1.2 \times 10^5\ M^{-1}$ ($\Delta G°_3 = -6.9$ kcal/mol). Similarly was shown the high preference of **3** over malonic acid (**2**) by a competitive binding in $CDCl_3$-CD_3OD (99:1).

In summary, a rigid and multidentate host **1** brings about an unprecedentedly large chain-length selectivity,[5c] $K_3/K_4 = 105$ ($\Delta\Delta G° = 2.8$ kcal/mol). The two-point hydrogen bonding is at least primarily responsible for the stability of the glutaric acid complex, although steric factors may also come into play.[14] The fact that $\Delta G°_3 < 2\Delta G°_5$ or $2\Delta G°_6$ indicates that an ideal two-point interaction is far more favorable than two independent one-point interactions.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on Priority Area from the Ministry of Science, Education, and Culture of Japan.

Supplementary Material Available: Evaluation of binding constants K (1 page). Ordering information is given on any current masthead page.

(12) Supplementary Material shows details of the evaluation of K's.

(13) The distribution of **1a**-**3**, **1a**-**4**, $\mathbf{3}_{free}$, and $\mathbf{4}_{free}$ was found to be independent of the order of addition of **1a**, **3**, and **4**, indicating reversibility of the complex formation process (eq 1).

(14) CPK models indicate that **3** in its most extended conformation ideally fits for the two-point interaction (refer to **7**); the significant ring current effects on the ^1H and ^{13}C resonances of bound **3** suggest a possible contribution of σ-π interactions to $\Delta G°_3$. If **4** is to be fixed via a similar two-point interaction, it must undergo bending of its pentamethylene backbone with freezing of rotations around two additional C-C bonds as compared with the case of **3**. This may result in an induction of steric strain, a loss of attractive σ-π interactions, and/or a significant loss in entropy as possible sources of $\Delta\Delta G°$ = 2.8 kcal/mol.

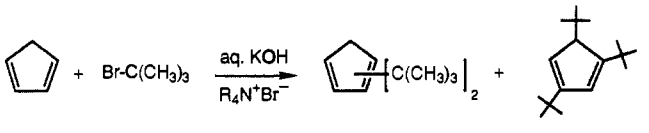
Di-*tert*-butylcyclopentadiene and Tri-*tert*-butylcyclopentadiene

Clifford G. Venier* and Edward W. Casserly*

Technology Division, Pennzoil Products Company
P.O. Box 7569, The Woodlands, Texas 77387

Received November 1, 1989

Bis(1,1-dimethylethyl)cyclopentadiene (**1**) and tris(1,1-dimethylethyl)cyclopentadiene (**2**) can be prepared in high yields by phase-transfer-catalyzed alkylation. This is the first reported preparation of tri-*tert*-butylcyclopentadiene. It is also the first example of carbon alkylation under phase-transfer conditions using a tertiary halide.



1a; 1,3-
1b; 1,4-
1c; 2,5-

2

In connection with a more general study of the preparation of multiply alkylated cyclopentadienes,[1] we have discovered that cyclopentadienes can be readily alkylated by tertiary halides under phase-transfer-catalysis conditions using quaternary ammonium halides. In view of the extensive interest in new cyclopentadiene ligands, we are reporting the easy preparation of these two molecules in preliminary form.

Steric effects on the reactivity of organometallic complexes as a function of *phosphine* ligand structure have received much attention, and useful catalysts have resulted.[2] Much less work on the steric effects of changing cyclopentadiene ligand structure has been reported,[3] primarily because sterically bulky cyclopentadienes have not been readily available.

Tumanov et al.[11] report that equilibria for ion-radical formation between tungsten-cyclopentadienyl complexes and TCNE or TCNQ are very sensitive to the bulk of substituents on the cyclopentadienyl ring. Changing from *n*-butylcyclopentadienyl as ligand to *tert*-butylcyclopentadienyl changes the equilibrium constants by a factors of up to 100. The changes correlate to the Charton steric parameter, ν.

A good measure of the steric effect of a substituent is the ligand cone angle, Θ. Tolman[2] calculated a Θ for unsubstituted cyclopentadienyl of 136°. Inspection of models for di- and tri-*tert*-butylcyclopentadienyls suggests that their cone angles may be 180° or more.

Phase-transfer-reaction conditions are reported to give only alkenes from tertiary alkyl halides.[12-14] The surprising fact that reactions of stoichiometric ratios of cyclopentadienyl[15-17] and *tert*-butylcyclopentadienyl anions[18,19] with *tert*-butyl bromide give about 50% yields of the *tert*-butylated products suggested to us that phase-transfer *tert*-butylation of cyclopentadiene with an excess of the *tert*-butyl bromide might give high yields of di-*tert*-butylcyclopentadienes. This proved to be the case.

Although the literature preparations of di-*tert*-butylcyclopentadiene use *tert*-butyl bromide and cyclopentadiene as the ultimate starting materials, they do so in two steps with preformed cyclopentadienyl anions.[18,19] Such procedures are cumbersome and involve the inconvenience of reaction in a dry, airless environment.

Tri-*tert*-butylcyclopentadiene has not been reported previously, but tetra-*tert*-butylcyclopentadiene has been prepared in connection with the synthesis of tetra-*tert*-butyltetrahedrane.[20] The preparation is a very long one.

The phase-transfer procedure we have found useful is as follows. KOH (aqueous 50%), *tert*-butyl bromide, and freshly distilled cyclopentadiene in the mole ratio 40:5:1 plus Adogen 464 (1 g per mole of KOH) were stirred together and heated to 60 °C for 75 min and 100 °C for an additional 45 min. (*CAUTION*: sudden foaming sometimes occurs.) The cooled reaction mixture was diluted with pentane, washed with water, and dried over $MgSO_4$. Pentane is removed in vacuo. The crude residue contains the product, Adogen 464, and amine byproducts of Adogen 464 de-

(1) Venier, C. G.; Casserly, E. W. Manuscripts in preparation.

(2) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.
(3) In addition to di-*tert*-butylcyclopentadiene, other cyclopentadienes with bulky substituents have been reported; for example: pentaphenyl;[4,5] pentabenzyl;[5,6] tetramethyl, 1-phenylpropyl;[7] tris(trimethylsilyl);[8] *tert*-butyl, bis(trimethylsilyl);[9] and di-*tert*-butyl with one additional group IV substituent.[10]
(4) Heeg, M. J.; Janiak, C.; Zuckerman, J. J. *J. Am. Chem. Soc.* **1984**, *106*, 4259 and references therein.
(5) Chambers, J. W.; Baskar, A. J.; Bott, S. G.; Atwood, J. L.; Rausch, M. D. *Organometallics* **1986**, *5*, 1635.
(6) Lorberth, J.; Shin, S.-H.; Wocadlo, S.; Massa, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 735 and references therein.
(7) Dormond, A.; El Bouadili, A.; Moise, C. *Tetrahedron Lett.* **1983**, *24*, 3087.
(8) Okuda, J.; Herdtweck, E. *Chem. Ber.* **1988**, *121*, 1899.
(9) Okuda, J. *Chem. Ber.* **1989**, *122*, 1075.
(10) Abu-Orabi, S. T.; Jutzi, P. *J. Organomet. Chem.* **1987**, *329*, 169.
(11) Tumanov, A. A.; Zakharov, L. N.; Sennikov, P. G.; Egorochkin, A. N.; Razuvaev, G. A.; Smirnov, A. S.; Dodonov, V. A. *J. Organomet. Chem.* **1984**, *263*, 213.
(12) Starks, C. M.; Liotta, C. *Phase Transfer Catalysis*; Academic Press: New York, 1978; p 330.
(13) Montanari, F.; Landini, D.; Rolla, F. *Top. Curr. Chem.* **1982**, *101*, 147-200, 184.
(14) Dehmlow, E. V.; Dehmlow, S. S. *Phase Transfer Catalysis*, 2nd ed.; Verlag Chemie: Deerfield Beach, FL, 1983; p 177.
(15) Riemschneider, R.; Nehring, R. *Monatsh. Chem.* **1959**, *90*, 568-570.
(16) Leigh, T. *J. Chem. Soc.* **1964**, 3294-3302.
(17) Hafner, K. U.S. Patent 2,953,607, 1960.
(18) Riemschneider, R. *Z. Naturforsch. B* **1963**, *18*, 641-645.
(19) Schonholzer, S.; Slongo, M.; Rentsch, C.; Neuenschwander, M. *Makromol. Chem.* **1980**, *181*, 37-45.
(20) Maier, G.; Pfriem, S.; Schafer, U.; Malsch, K.-D.; Matusch, R. *Chem. Ber.* **1981**, *114*, 3965-3987.

0002-7863/90/1512-2808$02.50/0