Ab Initio Study of the Complexation Behavior of Calix[5]arene Derivative toward Alkyl Ammonium Cations

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The structures and complexation energies of penta-O-alkylated **1b** and penta-O-*tert*-butyl ester **1e** of *p-tert*-butylcalix[5]arene and their simplified structures (**2b** and **2e**) toward a series of alkyl ammonium guests have been calculated by a semi-empirical AM1 method. For AM1 calculations, complexation efficiencies of the simplified host **2e** are very similar to the values of host **1e**. The complexes of simplified host **2e** with alkyl ammonium ions also have been optimized by *ab initio* HF/6-31G method. The calculated complexation efficiencies for **2e** by *ab initio* method have been found to be bigger in magnitude than the values obtained by AM1 calculations for linear alkyl ammonium guests. Calculation results show that all of the calix[5]aryl derivatives investigated in this study have much better complexation ability toward ammonium cation without alkyl group compared with other alkyl ammonium guests. *Ab initio* calculations also well duplicate the molecular discriminating behaviors of calix[5]arene derivative **2e** between butyl ammonium ions: n-BuNH$_3^+$ > iso-BuNH$_3^+$ > sec-BuNH$_3^+$ > $tert$-BuNH$_3^+$.

Key Words : Calix[5]arene, Alkyl ammonium ion, Molecular recognition, *Ab initio* HF/6-31G

Introduction

Calixarenes[1,2] have received much attention recently as one of the most widely employed molecular frameworks for the construction of many versatile supramolecular systems.[3,4] Among the varying structures of calixarenes, pentameric analogue calix[5]arene has received relatively less attention due to difficulties encountered both in its synthesis and selective derivatization compared with other widely employed calixarenes having four, six, or eight repeating units. However, a series of calix[5]arene derivatives having crown ether or ester functions has been prepared and is known to have strong affinity toward large alkali metal ions.[5] Selective recognition of organic ammonium guests is very important for many functional biogenic ammonium ions, and a number of sophisticated host systems are derived from calixarenes.[6-9] For calix[5]arene based amine selective ionophores, selective *endo*-calix complexation of alkyl ammonium cations by functionalized (1,3)-*p-tert*-butylcalix[5]crown ether[10] and by calix[5]arene-based molecular vessels **1b-1e**[11] have been reported. Giannetto *et al.* report very efficient discrimination behavior between butylammonium isomers by means of calix[5]arene-based ion selective electrode technique.[12] More recently, 1,3-bridged calix[5]crown-6-ether was investigated as a tool for the shape recognition of alkylammonium ions in focusing the *endo*- versus *exo*-cavity complexation.[13] These interesting host-guest properties are mainly related to the calix[5]arene backbone fixed in cone-type C_{5v}-symmetric structure by providing a highly preorganized three dimensional molecular framework assembled as efficient binding sites.

Parallel to this, a lot of computational studies have been performed for the supramolecular systems of calixarenes and their complexes.[14] We previously reported the computer simulations on the molecular recognition of butylamines by ester derivative of *p-tert*-butylcalix[5]arene, using several molecular modeling programs of AM1 semi-empirical and molecular mechanics.[15] The results show that *n*-butyl ammonium guests generally have larger complexation affinity over other branched butyl ammonium ions. Trends of these calculations in vacuum agree well with the published experimental[11] results in the following order: **1e** > **1b** > **1c** > **1d**.

Studies of the *p-tert*-butylcalix[4]crown-6-ether and its alkyl ammonium complexes show that cone conformation is the most stable for all the employed calculation methods.[16] In this paper, we have calculated the molecular recognition behaviors of penta-O-alkylated derivative **1b** and *tert*-butyl ester derivative **1e** of cone-shaped *p-tert*-butylcalix[5]arene and their simplified structures (**2b** and **2e**) toward a series of alkyl ammonium guests by semi-empirical AM1 method. The host **2e** (methyl calix[5]aryl ester) is a trimmed version of host **1e** (*tert*-butyl *p-tert*-butylcalix[5]aryl ester) for the purpose of *ab initio* HF/6-31G optimization. The main emphasis of this research is determining the selectivity of the host for different alkyl ammonium guests with varying structural characteristics, which are good model compounds for the biologically important organic amine guests. The calculation results might provide a deeper insight into these relatively less well studied but interesting molecular frameworks of calix[5]arenes.

Computational Methods

The initial structures of host and guest molecules were

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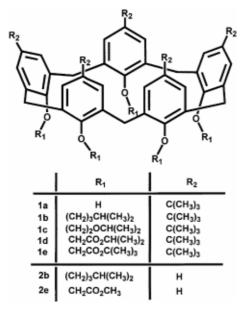
Figure 1. Chemical structure of calix[5]arene derivatives.

constructed by HyperChem.[17] To find optimized conformations, we executed a conformational search by simulated annealing method, which has been described in a previous publication.[16a] The structures of the hosts **1b**, **1e**, **2b**, **2e**, and their complexes obtained from MM/MD calculations of HyperChem and InsightII/Discover[18] were fully re-optimized to estimate the binding energies and the enthalpies of formation for the compounds, using the AM1 method. To confirm that the final structure is in the local minimum point, we have calculated the normal mode frequencies of the optimized complex. Each vibrational spectrum shows no negative value of frequency, which suggests that the optimized structure is really in minimum point. *Ab initio* HF/6-31G optimization of host **2e** or its complex by Gaussian 98 on a Fujitsu VPP 5000 supercomputer at Okazaki National Research Institute of Japan took more than 100 hours to reach an optimum conformation for each complex. Initially, we tried to calculate the host **1e** with guest ions, but this complex was too big to be optimized by *ab initio* HF/6-31G

method using the supercomputer. Therefore, we had to change the *tert*-butyl group in the upper rim of calix[5]arene to hydrogen atom and the *tert*-butyl group in the ester branch to methyl group. This way, host **2e** has the same basic skeleton of calix[5]arene as the smaller substituent as opposed to host **1e** without significantly affecting the basic binding site of **1e**.

Results and Discussion

There might be a variety of conformational isomers in ether and ester derivatives of calix[5]arene, depending on the degree and nature of substitution.[19] Among them, penta-O-alkylated *p-tert*-butylcalix[5]arenes frozen in C_{5v}-symmetric cone conformation have received much attention as one of the most efficient and selective synthetic neutral molecular receptors for linear alkylammonium ions.[10] As we discussed in a preliminary report,[15] we have focused our efforts on the most stable *endo*-cone-shaped complexes of hosts with various alkyl ammonium ions.

Semi-empirical (AM1) Method. The conformations of the host and complexes obtained from MM calculations were fully re-optimized to estimate the binding energies and the enthalpies of formation for the complexes, using the AM1 semi-empirical method. Since the binding energy and the enthalpy of formation are directly connected for the calculation of complexation energy, the complexation energy ($E_{Complex} - E_{Host} - E_{Guest}$) is exactly the same as the complexation enthalpies ($\Delta H_{Complex} - \Delta H_{Host} - \Delta H_{Guest}$). Therefore, we report only the values of the calculated enthalpy. Table 1 summarizes the calculated enthalpies of formation and the relative complexation efficiencies of the hosts with various alkyl ammonium cations.

In Table 1, the data more meaningful than the individual enthalpies are in fact the complexation enthalpies ($\Delta H_{Complex} - \Delta H_{Host} - \Delta H_{Guest}$) to cancel out the individual guest effects for the different alkyl ammonium cations. The hosts **2b** and **2e** (methyl calix[5]aryl derivative) are trimmed structures of host **1b** and **1e** (*tert*-butyl *p-tert*-butylcalix[5]aryl ester) having the same basic structural unit comprising possible

Table 1. AM1 Enthalpies (kcal/mol)[a] of Complexes of Calix[5]arene with Alkyl Ammonium Ions

Semi-empirical AM1 enthalpies using HyperChem			Alkyl ammonium guest[b]							
			NH_4^+	Me	Et	*n*-Pr	*n*-Bu[c]	*iso*-Bu[c]	*sec*-Bu[c]	*tert*-Bu[c]
			150.53	148.65	138.57	131.17	123.53	125.01	124.33	125.40
Host		Guest	Complexes with host							
-307.77	Host **1b**	RNH_3^+	-226.00	-219.15	-225.76	-231.72	-238.85	-237.30	-234.15	-226.23
-619.32	Host **1e**	RNH_3^+	-545.24	-535.22	-539.85	-545.54	-552.74	-550.14	-538.05	-534.36
-215.68	Host **2b**	RNH_3^+	-129.46	-124.00	-130.68	-136.45	-144.03	-142.02	-139.16	-131.57
-471.89	Host **2e**	RNH_3^+	-394.09	-386.62	-389.99	-395.47	-402.62	-399.42	-394.32	-387.23
Host **1b** + Guest complexation[d]			-68.76	-60.03	-56.56	-55.12	-54.61	-54.54	-50.71	-43.86
Host **1e** + Guest complexation[d]			-76.45	-64.55	-59.10	-57.38	-56.95	-55.83	-43.06	-40.44
Host **2b** + Guest complexation[d]			-64.31	-56.97	-53.57	-51.94	-51.88	-51.35	-47.81	-41.29
Host **2e** + Guest complexation[d]			-72.73	-63.38	-56.67	-54.75	-54.26	-52.54	-47.21	-40.74

[a]Error limits in these calculations are 0.01 kcal/mol. [b]Me = methyl ammonium, Et = ethyl ammonium, *n*-Pr = *n*-propyl ammonium, *n*-Bu = *n*-butyl ammonium ion, *etc.* [c]Butyl ammonium data for host **1e** are taken from reference 15. [d]Complexation enthalpy = $\Delta H_{Complex} - \Delta H_{Host} - \Delta H_{Guest}$.
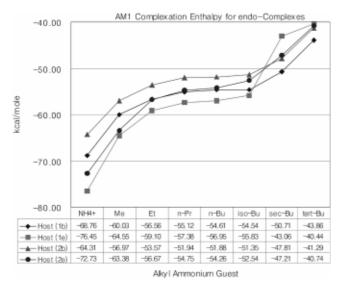
Figure 2. Plot of AM1 complexation enthalpies for *endo*-complexes of hosts.

binding sites of upper rim cavity and lower rim ester and ether functions.

To compare the complexation efficiencies for the alkyl ammonium guests in various calix[5]aryl hosts, we have converted the complexation energy data in Table 1 into a plot (Figure 2). When one sees the graphs in Figure 2, it is very clear that the trend of the complexation efficiencies for the trimmed host **2e** with alkyl ammonium ions is very similar to that of host **1e** in the order of $NH_4^+ > MeNH_3^+ > EtNH_3^+ > n$-$PrNH_3^+ \sim n$-$BuNH_3^+ > iso$-$BuNH_3^+ > sec$-$BuNH_3^+ > tert$-$BuNH_3^+$. Among the butylammonium ions, the complexation affinity decreases drastically from *n*-butyl to other isomeric butyl ammonium ions due to steric hindrance of the bulky substituents. The calculated results confirmed the earlier suggestion of the efficient discrimination of butyl-amine isomers by calix[5]arene based ether ionophore **1b** by ISE technique.[12] In that report the complexed *n*-butyl-ammonium guest is depicted as efficiently interacting with the preorganized ether oxygen atoms of **1b**, with its alkyl group pointing toward upper rim cavity of calix[5]arene. With this structure, the role of the carbonyl function seems to be relatively less important than the ether oxygen donor site in the complexation of alkyl ammonium guests. The complexation efficiencies of the trimmed host **2b** with alkyl

ammonium ions also show a similar trend to those of host **1b.** Therefore, it can be generalized that the complexation efficiency decreases gradually as the size of the alkyl group increases. The calculation results for **1e** and **2e** clearly suggest that the presence of *p-tert*-butyl groups in the upper rim of host **1e** does not affect significantly the relative stability of the host-guest complexes in the present calix[5]-arene systems.

Ab Initio **HF/6-31G Method**. As we mentioned in the "Computational Methods" section, we could not calculate the whole structure of the host **1e** due to the memory size, but fortunately the smaller calix[5]aryl ester **2e** could be optimized using the HF/6-31G method.

Table 2 summarizes the *ab initio* energies and the complexation efficiency of host **2e** with various alkyl ammonium cations. To compare the complexation efficiency of the AM1 semi-empirical method with *ab initio* HF/6-31G calculation for host **2e**, we have converted the complexation data of host **2e** in Tables 1 and 2 into a plot of Figure 3. When one sees the graphs in Figure 3, the trend of the complexation energies for host **2e,** using *ab initio* HF/6-31G method is similar to that of host **2e** with AM1 semi-empirical calculations. But, the complexation energies calculated by *ab initio* method is 10-17 kcal/mol bigger in magnitude than those by AM1 calculation for alkyl ammonium ions, except for *tert*-butyl ammonium.
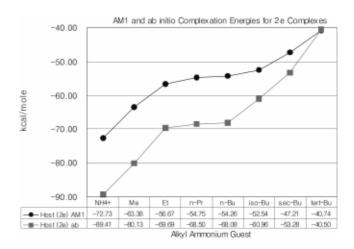

Figure 3. Plot of AM1 and *ab initio* complexation energies for *endo*-complexes of host **2e**.

Table 2. *Ab initio* HF/6-31G Energies (A.U.)*a* of Different Complexes of Calix[5]arene with Alkyl Ammonium Ions

Ab initio HF/6-31G energies Using Gaussian 98		Alkyl ammonium guest							
		NH_4^+	Me	Et	*n*-Pr	*n*-Bu	*iso*-Bu	*sec*-Bu	*tert*-Bu
		-56.5159	-95.5388	-134.5658	-173.5862	-212.6057	-212.6063	-212.6111	-212.6172
Host **2e**	Guest	Complexes with host							
-3044.1610	RNH_3^+	-3100.8194	-3139.8275	-3178.8378	-3217.8529	-3256.8751	-3256.8644	-3256.8570	-3256.8428
Host **2e** + Guest complexation energy*b*		-89.4145	-80.1284	-69.6833	-68.4953	-68.0851	-60.9592	-53.2837	-40.4973

*a*Error limits in these calculations are about 2×10^{-5} A.U. Units for the *ab initio* total energies are in A.U., and units for complexation energies are in kcal/mol using conversion factor 1 A.U. = 627.50955 kcal/mol. *b*Complexation energies (kcal/mol) = $E_{Complex} - E_{Host} - E_{Guest}$.
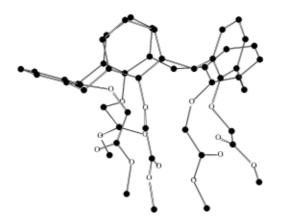
Figure 4. *Ab initio* calculated cone conformation of free host **2e**.

The *ab initio* optimized structure for the cone confor-
mation of free host **2e** is depicted in Figure 4. The free host
2e has a somewhat irregular distorted conformation with
ester carbonyl functions pointing relatively randomly with
respect to the central pseudo-cavity of the host. Figures 5(a)
through 5(d) show the *ab initio* calculated structures of
endo-cone-type complex of **2e** with smaller alkyl ammo-
nium cations, in which the hydrogen atoms are omitted for
clarity. The structure of host **2e** became more regular upon
complexation with ammonium ion, and ester carbonyl
functions are pointing toward the interior of the pseudo-

cavity of the host molecule. When one sees the structure
shown in Figure 5(a), the nitrogen atom in the host-guest
(**2e** + NH_4^+) complex is located just below the mean plane,
which is comprised of five ether-oxygen atoms of host **2e**
experiencing the intimate interaction with ether oxygen
atoms. The structure also implies that there exist multiple
hydrogen-bonding interactions between the hydrogen atoms
of NH_4^+ and the oxygen atoms of phenol ethers and some of
carbonyl groups of ester. These charge-dipole and hydrogen
bonding interactions resulted in the highest stability of the
2e + NH_4^+ complex among all complexes.

The optimized structures in Figures 5(b) through 6(d),
show the nitrogen atom in the **2e** + RNH_3^+ complex situated
somewhat above the mean plane of five ether-oxygen atoms
of host **2e**. With increasing bulkiness of the alkyl groups of
the ammonium ion, the ammonium group is progressively
located relatively away from the oxygen atoms of phenol
ethers. This weakens the interactions between alkyl ammo-
nium guests and oxygen atoms of the host. When we
counted the number of hydrogen bonding between the
nitrogen atom of alkyl ammonium guests and the ether-
oxygen atoms of host, we found that most of RNH_3^+ ions use
all three hydrogen atoms of ammonium moiety for hydrogen
bonding, except for *sec*-$BuNH_3^+$, which uses two hydrogen
atoms. *tert*-$BuNH_3^+$ uses only one hydrogen atom, with a
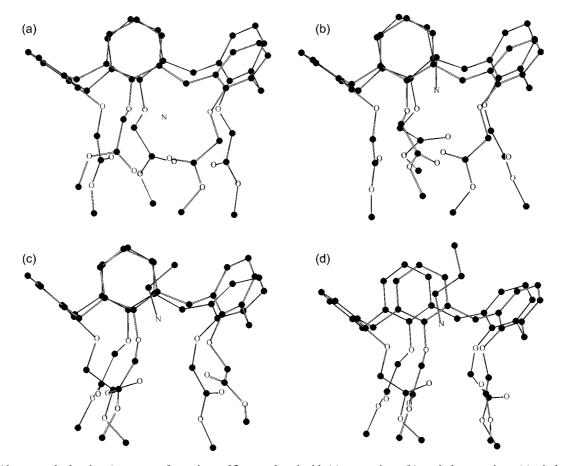longer H-bond distance than linear alkyl ammonium ions. A

Figure 5. Ab *initio* calculated *endo*-cone conformations of **2e** complexed with (a) ammonium, (b) methyl ammonium, (c) ethyl ammonium,
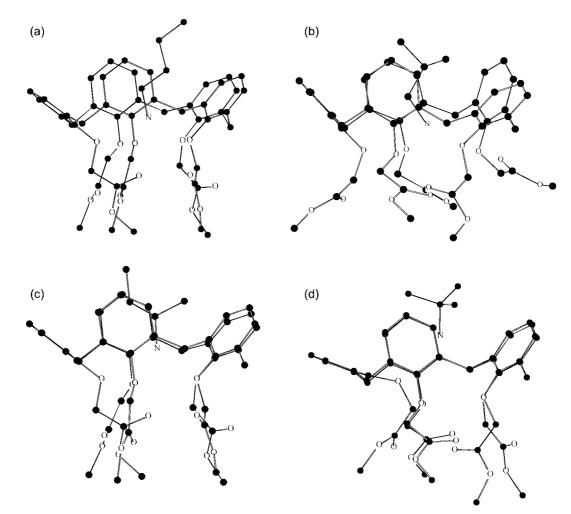and (d) *n*-propyl ammonium ions.

Figure 6. *Ab initio* calculated *endo*-cone conformations of **2e** complexed with (a) *n*-butyl ammonium, (b) *iso*-butyl ammonium, (c) *sec*-butyl ammonium, and (d) *tert*-butyl ammonium ions.

detailed comparison of the calculated complexation free energies with the distances between the nitrogen atom of butylammonium ion and the mean plane of five ether-oxygen atoms of host **1e** about four different isomers of butyl ammonium guest ions was reported in previously.[15]

Figures 6(a) through 6(d) show the *ab initio* calculated structures of *endo*-cone-type complex of **2e** with the isomers of butyl ammonium guests. For all the above calculated structures, most of the distances between the nitrogen atom of the guest with the carbonyl oxygen atoms are larger than 5.0 A, far exceeding the usual hydrogen-bonding interaction range of 2.865 A for the related systems.[20] This fact indicates that there is little influence of the carbonyl oxygen atoms of hosts on the *endo*-complexation with butyl ammonium guest in the calix[5]arene host molecules studied in this work.

Conclusion

Using *ab initio* HF/6-31G and semi-empirical AM1 quantum mechanics, we have performed computer simulations of the complexation behaviors of the derivatives of calix[5]arene toward a variety of alkyl ammonium ions. For all the calculation results in these simulations, ammonium cation without

alkyl group has a much better complexation ability than other alkyl ammonium guests in the order of $NH_4^+ >$ $MeNH_3^+ > EtNH_3^+ > n\text{-}PrNH_3^+ \sim n\text{-}BuNH_3^+ > iso\text{-}BuNH_3^+ >$ $sec\text{-}BuNH_3^+ > tert\text{-}BuNH_3^+$. We believe that the present simulations provide a general and useful insight into the molecular recognition behavior of the calix[5]arene derivatives toward alkylammonium guests, which will be applicable for the design of other functional ionophore systems for the recognition of biologically important amines.

References

1. Gutsche, C. D. *Calixarenes Revisited*; The Royal Society of Chemistry: Cambridge, 1998.
2. *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1991.
3. Balzani, V.; De Cola, L. *Supramolecular Chemistry*; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1992.

4. *Cation Binding by Macrocycles*; Inoue, Y., Gokel, G. W., Eds.; Marcel Dekker: New York, 1990.

5. (a) Gordon, J. L. M.; Böhmer, V.; Vogt, W. *Tetrahedron Lett*. **1995**, *36*, 2445. (b) Barrett, G.; McKervey, M. A.; Malone, J. F.; Walker, A.; Arnaud-Neu, F.; Guerra, L.; Schwing-Weill, M.-J. *J. Chem. Soc. Perkin Trans. 2* **1993**, 1475.

6. *Molecular Recognition: Chemical and Biochemical Problems*; Roberts, S. M., Ed.; The Proceedings of an International Symposium, Royal Society of Chemistry, Dorset Press: Dorset, Great Britain, 1989.

7. Fages, F.; Desvergne, J.-P.; Kampke, K.; Bouas-Laurent, H.; Lehn, J.-M.; Meyer, M.; Albrecht-Gary, A.-M. *J. Am. Chem. Soc.* **1993**, *115*, 3658.

8. (a) Chang, S.-K.; Hwang, H.-S.; Son, H.; Youk, J.; Kang, Y. S. *J. Chem. Soc., Chem. Commun*. **1991**, 217. (b) Chang, S.-K.; Jang, M.; Han, S. Y.; Lee, J. H.; Kang, M. H.; No, K. T. *Chem. Lett*. **1992**, 1937. (c) Han, S. Y.; Kang, M.-H.; Jung, Y. E.; Chang, S.-K. *J. Chem. Soc., Perkin Trans. 2* **1994**, 835.

9. (a) Kubo, Y.; Maeda, S.; Tokita, S.; Kubo, M. *Nature* **1996**, *382*, 522. (b) Odashima, K.; Yagi, K.; Tohda, K.; Umezawa, Y. *Anal. Chem.* **1993**, *65*, 1074. (c) Arnecke, R.; Böhmer, V.; Cacciapaglia, R.; Cort, A. D.; Mandolini, L. *Tetrahedron* **1997**, *53*, 4901.

10. Pappalardo, S.; Parisi, M. F. *J. Org. Chem.* **1996**, *61*, 8724.

11. Arnaud-Neu, F.; Fuangswasdi, S.; Notti, A.; Pappalardo, S.; Parisi, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 112.

12. Giannetto, M.; Mori, G.; Notti, A.; Pappalardo, S.; Paris, M. F. *Anal. Chem.* **1998**, *70*, 4631.

13. Salvo, G. D.; Gattuso, G.; Notti, A.; Parisi, M.; Pappalardo, S. *J. Org. Chem.* **2002**, *67*, 684.

14. *Computational Approaches in Supramolecular Chemistry*; Wipff, G., Ed.; Kluwar Academic Publishers: Dordrecht, The Netherlands, 1994.

15. Choe, J.-I.; Chang, S.-K. *Bull. Korean Chem. Soc*. **2002**, *23*, 48.

16. (a) Choe, J.-I.; Kim, K.; Chang, S.-K. *Bull. Korean Chem. Soc*. **2000**, *21*, 465. (b) Choe, J.-I.; Chang, S.-K.; Ham, S. W.; Nanbu, S.; Aoyagi, M. *Bull. Korean Chem. Soc*. **2001**, *22*, 1248. (c) Choe, J.-I.; Chang, S.-K.; Nanbu, S. *Bull. Korean Chem. Soc*. **2002**, *23*, 891.

17. *HyperChem Release 6.3*; Hypercube, Inc.: Waterloo, Ontario, Canada, 2001.

18. *Discover User's Guide*; Biosym Technologies (presently merged to MSI): San Diego, 1999.

19. Notti, A.; Parisi, M. F.; Pappalardo, S. In *Calixarenes 2001*; Asfari, Z.; Böhmer, V.; Harrowfield, J.; Vicens, J., Eds.; Kluwer: Dordrecht, 2001; pp 54-70.

20. Jeffrey, G. A. *An Introduction to Hydrogen Bonding*; Oxford University Press: Oxford, 1997; p 67.