IV. Conclusion

In this paper we have analyzed the cycloaddition of two ethylene molecules in terms of diabatic surfaces. We have shown that this analysis provides a clear understanding of the index and origin of the various critical points. We have also shown that the behavior of the constituent diabatic surfaces as well as that of the curve of intersection can be easily rationalized by using simple MO energy expressions.

Registry No. Ethylene, 74-85-1.

Aromaticity of Highly Bent Benzene Rings. An Investigation by High Field Deuterium NMR of [5]Metacyclophane and Model Compounds

P. C. M. van Zijl, L. W. Jenneskens, E. W. Bastiaan, C. MacLean,* W. H. de Wolf, and F. Bickelhaupt*

Contribution from the Chemical Laboratory, Free University, De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands. *Received September 19, 1985*

Abstract: High field deuterium NMR provides a new and simple method for establishing the degree of aromaticity of a compound. The procedure is based on the determination of the magnetic susceptibility anisotropy from quadrupolar deuterium couplings of molecules in solution aligned by the magnetic field. The technique is illustrated for some deuterated dialkylbenzenes (**2d**, **3e**, **4e**) and applied to [8,11-$^2H_2$][5]metacyclophane (**1d**). Surprisingly, **1d** is found to be fully aromatic in spite of its strongly bent benzene ring.

One of the most discussed topics in chemistry is undoubtedly the concept of aromaticity.[1-4] Although no general definition of aromaticity is available, a commonly accepted description is in terms of π-electron delocalization in a ring, which causes resonance stabilization.[5] Widely used criteria for aromaticity are the following:[1] the structure of the rings (planarity, bond lengths), heat of formation of the compound, reactivity of ring subtituents, and the presence of "ring-currents". The existence of ring-currents is a subject of discussion;[6] a better criterion is the magnetic susceptibility χ, which is directly related to the electronic structure of a molecule. Dauben et al.[7] suggested that the magnetic susceptibility exaltation, defined by

$$\Omega = \chi(\text{obsd}) - \chi(\text{local}) \quad (1)$$

is a measure for aromaticity. Here $\chi = 1/3(\chi_{xx} + \chi_{yy} + \chi_{zz})$ is the average molecular susceptibility, with x, y, z the principal axes of the susceptibility tensor. χ(local) is χ of a nonaromatic reference molecule calculated by means of known localized susceptibilities. Recently, Aihara[4] demonstrated that Ω is related to the resonance energy of the ring. An analogous measure of aromaticity is the enhancement Δ of the absolute value of the susceptibility component perpendicular to the ring, χ_{zz}, or, since the in-plane components of aromatic molecules and their nonaromatic analogues are about the same,[8] the change in the magnetic susceptibility anisotropy $\Delta\chi$

$$\Delta = \chi_{zz}(\text{obsd}) - \chi_{zz}(\text{local}) \approx \Delta\chi(\text{obsd}) - \Delta\chi(\text{local}) \quad (2)$$

Flygare et al.[8-10] demonstrated the applicability of this procedure for a series of aromatic and nonaromatic molecules. The method has been criticized by Benassi et al.[11] on the ground of semiempirical calculations. However, their criticism is dubious, since it only applies to Δ-values which are of the order of magnitude of the experimental error of the used local susceptibility values. In other cases the approach will be able to give a quantification of the aromatic character of the compound.

Compounds for which the question of aromaticity is of particular interest are the short-bridged cyclophanes,[12] where the benzene ring aromaticity may be influenced by the bending imposed by the bridge. In the [n]metacyclophane series, [5]metacyclophane (**1a**) is the shortest known representative. Indeed, large deviations from planarity of the benzene ring were revealed in the X-ray crystal structure of a derivative of **1a**: 8,11-dichloro-[5]metacyclophane (**1b**); the molecule possesses C_s symmetry and the benzene ring has an asymmetrical boat conformation, with the bow bending about 27° and the stern 12° out of the plane of the ring.[13] This geometry is reasonably well reproduced by MNDO[14,15] and MM[16] calculations. A surprising feature of the crystal structure is the length of the bonds in the benzene ring. Whereas the possibility of bond fixation toward a cyclohexatriene-like structure had been discussed in view of the strongly enhanced chemical reactivity of **1a** and **1b**,[17] the actually observed bond lengths (1.393 ± 0.007 Å) are uniform within experimental error and typical for a delocalized aromatic molecule. Furthermore, the chemical shifts of the benzene ring protons of **1a-c** are in the low-field region (about 6.5-8 ppm)[15,18] and it seems plausible

(1) Lewis, D.; Peters, D. *Facts and Theories of Aromaticity*; Macmillan: New York, **1975**; also references therein.
(2) Balaban, A. T. *Pure Appl. Chem.* **1980**, *52*, 1409.
(3) Mallion, K. B. *Pure Appl. Chem.* **1980**, *52*, 1541.
(4) Aihara, J. *J. Am. Chem. Soc.* **1979**, *101*, 558; **1981**, *103*, 5704.
(5) Hückel, E. *Z. Phys.* **1931**, *70*, 204; **1931**, *72*, 310. Hückel, E. *Grundzüge der Theorie Ungesättigter und Aromatischer Verbindungen*; Verlag Chemie: Berlin, 1938; p 71.
(6) Musher, J. I. *J. Chem. Phys.* **1967**, *46*, 1219.
(7) Dauben, H. J., Jr.; Wilson, J. D.; Laity, J. L. *J. Am. Chem. Soc.* **1968**, *90*, 811; **1969**, *91*, 1991.
(8) Sutter, D. H.; Flygare, W. H. *Topics in Current Chemistry*; Springer: Berlin, 1976; Vol. 63, p 89.
(9) Benson, R. C.; Flygare, W. H. *J. Chem. Phys.* **1973**, *58*, 2366.
(10) Schmalz, T. G.; Norris, C. L.; Flygare, W. H. *J. Chem. Phys.* **1973**, *95*, 7961.
(11) Benassi, R.; Lazzeretti, P.; Taddei, F. *J. Phys. Chem.* **1975**, *79*, 848.
(12) For a review: *Cyclophanes*; Keehn, P. M., Rosenfeld, S. M., Eds.; Academic: New York, 1983.
(13) Jenneskens, L. W.; Klamer, J. C.; De Boer, H. J. R.; De Wolf, W. H.; Bickelhaupt, F.; Stam, C. H. *Angew. Chem.* **1984**, *96*, 236.
(14) Turkenburg, L. A. M.; De Wolf, W. H.; Bickelhaupt, F.; Cofino, W. P.; Lammertsma, K. *Tetrahedron Lett.* **1983**, *24*, 1821.
(15) Jenneskens, L. W.; De Kanter, F. J. J.; Turkenburg, L. A. M.; De Boer, H. J. R.; De Wolf, W. H.; Bickelhaupt, F. *Tetrahedron* **1984**, *40*, 4401.
(16) Carballeira, L.; Pereiras, A. J.; Rios, M. A. *J. Chem. Phys.* **1984**, *80*, 4387.
(17) Turkenburg, L. A. M.; Blok, P. M. L.; De Wolf, W. H.; Bickelhaupt, F. *Angew. Chem.* **1982**, *94*, 291.

0002-7863/86/1508-1415$01.50/0

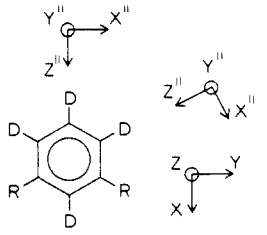
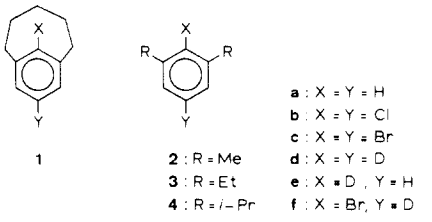


Figure 1. Local frames (x'', y'', z'') for para and meta deuterons and molecular frame (x, y, z) for meta-disubstituted planar benzenes.

to conclude that [5]metacyclophanes are essentially aromatic, according to the criteria of electron delocalization and "ring-current", so that the high reactivity is mainly a consequence of strain. However, proton chemical shifts are in general subject to various contributions and therefore we decided to investigate the anisotropy of the magnetic susceptibility, which is expected to be the main cause of the downfield shift in aromatics.

Experimental determination of $\Delta\chi$ of cyclophanes is extremely difficult by microwave spectroscopy, in view of the complexity of the spectra. Recently, a new and convenient method has been described to determine $\Delta\chi$ from high field ^{2}H NMR spectra.[19-22] In this paper, the technique will be illustrated for three meta-disubstituted benzenes (**2d**, **3e**, **4e**) and the [5]metacyclophane (**1d**), and the results are compared with calculations based on localized magnetic susceptibilities to demonstrate the aromatic character of the species under study.



Theory

Molecules possessing an anisotropic magnetic susceptibility tend to be aligned by a magnetic field. In the mobile phases this orienting mechanism is counteracted by the Brownian motion, and only at very high fields does a small measurable partial alignment result. As a consequence of this alignment, anisotropic nuclear interactions like quadrupolar and dipolar couplings may become apparent in the NMR spectrum; e.g., the ^{2}H nucleus in benzene-d_1 (at 5 mol % solution in diethyl ether) exhibits a quadrupolar splitting of 0.48 Hz[22] at a magnetic induction of 1.41×10^5 G. The splitting $\Delta\nu_i$ of a certain deuteron i is related to the magnetic susceptibility tensor elements by

$$\Delta\nu_i(\mathrm{Hz}) = (B^2/10kT)\,(\mathrm{eQ}/h)\{\Delta\chi V_{zz} + 1/2\,\delta\chi\,(V_{xx} - V_{yy})\} \quad (3)$$

B is the magnetic induction in Gauss, $\Delta\chi = \chi_{zz} - 1/2\,(\chi_{xx} + \chi_{yy})$ is the anisotropy, and $\delta\chi = \chi_{xx} - \chi_{yy}$ is the asymmetry in the magnetic susceptibility; the axes (x, y, z) define the molecular frame in which the susceptibility tensor is diagonal. $\Delta\chi$ and $\delta\chi$ are effective quantities if angular correlation with other molecules plays a role. For the compounds under investigation, dissolved at low concentration in a noncomplexing solvent, it is assumed that $\Delta\chi$ and $\delta\chi$ are the molecular values. eQ is the nuclear quadrupole moment and $V_{\alpha\alpha}$ ($\alpha \in x, y, z$) the electric field gradient at the site of the nucleus; it is related to the major local field gradient eq ($=V_{z''z''}$) at a certain deuteron (Figure 1) by

$$V_{\alpha\alpha} = \mathrm{eq}\{[3/2\,\cos^2\delta_{z''\alpha} - 1/2] + 1/2\eta[\cos^2\delta_{x''\alpha} - \cos^2\delta_{y''\alpha}]\} \quad (4)$$

The asymmetry parameter η denotes the deviation from axial symmetry of the field gradient around the z'' axis (C-D bond). The product (e^2qQ/h) is called the quadrupole coupling constant. For deuterium the latter two quantities are well known:[23] in aromatic compounds in the liquid phase $(e^2qQ/h) = 186 \pm 6$ kHz and $\eta = 0.05 \pm 0.02$. In aliphatic species $(e^2qQ/h) = 167 \pm 10$ kHz assuming $\eta = 0$.

It follows directly from the equations that $\Delta\chi$ and $\delta\chi$ can be calculated, if the position of the nuclei in the susceptibility frame and splittings of two deuterons with different geometrical positions are known. Depending on symmetry a single splitting suffices. In most compounds[20] $\delta\chi$ can be neglected, which also reduces the number of required splittings to one. For [5]metacyclophane (**1d**) the definition of the principal susceptibility axis is not straightforward. However, on the basis of the experimental splittings and considerations using local susceptibilities, their orientation can be determined.

To obtain the enhancement of χ_{zz}, the χ_{ii}-values of a nonaromatic reference compound have to be evaluated. For nonaromatic species the use of local susceptibilities to calculate the molecular susceptibility components has been proven to give reasonable results within 10% of the experimental values.[8-10,24] In this procedure[24] it is assumed that each electron circulation is confined to localized orbitals and that the electron distribution around a certain type of bond is the same in different molecules. In Table I bond susceptibilities (χ_{aa}, χ_{bb}, χ_{cc}) are given as determined from a large series of reference compounds. To obtain the molecular susceptibility values χ_{ij} ($i,j \in x_{ij}$ ($i, j \in x, y, z$)) of the localized model, the bond susceptibilities have to be transformed and a summation over the contributions of all bonds n has to be made

$$\chi_{ij}(\mathrm{local}) = \sum_n \cos\theta_{ia}{}^n \cos\theta_{ja}{}^n\chi_{aa}{}^n + \cos\theta_{ib}{}^n \cos\theta_{jb}{}^n\chi_{bb}{}^n + \cos\theta_{ic}{}^n \cos\theta_{jc}{}^n\chi_{cc}{}^n \quad (5)$$

The susceptibility frame can then be found from a diagonalization procedure. So, comparison of $\Delta\chi$(experimental) with $\Delta\chi$(local), under the assumption that χ_{xx} and χ_{yy} do not differ much in the aromatic and the localized situation, provides a criterion for the aromaticity of the compound under study.[8-10] In this paper the procedure will be demonstrated for a few model compounds that are certainly aromatic and for [5]metacyclophane.

It should be mentioned that the validity of the use of local susceptibilities has not been proven for strained compounds and the values in Table I might not be entirely correct if the bond angles deviate from their normal values. This might induce small errors in the results for the nonaromatic reference compound, but it is not expected to influence the main trend in the results.

Table I. Bond Susceptibilities[10] (in 10^{-28} cm^3)

bond	a	b	c[a]
C-H	-0.051	-0.051	-0.093
C-C	-0.003	-0.003	-0.131
C=C	-0.229	+0.066[b]	-0.013

[a] c coincides with the bond axis; a and b are perpendicular to each other and to c. [b] b lies in the plane of the σ-skeleton.

NMR Measurements

Samples were prepared as 1-2% solutions in $CDCl_3$ in 5-mm NMR tubes (Wilmad, 507 pp) which were degassed and sealed under vacuum. The experiments were conducted at the 14.1-T (^{1}H frequency 600 MHz) NMR facility for Biochemical Studies, Pittsburgh. Locking on a reference deuterium signal and observation of the deuterium resonance (under proton decoupling)

(18) Van Straten, J. W.; De Wolf, W. H.; Bickelhaupt, F. *Tetrahedron Lett.* **1977**, 4667.
(19) Lohman, J. A. B.; MacLean, C. *Chem. Phys.* **1978**, *35*, 269; **1979**, *43*, 144. Lohman, J. A. B.; MacLean, C. *Chem. Phys. Lett.* **1978**, *58*, 483; **1979**, *65*, 617.
(20) For a review: van Zijl, P. C. M.; Ruessink, B. H.; Bulthuis, J.; MacLean, C. *Acc. Chem. Res.* **1984**, *17*, 172.
(21) Bothner-By, A. A.; Gayathri, C.; van Zijl, P. C. M.; MacLean, C. *J. Magn. Reson.* **1984**, *56*, 456.
(22) van Zijl, P. C. M.; MacLean, C.; Bothner-By, A. A. *J. Chem. Phys.* **1985**, *83*, 4410.
(23) Loewenstein, A. *Advances in Nuclear Quadrupole Resonance*; Heyden: London, 1983; Vol. 5, p 53 and references therein.
(24) Pascal, P. *Chimie Generale*; Masson et Cie: Paris, 1949.

Table II. Susceptibilities[a] and Quadrupolar Splittings[b] from Experiment and Calculated for a Nonaromatic Reference Compound

	experiment			reference			
	$\Delta\nu$		$10^{28}\Delta\chi$[c]	$10^{28}\Delta\chi$	$10^{28}\delta\chi$	$\Delta\nu$	
benzene[d]	(D1)	0.48[e]	−1.01	−0.45	0		0.21
m-dimethylbenzene (**2d**)	(D2, D5)	0.51[e]	−1.07	−0.40	−0.04	(D2, D5)	0.26
m-diethylbenzene (**3e**)	(D2)	0.54[f]	−1.14	−0.51	−0.03	(D2)	0.26
m-diisopropylbenzene (**4e**)	(D2)	0.64[f]	−1.35	−0.56[g]	0.00[g]	(D2)	0.27
[5]metacyclophane (**1d**)	(D8, D11)	0.63[f]	−1.49[h]	−0.42[h]	−0.05[h]	(D8)	0.17[h]
						(D11)	0.21[h]
			−1.58[i]	−0.43[i]	−0.03[i]	(D8)	0.11[i]
						(D11)	0.15[i]

[a] In cm³ (emu). [b] In Hz. [c] For $\delta\chi = 0$. [d] Reference 22. [e] Error: 0.02 Hz. [f] Error: 0.03 Hz. [g] MNDO structure. [h] X-ray of 8,11-dichloro analogue (ref 13): $\delta_{z''z} = 98.6°$. [i] MNDO structure: $\delta_{z''z} = 101.6°$.

at 92.1 MHz was accomplished with use of the rapid-scan correlation console designed by Dadok.[25] The probe temperature was 296 K.

Results and Discussion

In Table II experimental quadrupolar splittings and susceptibility anisotropies which were calculated from local bond susceptibilities, are compared with those of a nonaromatic reference compound. A few remarks concerning these values have to be made. In the planar meta-disubstituted benzenes (**2d**, **3e**, **4e**) the position of the principal susceptibility frame can be deduced from symmetry (Figure 1). As mentioned in the Theory section, this is not the case for [5]metacyclophane. In this compound, however, experimental splittings of two deuterons in the symmetry plane are available. These splittings are equal and for a nonplanar geometry this can be so only if the angles between the C–D bonds of the two deuterons and one of the susceptibility axes in the symmetry plane is the same (in a planar molecule for any position of the susceptibility axis in the symmetry plane $\cos^2 \delta_{z''z}$ (D8) = $\cos^2 \delta_{z''z}$ (D11)). This fortunate situation enables us to calculate $\Delta\chi$ from the known structure and splitting, assuming that $\delta\chi = 0$. The latter assumption is warranted by an abundance of experimental data[8,20] and by theoretical calculations,[8] which show that $\delta\chi$ will contribute to the splitting 5–10% at most. The small deviations induced by this contribution cannot account for the large differences found in Table II. For **1a**, two structures have been used in the calculations for the nonaromatic reference compound: an X-ray structure[13] of the 8,11-dichloro analogue **1b** ($\delta_{z''z} = 98.6°$) and a MNDO structure ($\delta_{z''z} = 101.6°$). It could be argued that in the 8,11-dideuterio compound (**1d**) the steric hindrance would be less and the angle smaller. However, $\delta_{z''z} = 90°$ leads to $\Delta\chi = 1.39 \times 10^{-28}$ emu, which is still large compared to the value of the nonaromatic reference.

A second point to be discussed is the quadrupole coupling constant used to evaluate $\Delta\chi$(experimental) and the splittings of the reference compound. For the planar disubstituted compounds the aromatic values (e^2qQ/h) = 186 kHz and $\eta = 0.05$ have been applied. If the quadrupolar coupling constant of a C–D bond in a nonaromatic compound would have been used, the difference between the experimental and reference data would even have been more pronounced. For the [5]metacyclophane (**1d**) (e^2qQ/h) and η are not known explicitly, but since the quadrupolar coupling in a C–D bond in an aromatic and an aliphatic environment hardly differs (186 vs. 167 kHz) this will not severely disturb the results. Therefore in the calculations 186 kHz and $\eta = 0$ have been used for simplicity. Again use of 167 kHz and/or $\eta = 0.05$ only increases the deviation between experiment and the reference. On the basis of the above arguments and the results in Table II, **1d** is beyond doubt aromatic.

It would be interesting if $\Delta\chi$ and $\delta\chi$ of an aromatic reference molecule could also be evaluated. Of course localized susceptibilities cannot be assumed, but an attempt can be made with use of an average susceptibility contribution per bond determined from a few reference compounds with known $\Delta\chi$, $\delta\chi$, and χ. From anthracene and benzene one has $\chi_{aa} = -0.261 \times 10^{-28}$ emu, $\chi_{bb} = -0.037 \times 10^{-28}$ emu, and $\chi_{cc} = -0.107 \times 10^{-28}$ emu, leading to the molecular values in Table III for the compounds under study. The table shows that the approach is reasonable in the case of dimethyl- and diethylbenzene and that $\delta\chi$ does not contribute more than about 5%, warranting our assumption just made. In diisopropylbenzene (**4e**) and [5]metacyclophane (**1d**) $\Delta\chi$ and $\Delta\nu$ are still too low. This can perhaps be ascribed to hyperconjugation effects or, in case of **1d**, to small deviations in the local susceptibility values as a consequence of bond strain.

Table III. Calculated $\Delta\chi$ (in emu) and $\Delta\nu$ (in Hz) for an Aromatic Reference Compound Assuming Localized Contributions from Each Aromatic Bond[a]

compound	$10^{28}\Delta\chi$	$10^{28}\delta\chi$	$\Delta\nu$	
benzene	−1.01	0		0.48
m-dimethylbenzene (**2d**)	−0.96	−0.04	(D2)	0.49
m-diethylbenzene (**3e**)	−1.07	−0.03	(D2, D5)	0.52
m-diisopropylbenzene (**4e**)	−1.12	0.00	(D2)	0.53
[5]metacyclophane (**1d**)	−0.89[b]	−0.01[b]	(D8)	0.35[b]
			(D11)	0.40[b]
	−0.89[c]	−0.04[c]	(D8)	0.28[c]
			(D11)	0.36[c]

[a] Calculated from anthracene and benzene. [b] X-ray structure of **1b**. [c] MNDO structure of **1a**.

It may be argued that the anisotropy in the magnetic susceptibility in **1d** could depend strongly on the degree of bending of the benzene ring, which might induce erroneous conclusions if the geometries used would differ a few degrees from reality. For this reason we have calculated $\Delta\chi$ as a function of the bow-bending angle α and found that $\Delta\chi$ decreases only slightly with increasing α. However, the same holds for the localized model and the difference turns out to be constant with respect to variations of a few degrees in α. We therefore conclude that the reliability of the calculations will not be influenced by possible deviations in the bending angles.

Conclusions

High field high resolution deuterium NMR has been employed to obtain the anisotropy in the magnetic susceptibility of some meta-disubstituted benzenes and [5]metacyclophane (**1a**). With use of local susceptibilities, $\Delta\chi$ and the quadrupolar splittings of olefinic reference compounds have been evaluated. Despite a few assumptions, the measurements prove beyond doubt that [5]-metacyclophane is fully aromatic.

Experimental Section

Preparation of the Compounds. [8,11-$^2H_2$][5]Metacyclophane (1d). A solution of 8,11-dibromo[5]metacyclophane (**1c**, 100 mg, 0.33 mmol) in dry tetrahydrofuran (3 mL) was cooled to −70 °C and treated under stirring with 2 equiv of *tert*-butyllithium in *n*-hexane under an Argon atmosphere. After 5 h, EtOD (100 μL) was added and the temperature was slowly raised to room temperature. Diethyl ether (10 mL) was added and the organic layer was washed with water (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by preparative GLC (5% Carbowax, Chromosorb W-60M, 1.5 m) to yield **1d** as a colorless liquid (34 mg, 0.23 mmol, 70%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.81 (2 H, br s), 2.85 (ddd, 2 H, $^2J_{HH}$ = 12.5 Hz, $^3J_{HH}$ = 12.3 Hz, and $^3J_{HH}$ = 3.0 Hz), 2.54 (ddd, 2 H, $^2J_{HH}$ = 12.5 Hz, $^3J_{HH}$ = 3.3 Hz, and $^3J_{HH}$ = 3.3 Hz), 1.92 (ddddd, 2 H, $^2J_{HH}$

(25) Dadok, J.; Sprecher, R. F. *J. Magn. Reson.* **1974**, *13*, 243.

= 14.4 Hz, $^3J_{HH}$ = 12.5 Hz, $^3J_{HH}$ = 7.7 Hz, $^3J_{HH}$ = 3.3 Hz, and $^3J_{HH}$ = 3.0 Hz), 1.67 (dtt, 1 H, $^2J_{HH}$ = 16.2 Hz, $^3J_{HH}$ = 7.7 Hz, and $^3J_{HH}$ = 1.1 Hz), 1.33 (dtt, 1 H, $^2J_{HH}$ = 16.2 Hz, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ < 0.5 Hz), 0.25 (ddddd, 2 H, $^2J_{HH}$ = 14.4 Hz, $^3J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 3.3 Hz, and $^3J_{HH}$ = 1.1 Hz). ^{1}H NMR data are in agreement with published data.[15] ^{2}H NMR (38.39 MHz, diethyl ether/diethyl ether-d_{10} 1:1) δ 7.90 (s), 7.21 (t, $^3J_{HD}$ = 0.9 Hz); mass spectrum m/z (%, fragment) 148 (38, $M^{+\cdot}$), 133, (43, $[M - CH_3]^+$), and 106 (100). On the basis of the ^{1}H NMR spectrum of **1d** the deuterium incorporation at C-8 was 97% and at C-11 it was 81%.

1,3-Diethyl[2-^{2}H]benzene (3e) or 1,3-Diisopropyl[2-^{2}H]benzene (4e). To a solution of 1,3-diethyl- or 1,3-diisopropyl-2-bromobenzene (47 mmol) in dry diethyl ether (7 mL), *n*-butyllithium in *n*-hexane (10 mmol) was added. After being heated at reflux temperature for 5 h, the reaction mixture was cooled to room temperature and D_2O (1 mL) was added. The organic layer was separated, washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated at reduced pressure. The crude product was purified by preparative GLC (15% SE-30, Chromosorb W-60M, 1.5 m, 100 °C) to yield **3e** and **4e**, respectively, as a colorless liquid. **3e** (0.61 g, 4.5 mmol 95%): ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.31-6.93 (AB_2 system δ_A 7.22, δ_B 7.02, 3 H, J_{AB} = 8.0 Hz), 2.65 (q, 4 H, $^3J_{HH}$ = 7.6 Hz), and 1.25 (t, 6 H, $^3J_{HH}$ = 7.6 Hz); ^{2}H NMR (38.39 MHz, diethyl ether/diethyl ether-d_{10} 1:1) δ 7.08 (s); mass spectrum m/z (%, fragment) 135 (43, $M^{+\cdot}$), 120 (85, $[M - CH_3]^+$) and 106 (100, $[M - C_2H_5]^+$). On the basis of the ^{1}H NMR spectrum the deuterium incorporation at C-2 was 80%. **4e** (0.69 g, 4.23 mmol, 90%): ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.42-6.96 (AB_2 system δ_A 7.29, δ_B 7.11, 3 H, J_{AB} = 8.0 HZ), 2.86 (2 H. M), 1.22 (D, 12 H, $^3J_{HH}$ = 6.9 HZ); ^{2}H NMR (38.39 MHz, diethyl ether/diethyl ether-d_{10} 1:1) δ 7.14 (s); mass spectrum m/z (%, fragment) 163 (38, $M^{+\cdot}$) and 148 (100, $[M - CH_3]^+$). On the basis of the ^{1}H NMR spectrum the deuterium incorporation at C-2 was 80%.

1,3-Dimethyl[2,5-$^2H_2$]benzene (2d). Compound **2d** was prepared from 2,5-dibromo-1,3-dimethylbenzene (**2c**) by a procedure similar to that described for **3e** and **4e**. Direct dilithiation was impossible under our reaction conditions, probably as a consequence of the low solubility of the monolithiated compound. Therefore, the monolithiated compound was quenched with D_2O and after workup subjected to another reaction sequence as described above. The intermediate product was identified to be 2-bromo-1,3-dimethyl[5-^{2}H]benzene (**2f**). Compound **2f** is a colorless liquid (0.63 g, 3.4 mmol, 90%): ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.07 (2 H, br s), 2.42 (6 H, s); ^{2}H NMR (38.39 MHz, diethyl ether/diethyl ether-d_{10} 1:1) δ 7.15 (t, $^3J_{HD}$ = 1.0 Hz); mass spectrum m/z (%, fragment) 185 (52, $M^{+\cdot}$) and 106 (100, $[M - Br]^+$). On the basis of the ^{1}H NMR spectrum the deuterium incorporation at C-5 was 95%. Compound **2d** is a colorless liquid (0.25 g, 2.3 mmol, 68%): ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.99 (2 H, s), 2.33 (6 H, s); ^{2}H NMR (diethyl ether/diethyl ether-d_{10} 1:1) δ 7.15 (t, $^3J_{HD}$ = 1.2 Hz), 7.03 (s); mass spectrum m/z (%, fragment) 108 (70, $M^{+\cdot}$) and 93 (100, $[M - CH_3]^+$). On the basis on the ^{1}H NMR spectrum the deuterium incorporation at C-2 was 70%.

Acknowledgment. The authors thank P. A. Kraakman, Dr. F. J. J. de Kanter, and C. Skoglund for experimental help and Professors Bothner-By and Dadok are acknowledged for discussions and for access to the 14.1-T NMR Facility for Biomedical studies in Pittsburgh. The investigations were supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for the Advancement of Pure Research (ZWO). P.C.M.v.Z. and C.M. are grateful for a NATO travel grant (RG 486.82) which strongly facilitated this research.

Registry No. 1c, 96426-52-7; **1d**, 100243-46-7; **2c**, 100189-84-2; **2d**, 100189-86-4; **2f**, 100189-85-3; **3e**, 100189-82-0; **4e**, 100189-83-1; 1,3-diethyl-2-bromobenzene, 65232-57-7; 1,3-diisopropyl-2-bromobenzene, 57190-17-7.

Efficient Detection and Evaluation of Cyclodextrin Multiple Complex Formation

Daniel W. Armstrong,* Faruk Nome, Larry A. Spino, and Teresa D. Golden

Contribution from the Department of Chemistry, Texas Tech University, Lubbock, Texas 79409.
Received July 3, 1985

Abstract: Equations are derived which allow one to determine α-cyclodextrin-substrate complex stoichiometries as well as primary and secondary binding constants by using liquid chromatographic retention values. Retention is dependent on the concentration of cyclodextrin in the mobile phase as well as the stoichiometry of the cyclodextrin-substrate complex. It was found that two cyclodextrin molecules bind to prostaglandin B_1, prostagladin B_2, 4,4'-biphenol, and *p*-nitroaniline. Conversely, *o*-nitroaniline and *m*-nitroaniline form complexes of 1:1 stoichiometry. The fact that closely related compounds such as the nitroanilines can exhibit different binding behaviors may result in the reevaluation of some cyclodextrin-based studies.

The ability of cyclodextrins (CDs) and synthetically modified cyclodextrins to form inclusion complexes with a variety of molecules is well-known.[1-6] Cyclodextrins have been used as enzyme models,[1,2,6-8] catalysts,[9,10] emulsifiers,[11] novel reaction media,[12] stationary phases for chiral and isomeric separations,[13-16] and so on. Because of their unique properties and inherent usefulness, several basic studies have been done to evaluate cyclodextrin complexation. Most of these studies assume a 1:1 stoichiometry between the cyclodextrin host and the guest molecule of interest. However, a few research groups have reported that in some cases, two or more cyclodextrins can bind to a single solute.[17-24] Indeed this phenomenon may be a good deal more

(1) Griffiths, D. W.; Bender, M. L. "Advances in Catalysis"; Eley, D. D., Pines, H., Weisz, P. B., Eds.; Academic: New York, 1973; Vol. 23, p 209.
(2) Bender, M. L.; Komiyama, M. "Cyclodextrin Chemistry"; Springer-Verlag: Berlin, 1978.
(3) Hinze, W. L. *Sep. Purif. Methods* **1981**, *10*, 159.
(4) Szejtli, J. "Cyclodextrins and Their Inclusion Complexes"; Akademai Kiado: Budapest, 1982.
(5) Tabushi, I. *Acc. Chem. Res.* **1982**, *15*, 66.
(6) Breslow, R. *Science* **1982**, *218*, 532.
(7) Van Etten, R. L.; Sebastian, J. F.; Clowes, G. A.; Bender, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 3242-3253, 3253-3262.
(8) Siegel, B.; Breslow, R. *J. Am. Chem. Soc.* **1975**, *97*, 6869.
(9) Trainor, G. L.; Breslow, R. *J. Am. Chem. Soc.* **1981**, *103*, 154.
(10) Breslow, R.; Trainor, G.; Veno, A. *J. Am. Chem. Soc.* **1983**, *105*, 2739.
(11) Menger, F. M.; Dulany, M. A. *Tetrahedron Lett.* **1985**, *26*, 267.
(12) le Noble, W. J.; Srivastava, S.; Breslow, R.; Trainor, G. *J. Am. Chem. Soc.* **1983**, *105*, 2745.
(13) Armstrong, D. W.; DeMond, W. *J. Chromatogr. Sci.* **1984**, *22*, 411.
(14) Armstrong, D. W.; DeMond, W.; Alak, A.; Hinze, W. L.; Ried, T. E.; Bui, K. H. *Anal. Chem.* **1985**, *57*, 234.
(15) Hinze, W. L.; Riehl, T. E.; Armstrong, D. W.; DeMond, W.; Alak, A.; Ward, T. *Anal. Chem.* **1985**, *57*, 237.
(16) Armstrong, D. W.; DeMond, W.; Czech, B. P. *Anal. Chem.* **1985**, *57*, 481.
(17) Harata, K. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1493.

0002-7863/86/1508-1418$01.50/0