3a. The presence of a larger fluorine atom in **8b** and **9b** should increase this difference. Similarly, relief of the electrostatic repulsion between the pseudoaxial enolate anion at C-4 and the axial fluorine atom in **8b** should be more important than relief of the corresponding interaction in **9b**. Both steric and electrostatic effects therefore favor the formation of the observed β-epoxide **2a**.

Experimental Section

Optical rotations were determined in chloroform at ambient temperature on a Perkin-Elmer 141 polarimeter. NMR spectra were determined in deuteriochloroform on Varian A-60 or XL-100 spectrometers. Preparative thin layer chromatography was performed with Merck silica gel plates (PF-254, 20 × 20 × 0.2 cm).

21-Chloro-4β,5-epoxy-11β-hydroxy-2′,2′-dimethyl-5β-pregnano[16α,17-d][1,3]dioxolane-3,20-dione (2a). A solution of 3 g (0.00662 mol) of **1a** ([α]D +153°, c 0.56) in 300 ml of methanol was stirred with 7.2 ml (0.07 mol) of 30% hydrogen peroxide and 4.8 ml (0.0192 mol) of 4 N sodium hydroxide solution. After 4 h no **1a** could be detected by TLC and the solution was diluted with water and extracted with chloroform to give 2.0 g of a mixture of epoxides **2a** and **3a** in the ratio of ca. 2:1. Preparative TLC using chloroform–ethyl acetate (3:1) as the developing solvent gave a pure sample of the major isomer **2a** (higher R_f material), mp 265–267 °C from methanol, [α]D +154° (c 0.45). A similar sample had mp 262–264 °C and [α]D +145.5° (c 0.26); NMR 1.34 ppm (s, C-19 CH₃).

Anal. Calcd for C₂₄H₃₃ClO₆: C, 63.64; H, 7.34; Cl, 7.83. Found: C, 63.90; H, 7.09; Cl, 7.89.

21-Chloro-4β,5-epoxy-9-fluoro-11β-hydroxy-2′,2′-dimethyl-5β-pregnano[16α,17-d][1,3]dioxolane-3,20-dione (2b). A solution of 30 g of **1b** ([α]D +156°, c 0.73) in 3 l. of methanol was stirred with 72 ml of 30% hydrogen peroxide and 48 ml of 4 N sodium hydroxide solution for 4 days and poured into 36 l. of water, and the resulting solid filtered. This was combined with three identical batches and chromatographed on silica gel to give a total of 60.11 g of **2b** and 30.4 g of recovered **1b**. A similar sample of **2b** had mp 254–256 °C from ethanol–water; [α]D +146.5° (c 0.24); NMR 1.40 ppm (s, C-19 CH₃).

Anal. Calcd for C₂₄H₃₂ClFO₆: C, 61.21; H, 6.85; Cl, 7.53; F, 4.03. Found: C, 61.48; H, 6.75; Cl, 7.30; F, 3.91.

Similar experiments worked up by extraction gave no TLC or NMR evidence for the presence of a second epoxide or any other nonacidic compound.

3β-(Acetyloxy)-21-chloro-9-fluoro-11β-hydroxy-2′,2′-dimethylpregn-4-eno[16α,17-d][1,3]dioxolan-20-one (4b). A solution of 1.83 g (0.004 mol) of **1b** in 200 ml of methanol was stirred for 1 h at room temperature with 2.2 equiv of sodium borohydride. After the usual workup the product was acetylated with 10 ml of pyridine and 5 ml of acetic anhydride overnight. The reaction mixture was poured into ice–water, stirred for 1 h, and filtered to give 2.1 g of solid. Purification by preparative TLC with chloroform as the developing solvent gave 738 mg (37%) of **4b**, mp 218–220 °C dec from methanol, [α]D +80.0° (c 1.6).

Anal. Calcd for C₂₆H₃₆ClFO₆: C, 62.58; H, 7.27; Cl, 7.11. Found: C, 62.64; H, 7.01; Cl, 6.91.

21-Chloro-9-fluoro-3β,11β-dihydroxy-2′,2′-dimethylpregn-4-eno[16α,17-d][1,3]dioxolan-20-one (5b). A solution of 500 mg of **4b** in 80 ml of methanol and 20 ml of tetrahydrofuran was stirred for 1 h under nitrogen with 10 ml of 10% potassium carbonate solution, and then diluted with water and extracted with chloroform to give 455 mg of crude product. Preparative TLC twice with chloroform as the developing solvent followed by crystallization from benzene–hexane gave **5b**: mp 182–184 °C dec; [α]D +101° (c 0.746); NMR 5.41 ppm (broad s, width at half-height = 5 Hz, C-4 H).

Anal. Calcd for C₂₄H₃₄ClFO₅: C, 63.10; H, 7.50; Cl, 7.76; F, 4.16. Found: C, 63.40; H, 7.49; Cl, 7.62; F, 4.08.

21-Chloro-4β,5-epoxy-9-fluoro-2′,2′-dimethyl-5β-pregnano[16α,17-d][1,3]dioxolane-3,11,20-trione (7). A solution of 200 mg (0.0044 mol) of **4b** in 10 ml of dichloromethane was stirred for 1 h with 100 mg (0.005 mol) of 85% m-chloroperbenzoic acid. After the usual workup a solution of the product in 25 ml of acetone was stirred with excess Jones reagent for 1.5 h. The usual workup gave a crude product that crystallized from methanol to give 139 mg (70%) of **7**, mp 202–204 °C.

Anal. Calcd for C₂₄H₃₀ClFO₆: C, 61.47; H, 6.45; Cl, 7.56; F, 4.05. Found: C, 61.53; H, 6.26; Cl, 7.51; F, 4.09.

Oxidation of 240 mg of **2b** as above gave 145 mg (60%) of **7**, mp and mmp with material from above 202–204 °C.

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The Association Constants of Organic Complexes of Iodine. A Competitive Equilibrium Study[1]

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Since Benesi and Hildebrand first studied the benzene–iodine complex,[2] many other organic complexes of iodine have been investigated in carbon tetrachloride. Andrews and Keefer have studied complexes of organic halides,[3] polymethylbenzenes,[4] and alkylbenzenes,[5] Tamres, Virzi, and Searles studied iodine complexes of alkylbenzenes.[6] Fluorobenzenes and fluorotoluenes were studied by Tamres,[7] and the iodine complex of benzonitrile was studied by Klaboe.[8] The complexes of polynuclear aromatics have been investigated by Bhattachara and Basu,[9] Peters and Person,[10] Blake, Winston, and Patterson,[11] and de Maine and Peone.[12] The association constants for all these complexes were found using ultraviolet spectroscopy and usually a modification of the Benesi–Hildebrand equation, such as the Scott equation.[13]

In this investigation the association constants were measured by a different technique. In the iodine–alkene addition reaction the position of the equilibrium is dependent on the nature of the solvent system.[14] A very convenient reaction to study is to determine the effects of a donor in the position of equilibrium in the cyclohexene–iodine addition reaction. A solution of 0.064 M cyclohexene and 0.032 M iodine in carbon tetrachloride reacts to 61.6% completion at 25.0 °C. A donor compound was added to the carbon tetrachloride solvent, generally to make a 1.0 M solution of the donor. The difference in the cyclohexene–iodine reaction in pure carbon tetrachloride and in the carbon tetrachloride–donor solvent system was used to determine the association constant of the complex formed. Assuming that only a 1:1 complex is formed, the association constant for the donor–iodine complex can be determined using eq 1.[15]

$$K_{sd} = \frac{X_1(S - d + X_1/K_a(b - X_1))}{K_a(b - X_1)d - X_1} \quad (1)$$

K_a = equilibrium constant for I_2 addition to cyclohexene no donor in solvent)

X_1 = concentration of I_2 reacted = concentration of alkene reacted = concentration of diiodoalkane formed

S = initial concentration of donor

a = initial concentration of iodine

b = initial concentration of cyclohexene

Table I. Association Constants for the Iodine Complexes of Organic Compounds in Carbon Tetrachloride at 25.0 °C

		l, mol^{-1}	
Registry no.	Compd	This work	Lit.
1772-22-1	Benzene	0.175 ± 0.006	0.15,[a,h,d] 0.17[c]
	Polyalkylbenzenes		
2789-26-6	*o*-Xylene	0.29 ± 0.001	0.27[a]
2605-03-0	*m*-Xylene	0.33 ± 0.005	0.31[a]
2768-91-4	*p*-Xylene	0.30 ± 0.004	0.31,[a] 0.32[b]
2605-05-2	1,2,5-Trimethylbenzene	0.55 ± 0.02	0.82,[a] 0.63[b]
2768-93-6	1,2,3,4-Tetramethylbenzene	0.78	
60978-40-7	1,2,4,5-Tetramethylbenzene	0.64	
2603-90-9	Pentamethylbenzene	0.82 ± 0.03	0.88,[a] 0.94[c]
24317-90-6	Hexamethylbenzene	1.29 ± 0.03	1.35,[a] 1.52,[b] 1.48[c]
	Monoalkylbenzenes		
2605-02-9	Methylbenzene	0.25 ± 0.003	0.16,[a] 0.15[f]
39573-42-7	Ethylbenzene	0.23 ± 0.003	
60944-81-2	Propylbenzene	0.23	
60944-83-4	Butylbenzene	0.19	
60978-41-8	Pentylbenzene	0.20	
60978-42-9	Hexylbenzene	0.17	
60978-43-0	Heptylbenzene	0.17 ± 0.01	
60944-82-3	Isopropylbenzene	0.25	
60944-85-6	*tert*-Butylbenzene	0.24	
60978-44-1	Cyclohexylbenzene	0.24	
	Substituted Benzenes		
60978-45-2	Nitrobenzene	0.03	
2649-27-6	Benzonitrile	0.28	0.8[g]
1650-58-4	Fluorobenzene	0.06	
3879-17-2	Chlorobenzene	0.07	
3797-16-8	Bromobenzene	0.11 ± 0.01	0.13[a]
4015-94-5	Iodobenzene	0.34	
60978-46-3	*o*-Dichlorobenzene	0.00	
60978-47-4	Trifluoromethylbenzene	0.00	
	Aliphatic Compounds		
31036-98-3	Hexane	0.03	
18681-91-9	Methylcyclohexane	0.04	
60978-48-5	1-Chlorobutane	0.11	
60978-49-6	Chlorocyclohexane	0.15	
58993-03-6	1-Bromopropane	0.27 ± 0.013	
60978-50-9	2-Bromopropane	0.33 ± 0.05	
58992-99-7	Iodomethane	0.67	
58993-00-3	Iodoethane	0.82	0.29[f]
58993-01-4	1-Iodopropane	0.79	
58993-02-5	2-Iodopropane	0.77	
60978-51-0	Tetrachloroethane	0.00	
	Polynuclear Aromatics		
60978-52-1	Biphenyl	0.26	0.37[h]
60978-53-2	Acenaphthene	0.42	
26977-60-6	Phenanthrene	0.24 ± 0.03	0.15,[a] 0.45,[i] 1.06[h]
13531-66-3	Naphthalene	0.24 ± 0.01	0.25,[a] 03,57,[j] 0.62[k]
60978-54-3	1-Nitronaphthalene	0.06	

[a] Reference 4. [b] Reference 5. [c] Reference 2. [d] reference 7. [e] Reference 6. [f] Reference 3. [g] Reference 8. [h] Reference 9. [i] Reference 10. [j] Reference 11. [k] Reference 12.

$d = a - X_1$

K_{sd} = dissociation constant

K_s = association constant = $1/K_{sd}$

When the association constant was experimentally determined a minimum of four times for a particular complex, the uncertainty was computed using Student's method at 90% confidence limit.[16] All complexes were done at least in duplicate. Although the uncertainty may indicate more signifi-

cant figures, to ensure the reliability of this data the association constants are reported to only two decimal places with the exception of benzene. The benzene–iodine complex was run a number of times, and the value reported here agrees well with literature values for the association constant.

As the reviewers of this paper have correctly pointed out, this derivation does assume that the association constant of the iodine cyclohexene charge transfer complex is small enough to be ignored. An estimate of the association constant

for the cyclohexene iodine complex shows that the error from this assumption is small and within the confidence limits given. Moreover, kinetic work we have done on olefin systems indicates that at least part of the charge transfer complex between cyclohexene and iodine yields the diiodoalkane upon quenching in KI/H_2O.

Results and Discussion

The association constant for the benzene–iodine complex has been measured by several people, and the values found in the literature agree with the value reported in this work (Table I). The values reported here for the xylene complexes are also very close to the values reported in the literature, although there is a slight discrepancy in the order of the xylenes. This work indicates that the m-xylene has the greatest complexing ability with iodines. There is considerable disagreement in the literature on the value for the association constant of the 1,3,5-trimethylbenzene complex, but this work does agree with one of the values reported by Andrews and Keefer.[5] One would expect, since the methyl group is an electron donor, that the aromatic ring would become an increasingly better donor as more methyl groups are attached. This work agrees with such predictions as well as with the values reported in the literature for the polymethylbenzene complexes.

Toluene has the largest K_a value for any monoalkylbenzene. Longer alkyl groups probably sterically interfere with the approach of the iodine causing association constants which are less than that of toluene.

The association constants for other substituted benzenes are also determined. Nitrobenzene is a poor iodine complexer, which is expected from the electron-withdrawing properties of the nitro group. Surprisingly, although the cyano group is deactivating, benzonitrile is a relatively good complexer. Apparently the lone pair of electrons on the nitrogen are available for n-type complex formation with iodine. The halogens also deactivate the ring, but they, like nitrogen, have lone pair electrons. As the size of the halogen is increased, these lone pair electrons become more available for n-type complex formation. Two chloro groups on the ring deactivate the system so that essentially no complex can form, neither π nor n type.

Since the halogens have lone pair electrons, the aliphatic halides have the potential for n-type complex formation. Again the size of the halogen is controlling factor in the availability of the lone pair electron. One observes that the haloaliphatic compounds are better complexers than the corresponding halobenzene compounds.

Although Bhattachara and Basu indicated that biphenyl was twice as good a complexer as benzene,[9] this study indicates that it is not. In fact, it seems to be only one and a half times better than benzene. The spectrophotometric determination of the association constant for phenanthrene is difficult. Peters and Person discussed the difficulties involved in the determination of the value for phenanthrene,[10] and the wide range in values reported in the literature certainly supports their view. This method avoids these difficulties, and, as shown in Table I, it appears that phenanthrene has essentially the same complexing ability as naphthalene. The value reported in this work for naphthalene agrees with literature values. It is interesting that a deactivating group, such as the nitro group, deactivates both rings in naphthalene for π complex formation.

Although an older, less sophisticated technique was used, the results of this investigation do fit the current concepts of organic complexes. Often difficulties arise in studying the complexes spectrophotometrically. In the iodoethane complex, for example, Andrews and Keefer were forced to work on the shoulder of the ultraviolet absorption curve, where error is maximized.[3] Absorption of the starting materials in the region of interest also may cause serious problems. This method avoids such problems. It seems that in some cases titration is the preferable method. Besides reducing the number of problems involved in the determination, this method has added advantage in that several different donors may be studied at the same time under exactly the same conditions. Although the numerical values for the association constants may vary somewhat because of slight variations in conditions, the relative order of the values does not vary. Thus, this study has been able to compile the longest and most self-consistent list of association constants for the organic complexes of iodine. Further research is currently in progress at this laboratory to determine the correlation between complexing ability and reactivity of aromatic compounds.

Experimental Section

The chemicals used were purchased as 99.9% pure or were purified and physical properties checked by conventional procedures. All equilibria were measured at 25.0 ± 0.05 °C. The equilibrium constant for the reaction of iodine with cyclohexene was determined for a solution 0.0640 M in cyclohexene and 0.0320 M in iodine in the solvent carbon tetrachloride. Along with each determination of the equilibrium between cyclohexene and iodine, identical mixtures containing added donor compounds were simultaneously run in order to obtain the K_a values of the donor compounds. In a typical run 2.025 g of iodine was dissolved in carbon tetrachloride to give 100 ml. A total of 1.3145 g of freshly distilled cyclohexene was also made up to 100 ml with carbon tetrachloride. After equilibration at 25.0 °C, 10 ml each of the iodine and alkene solutions were pipetted into 25-ml volumetric flasks. To six such flasks were added the following donors: (1) no donor, blank; (2) 1.9528 g of benzene; (3) 3.075 g of 2-bromopropane; (4) 2.303 g of toluene; (5) 2.655 g of ethylbenzene; and (6) 5.310 g of p-xylene. The solutions were made up to 25 ml with solvent and allowed to react at 25.0 °C. Solutions prepared in this manner were 0.0320 M in iodine, 0.0640 M in cyclohexene, and 1.00 M in donor, except for the p-xylene which was 2.00 M. Aliquots were titrated in triplicate after 48, 72, and 96 h. For the 2.00-ml aliquots of the above samples the milliliters of 0.0500 M thiosulfate required for the blank and the donor solutions, and the K_a calculated for the donors follow: blank, 0.704; benzene, 0.776, K_a = 0.175; 2-bromopropane, 0.830, K_a = 0.320; toluene, 0.802, K_a = 0.250; ethylbenzene, 0.796, K_a = 0.232; and p-xylene, 0.922, K_a = 0.296.

The K_a for each donor was determined at least twice from separate runs. The three xylene isomers, naphthalene, and phenanthrene were simultaneously run a number of times so as to check their relative K_a values. Although the absolute K_a values might vary slightly from one determinations to another, the order of complexing ability of the xylenes was always meta > para > ortho, and the values for naphthalene and phenanthrene were always identical within experimental error. While laboratory light in many cases accelerated the rate of obtaining equilibrium, it had no apparent effect on the value of K_a.

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