

**PHOTOHYDROXYLATION, PHOTOCYANATION AND FLUORESCENCE QUENCHING OF 2-FLUOROANISOLE COMPLEXED WITH CYCLODEXTRINS: A COMPARISON WITH 4-FLUOROANISOLE-CYCLODEXTRIN COMPLEXES**

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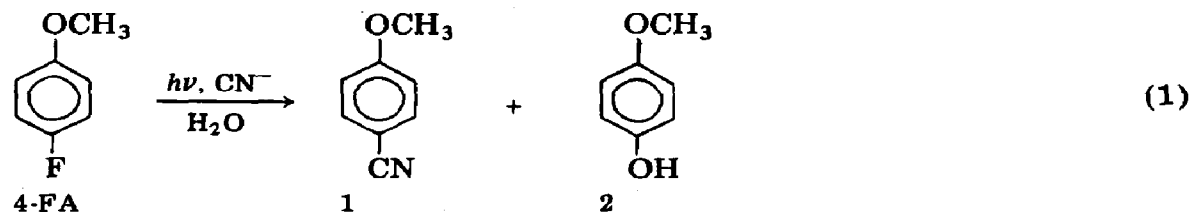
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**Summary**

The influence of cyclodextrin (CD) on the efficiency and selectivity of aromatic nucleophilic substitutions of 2-fluoroanisole (2-FA) has been investigated. Results are compared with the effect of CD on the quenching of 2-FA fluorescence by iodide as well as aromatic nucleophilic substitutions on 4-fluoroanisole. It is found that both nucleophiles, water and cyanide, are inhibited strongly by  $\alpha$ -CD from reacting with irradiated 2-FA. Surprisingly,  $\beta$ -CD retards photohydroxylation of 2-FA to a much greater extent than it does photocyanation. An additional process, photo-reduction to form anisole, appears to proceed via an independent pathway. A hypothesis which includes the possible influence of water structure near the CD openings is advanced to explain the results.

**1. Introduction**

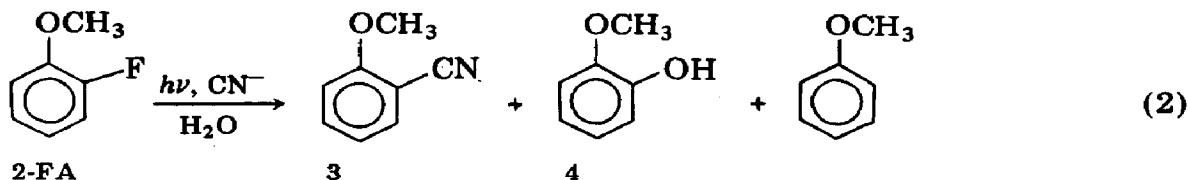
Previously, we investigated the effects of complexation by cyclodextrins (CDs) on the efficiencies of photohydroxylation and photocyanation of 4-fluoroanisole (4-FA) [1] (reaction (1)).



Strong inhibitive effects were observed with  $\alpha$ - and  $\beta$ -CD, but virtually none with  $\gamma$ -CD. In contrast, complexation by  $\alpha$ -,  $\beta$ - or  $\gamma$ -CD had no measurable effect on the rate of fluorescence quenching of 4-FA by iodide. These results are compatible with (but do not demand) a simple mechanistic picture in which both the excited singlet state of 4-FA and the immediate precursor to photosubstitution, the 4-FA cation radical (4-FA<sup>+</sup>) [2 - 4], are

complexed by  $\alpha$ - and  $\beta$ -CD with the fluorine atom projected toward the narrower end of the torus.

As a means of investigating the projection afforded the ortho position of anisole by CD, we have examined the efficiencies with which 2-fluoroanisole (2-FA) in water or aqueous CD undergoes photosubstitution by water and cyanide (reaction (2))



and fluorescence quenching by iodide. Photoreduction to form anisole has been examined with 2-FA; this is an additional process of very minor importance during irradiations of 4-FA [5], anisole being detected in trace amounts when 4-FA was irradiated in aqueous CD solutions. The results show that the protective influence of CD on 2-FA<sup>+</sup> or 2-FA excited singlet states is selective and that photosubstitution and photoreduction occur from independent pathways. Moreover, the 2-FA·CD and 4-FA·CD complexes cannot be accommodated by one simplistic mechanistic picture. Recent experiments from our laboratory [6] suggest that our results may be, in part, a consequence of dynamic changes in water structure near the substitution site which accompany 2-FA<sup>+</sup> complexation by CD. In fact, the effect of CD on 4-FA is probably much more complex than originally anticipated [1].

## 2. Experimental details

Instrumental and analytical methods are as described previously [1] unless stated otherwise.

$\alpha$ -,  $\beta$ - and  $\gamma$ -CD, and anisole (Aldrich) were used as received. 2-FA (Aldrich) was distilled and a center fraction was collected (boiling point, 155 °C (literature value, 154 - 155 °C [7])). Its purity was better than 98% as indicated by high performance liquid chromatography (hplc) analysis. 2-Cyanoanisole (3) was synthesized from 2-cyanophenol (Aldrich) by a standard preparative method [8] and was shown to be better than 98% pure by gas chromatography analysis. Dextrose (Fischer, anhydrous ACS grade), sodium iodide (Fischer, USP grade), and 2-methoxyphenol (4) (Aldrich; purity, 98%) were used as received.

### 2.1. Dissociation constant determinations

Portions of CD were weighed into several volumetric flasks. Each flask was filled to the mark with an aqueous solution of  $1.02 \times 10^{-4}$  M 2-FA. Optical density changes in the UV absorption spectra of the solutions were monitored at 265 nm and at  $20.0 \pm 0.2$  °C and were used in subsequent calculations to construct Benesi-Hildebrand plots [9, 10].

## 2.2. Fluorescence quenching measurements

Fluorescence intensity changes of  $1.36 \times 10^{-3}$  M 2-FA in aqueous CD or water (no deoxygenation) were monitored at 300 nm ( $\lambda_{\text{excit}} = 280$  nm). Spectra were recorded before and after incremental aliquots of solid sodium iodide were added and dissolved.

## 2.3. Irradiation procedures

Nitrogen-saturated solutions of 2-FA were placed in tightly-stoppered quartz cuvettes in a nitrogen atmosphere. The cuvettes were rotated in a Moses merry-go-round apparatus [11] and irradiated at ambient room temperature with a low-pressure mercury lamp. More than 99% of the radiation at 254 nm was absorbed by each sample. Conversions were 10% or below in order to minimize secondary reactions and competitive light absorption by products.

## 2.4. Relative quantum yield determinations

Samples were irradiated concurrently as described above. Product appearance and 2-FA disappearance were followed quantitatively by hplc. Concentration ratios of 2-FA, 3 or 4, or anisole relative to 4-FA were plotted against the ratios of the respective hplc responses. A measured portion of 4-FA was added to each experimental sample. Hplc analyses and correlation with the previously prepared response curves allowed the percentage

TABLE 1

Relative photohydroxylation quantum yields of  $2 \times 10^{-3}$  M 2-FA in water

CD	$\Phi'_{\text{OH}}^a$	$\Phi'_r^a$	Initial complexation of 2-FA with CD (%)
None	1.0 <sup>b</sup>		0
$\alpha$	$0.76 \pm 0.05$	$0.044 \pm 0.005$	$30 \pm 10$
$\alpha$	$0.52 \pm 0.04$	$0.057 \pm 0.008$	$46 \pm 15$
$\alpha$	$0.55 \pm 0.05$	<sup>c</sup>	$48 \pm 16$
$\alpha$	$0.34 \pm 0.03$	$0.050 \pm 0.007$	$56 \pm 19$
$\alpha$	$0.25 \pm 0.02$	$0.048 \pm 0.006$	$60 \pm 20$
$\alpha$	$0.26 \pm 0.04$	<sup>c</sup>	$64 \pm 21$
$\alpha$	$0.23 \pm 0.03$	$0.052 \pm 0.009$	$65 \pm 21$
$\alpha$	$0.14 \pm 0.02$	<sup>c</sup>	$74 \pm 25$
$\beta$	$0.81 \pm 0.03$	<sup>c</sup>	$31 \pm 5$
$\beta$	$0.76 \pm 0.04$	$0.044 \pm 0.007$	$35 \pm 6$
$\beta$	$0.69 \pm 0.05$	$0.033 \pm 0.005$	$36 \pm 6$
$\beta$	$0.68 \pm 0.04$	<sup>c</sup>	$42 \pm 8$
$\beta$	$0.67 \pm 0.10$	$0.020 \pm 0.005$	$46 \pm 8$
$\beta$	$0.58 \pm 0.04$	$0.026 \pm 0.005$	$52 \pm 9$
$\beta$	$0.61 \pm 0.05$	$0.040 \pm 0.008$	$54 \pm 10$
$\beta$	$0.55 \pm 0.02$	<sup>c</sup>	$54 \pm 10$

<sup>a</sup>Errors are one standard deviation and represent precision.

<sup>b</sup>The relative quantum yield is defined as unity in the absence of CD and cyanide.

<sup>c</sup>Not determined.

TABLE 2

Relative photohydroxylation and photocyanation quantum yields of  $2 \times 10^{-3}$  M 2-FA in aqueous 0.10 M KCN

CD	$\Phi'_{OH}$ <sup>a, b</sup>	$\Phi'_{CN}$ <sup>b</sup>	$\Phi'_r$ <sup>b</sup>	[4]/[3]	Initial complexation of 2-FA with CD (%)
None	$0.84 \pm 0.12$	$0.14 \pm 0.02$	—	6.0	0
None <sup>c</sup>	$0.76 \pm 0.05$	$0.15 \pm 0.05$	—	5.1	0
None	$0.70 \pm 0.02$	$0.11 \pm 0.01$	—	6.4	0
None	$0.76 \pm 0.03$	$0.12 \pm 0.01$	—	6.3	0
None	$0.76 \pm 0.04$	$0.12 \pm 0.01$	—	6.3	0
$\alpha$	$0.50 \pm 0.08$	$0.11 \pm 0.01$	$0.030 \pm 0.004$	4.5	$29 \pm 10$
$\alpha$	$0.36 \pm 0.04$	$0.097 \pm 0.010$	$0.029 \pm 0.005$	3.7	$43 \pm 14$
$\alpha$	$0.35 \pm 0.05$	$0.10 \pm 0.02$	d	3.5	$48 \pm 16$
$\alpha$	$0.27 \pm 0.04$	$0.089 \pm 0.009$	$0.040 \pm 0.004$	3.0	$55 \pm 19$
$\alpha$	$0.21 \pm 0.02$	$0.07 \pm 0.01$	$0.022 \pm 0.004$	3.0	$61 \pm 20$
$\alpha$	$0.14 \pm 0.02$	$0.06 \pm 0.01$	$0.029 \pm 0.005$	2.3	$64 \pm 21$
$\alpha$	$0.16 \pm 0.02$	$0.078 \pm 0.009$	d	2.0	$64 \pm 21$
$\alpha$	$0.12 \pm 0.02$	$0.061 \pm 0.016$	d	2.0	$73 \pm 25$
$\beta$	$0.50 \pm 0.07$	$0.11 \pm 0.01$	$0.027 \pm 0.004$	4.5	$33 \pm 5$
$\beta$	$0.44 \pm 0.05$	$0.12 \pm 0.01$	d	3.7	$35 \pm 6$
$\beta$	$0.49 \pm 0.05$	$0.13 \pm 0.01$	$0.015 \pm 0.002$	3.8	$39 \pm 7$
$\beta$	$0.43 \pm 0.04$	$0.13 \pm 0.01$	d	3.3	$41 \pm 7$
$\beta$	$0.41 \pm 0.03$	$0.11 \pm 0.02$	$0.027 \pm 0.003$	3.7	$45 \pm 8$
$\beta$	$0.41 \pm 0.08$	$0.12 \pm 0.01$	$0.022 \pm 0.004$	3.4	$53 \pm 9$
$\beta$	$0.38 \pm 0.05$	$0.12 \pm 0.02$	$0.045 \pm 0.010$	3.2	$54 \pm 10$
$\beta$	$0.35 \pm 0.04$	$0.12 \pm 0.02$	d	2.9	$56 \pm 10$
$\gamma^e$	d	d	d	4.5	d

<sup>a</sup>The relative quantum yield for photohydroxylation is defined as unity in the absence of CD and cyanide.

<sup>b</sup>Errors are one standard deviation and represent precision.

<sup>c</sup>[KCN] = 0.12 M.

<sup>d</sup>Not determined; see text.

<sup>e</sup>[ $\gamma$ -CD] =  $1.0 \times 10^{-2}$  M.

conversion of 2-FA and the amount of each product obtained to be calculated. In a few experiments, 2-FA, 3 and 4 were monitored relative to anisole, added in at least fiftyfold excess of that produced photochemically. Mass balances ranged from 64% to 120% with a rather large experimental error (estimated at 25% for the lower conversion runs). The average mass balance was above 80%. Specific concentrations are included in Tables 1 and 2.

### 2.5. Experiments in aqueous dextrose

Solutions of  $1.6 \times 10^{-3}$  M 2-FA in water or in aqueous potassium cyanide, half of each containing dextrose, were irradiated concurrently

as before in a merry-go-round apparatus. Analyses were performed as described above. The results are summarized in Table 3.

TABLE 3

Relative quantum yields for photohydroxylation and photocyanation of  $2 \times 10^{-3}$  M 2-FA in the presence of dextrose<sup>a</sup>

[Dextrose] (M)	[KCN] (M)	$\Phi'_{OH}$ <sup>b</sup>	$\Phi'_{CN}$ <sup>b</sup>	$\Phi'_r$ <sup>b</sup>
0.044	0	$0.93 \pm 0.07$		<sup>c</sup>
0.28	0	$0.96 \pm 0.02$		$0.062 \pm 0.008$
0.28	0	$1.03 \pm 0.06$		$0.064 \pm 0.038$
0.045	0.12	$0.78 \pm 0.05$	$0.12 \pm 0.01$	<sup>c</sup>
0.32	0.10	$0.46 \pm 0.04$	$0.064 \pm 0.008$	$0.016 \pm 0.010$

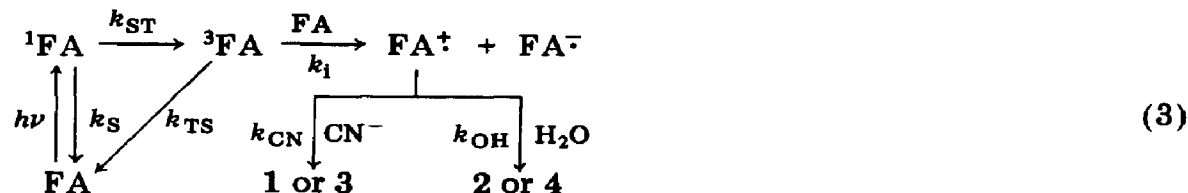
<sup>a</sup>For corresponding experiments in the absence of dextrose, see Tables 1 and 2.

<sup>b</sup>Errors are one standard deviation and represent precision.

<sup>c</sup>Not determined.

### 3. Results and discussion

Nucleophilic photosubstitutions of FA (especially 4-FA) have been shown to proceed via a radical cation intermediate according to reactions (3) [2].



There is ample evidence to support the important features of this mechanism, including the inability of  $\text{FA}^\ddagger-\text{FA}^-$  radical recombination to compete with trapping of  $\text{FA}^\ddagger$  by nucleophiles [2-4]. In our discussion we accept this mechanism as the basis for photosubstitutions. A species other than  $2\text{-FA}^\ddagger$  is responsible for anisole formation [5].

#### 3.1. Absorption spectra

Aqueous solutions of 2-FA experienced an increase in spectral intensity but no discernable change in spectral shape upon addition of  $\beta$ - or  $\gamma$ -CD (Fig. 1). Addition of  $\alpha$ -CD resulted in a bathochromic shift and a pronounced increase in vibrational band structure. At high concentrations of  $\alpha$ -CD, the absorption spectrum of aqueous 2-FA resembled that obtained in less polar solvents like *tert*-butyl alcohol or cyclohexane.

The effect of the inclusion of solutes within CD interiors on the shapes and intensities of absorption spectra has been noted previously [1, 12] and

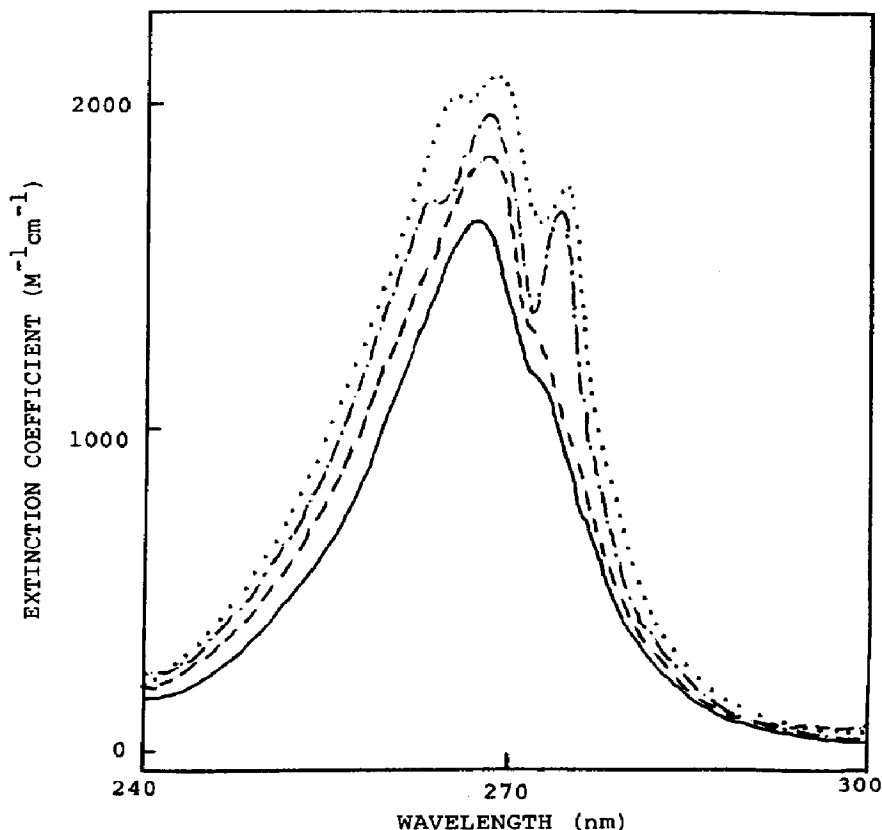


Fig. 1. Absorption spectra of 2-FA in various solvents: — · —, cyclohexane or *tert*-butanol; —, water; · · ·, aqueous  $4 \times 10^{-2}$  M  $\alpha$ -CD; — — —, aqueous  $1 \times 10^{-2}$  M  $\beta$ -CD.

has been correlated with the molecular structure of the complex and the interior polarity of a CD. On this basis, we conclude that the environment experienced by  $\alpha$ -CD-complexed 2-FA is similar in polarity to that of *tert*-butyl alcohol (using dialkylaminobenzonitriles as fluorescence probes, the polarity of an  $\alpha$ -CD cavity was estimated to be near that of *tert*-butyl alcohol or ethylene glycol [13]); the interiors of the  $\beta$ - and  $\gamma$ -CD toruses appear to 2-FA to be more polar.

Space-filling Corey-Pauling-Koltun (CPK) molecular models indicate that an  $\alpha$ -CD torus can accommodate a smaller (or equal) fraction of the 2-FA atoms than can  $\beta$ -CD. They indicate also that a number of water molecules can fit easily into a  $\beta$ - or  $\gamma$ -CD torus which contains a 2-FA, but only with difficulty into a 2-FA· $\alpha$ -CD complex. Thus, the vibrational structure observed with 2-FA· $\alpha$ -CD complexes cannot be attributed to how deeply a 2-FA resides in a CD torus; the local *apparent* polarity should depend on the substrate geometry within a torus and the co-inclusion of other species.

From molecular models, it appears that a  $\gamma$ -CD is capable of complexing more than one 2-FA. An indication that this may be occurring comes from attempts to prepare solutions of 2-FA in aqueous  $\gamma$ -CD. Initially

the solutions are clear. However, they become cloudy on standing and eventually a fine powdery solid precipitates. The structure of the precipitate has not been investigated as yet. Its presence precluded a reasonable determination of quantitative spectral and photochemical properties of 2-FA in aqueous  $\gamma$ -CD. At higher concentrations of 2-FA, similar powdery solids precipitate from aqueous  $\alpha$ - and  $\beta$ -CD.

Dissociation constants  $K_d$  for 2-FA $\cdot$ CD complexes at 20 °C were determined graphically by the Benesi–Hildebrand method [9, 10]. The  $K_d$  obtained are  $(2.4 \pm 0.8) \times 10^{-2}$  M for  $\alpha$ -CD,  $(7.8 \pm 1.4) \times 10^{-3}$  M for  $\beta$ -CD and  $(2.9 \pm 0.9) \times 10^{-2}$  M for freshly prepared solutions of  $\gamma$ -CD. These compare favorably with  $K_d$  of 4-FA $\cdot$ CD complexes but are larger than values reported for anisole $\cdot$ CD complexes [9].

### 3.2. Fluorescence and fluorescence quenching studies

Fluorescence spectra of 2-FA in water and aqueous CD solutions show a broad structureless peak ( $\lambda_{\max} = 300$  nm). From plots of the inverse of the fluorescence intensity *versus* iodide (quencher) concentration, Stern–Volmer constants were calculated [14]. In water, aqueous  $6.2 \times 10^{-2}$  M  $\alpha$ -CD (corresponding to 72% 2-FA complexation) and aqueous  $1.0 \times 10^{-2}$  M  $\beta$ -CD (corresponding to 55% complexation) the Stern–Volmer constants  $K_{sv}$  were  $26 \pm 3$  M $^{-1}$  s $^{-1}$ ,  $4.2 \pm 0.4$  M $^{-1}$  s $^{-1}$  and  $12.8 \pm 1.4$  M $^{-1}$  s $^{-1}$  respectively.

Iodide is known to bind weakly to both  $\alpha$ - and  $\beta$ -CD [15, 16]. Published  $K_d$  values indicate that about 60% of the CD employed would complex iodide at the highest quencher concentrations in the absence of 2-FA. Competing complexation with CD by iodide and 2-FA should complicate the kinetics of quenching. In spite of this, linear Stern–Volmer relationships were observed with both  $\alpha$ - and  $\beta$ -CD solutions, and the fractional decrease in  $K_{sv}$  for  $\alpha$ -CD cannot be accommodated by a hypothesis which relies solely on complexed iodide being an inefficient quencher.

Stern–Volmer plots for 4-FA fluorescence being quenched by iodide were similarly well-behaved [1]. Significantly, the  $K_{sv}$  of 4-FA was the same in the presence or absence of CD. Thus, at least a part of the decrease in the efficiency of the quenching of 2-FA must be ascribed to its manner of complexation by CD. Since  $K_{sv} = k_q \tau_f$  and since we have not been able to measure the fluorescence lifetime  $\tau_f$  of unbound and CD-bound 2-FA singlets, one may argue that the rate constant  $k_q$  for quenching  $^1$ FA by iodide, remains constant. In this case, all changes in  $K_{sv}$  would be ascribed to  $\tau_f$ . While we cannot reject this possibility, our results with 4-FA [1] lead us to favor an explanation in which  $k_q$  is different for bound and unbound 2-FA singlets. Were 2-FA and 4-FA complexed similarly, we would expect that either both or neither of the molecules would exhibit Stern–Volmer quenching constants which are sensitive to CD complexation; in both systems, a portion of the iodide quencher must be complexed. However, although addition of up to 0.2 M NaI resulted in a new tail absorption (of iodide), the previously mentioned vibrational absorption structure (char-

acteristic of 2-FA bound to  $\alpha$ -CD) appeared unaltered. This may be an indication that 2-FA competes more strongly for  $\alpha$ -CD than does iodide (*i.e.* both the entry and exit rate constants with  $\alpha$ -CD may be slower for 2-FA than for iodide). As a consequence, complexation of either species should rely on the binding efficiencies of both. Regardless of the exact reasons, 2-FA singlet states are clearly protected from quenching by iodide in the presence of  $\alpha$ - and  $\beta$ -CD.

### 3.3. General quantum yield considerations for photohydroxylation and photocyanation of 2-FA

As indicated in reactions (3) and demonstrated by Cornelisse and coworkers [3, 4] for 4-FA, the quantum efficiency for total substitution product formation from 2-FA ( $\Phi_p = \Phi_{OH} + \Phi_{CN}$ ) should be independent of cyanide concentration; addition of cyanide serves only to open an alternative pathway for reaction of  $FA^\ddagger$ . However, data in Tables 1 and 2 (in the absence of CD) show a decrease of about 10% in the efficiency of product formation from 2-FA; cyanide must inhibit reactivity. Although the specific nature of this effect is not known, several possibilities (such as quenching of 2-FA excited states, opening new reaction channels which do not lead to 3 or 4 and promoting back electron transfer to 2-FA $^\ddagger$ ) come to mind.

The relative quantum efficiencies for photohydroxylation and photoreduction have been defined respectively as  $\Phi'_{OH} = \Phi_{OH}/\Phi_{OH}^\circ$  and  $\Phi'_r = \Phi_{anisole}/\Phi_{OH}^\circ$  (where  $\Phi_{OH}$  and  $\Phi_{anisole}$  are the quantum yields for formation of 4 and anisole from  $2 \times 10^{-3}$  M 2-FA in the presence or absence of CD or KCN and  $\Phi_{OH}^\circ$  is the quantum efficiency for the formation of 4 from  $2 \times 10^{-3}$  M 2-FA in the absence of both CD and KCN; in the absence of both CD and cyanide,  $\Phi_{OH}^\circ = \Phi_p$ ). Similarly, the relative quantum yield  $\Phi'_{CN}$  for photocyanation of 2-FA is expressed as  $\Phi_{CN}/\Phi_{OH}^\circ$  (where  $\Phi_{CN}$  is the quantum yield for formation of 3 from  $2 \times 10^{-3}$  M 2-FA in the presence of KCN and the presence or absence of CD).

### 3.4. Quantum yields for CD-complexed 2-FA

Our experiments have measured the fraction of ground state 2-FA complexed by CD. This represents only one of the parameters necessary to define the influence of CD on the photoreactivity of FA. Others include the ability of complexed 2-FA excited states to yield radical ions, the fraction of radical ions which remain complexed during reaction and the  $K_d$  of the other mechanistically important transients. We have no means at this time of determining whether 2-FA and 2-FA $^\ddagger$ , for instance, are complexed similarly. *If* they are and *if* the physical and dynamic properties of bound and free 2-FA $^\ddagger$  are similar, eqn. (4) (in which  $x \equiv OH$  or  $CN$ ;  $c$  and  $u$  refer to complexed and uncomplexed 2-FA;  $f$  is the fraction of 2-FA complexed by CD and  $\epsilon_c/\epsilon_u$  is an approximate corrective factor for the molecular extinction coefficients of complexed and free 2-FA) should be valid. The values of  $f$  are calculated from ground-state derived  $K_d$  and the concentrations of 2-FA and CD. The ratios  $\epsilon_c/\epsilon_u$  have been computed from



$f$  and UV absorption spectra. Thus, a plot of  $\Phi'_x$  versus  $f$  is predicted to have a slope equal to  $\Phi'_{c,x}\epsilon_c/\epsilon_u - \Phi'_{u,x}$  and an intercept of  $\Phi'_{u,x}$ . In the absence of CD,  $\Phi'_{u,x} = \Phi'_x$  and, therefore, is known independently. The relative quantum yield for the component of the reaction occurring in the complex is obtainable from eqn. (5).

$$\Phi'_x = \Phi'_{u,x}(1 - f) + \Phi'_{c,x}f \frac{\epsilon_c}{\epsilon_u} \quad (4a)$$

$$= \Phi'_{u,x} + \left( \Phi'_{c,x} \frac{\epsilon_c}{\epsilon_u} - \Phi'_{u,x} \right) f \quad (4b)$$

$$\Phi'_{c,x} = (\text{slope} + \Phi'_{u,x}) \frac{\epsilon_u}{\epsilon_c} \quad (5)$$

The data in Tables 1 and 2 indicate qualitatively that both photohydroxylation and photocyanation are inhibited by complexation of 2-FA. The magnitude of the inhibition on photohydroxylation, as expressed through eqns. (4) and (5), is virtually complete; for  $\alpha$ -CD complexation,  $\Phi'_{c,OH}$  in the absence and presence of cyanide is calculated to be  $-0.10 \pm 0.20$  and  $-0.09 \pm 0.13$  respectively. We believe that the negative relative quantum efficiencies have no physical significance. They arise as a result of our extrapolating relative quantum efficiencies for partially bound FA to a value for completely bound FA. The error limits place both quantum efficiencies within zero. For  $\beta$ -CD complexation,  $\Phi'_{c,OH}$  becomes  $0.20 \pm 0.18$  in the absence of cyanide and  $0.07 \pm 0.10$  in its presence. These results are completely analogous to those obtained with 4-FA [1]. For both substrates photohydroxylation is blocked by complexation with  $\alpha$ - or  $\beta$ -CD.

Photocyanation of 4-FA is almost completely suppressed as well by complexation with  $\alpha$ - or  $\beta$ -CD. However, we find from eqns. (4) and (5) that  $\Phi'_{c,CN}$  of 2-FA behaves differently:  $\Phi'_{c,CN} = 0.023 \pm 0.022$  with  $\alpha$ -CD but is invariant with  $\beta$ -CD. Although the  $\alpha$ -CD-complexed 2-FA appears to undergo photocyanation, albeit inefficiently ( $\Phi'_{c,CN}/\Phi'_{u,CN} \approx 0.2$ ), we prefer not to emphasize its importance owing to the large error limits. With  $\beta$ -CD,  $\Phi'_{c,CN}$  is clearly outside experimental error of zero and  $\Phi'_{c,CN}/\Phi'_{u,CN} \approx 1$ .

In contrast,  $\Phi'_r$  is virtually independent of CD above the lowest concentration ( $5 \times 10^{-3}$  M) employed. Thus, it does not depend on the photo-reduction precursor being complexed by CD, but requires only that an adequate supply of hydrogen atom donor be present. The mechanism in reactions (3) [2-4], experiments performed in methanol [5], and our investigations with dextrose (Table 3) indicate that photoreduction proceeds via a pathway which is different from that leading to photosubstitution. A leading candidate for a precursor to anisole is the anion radical of 2-FA or a species derived from it.

Dextrose (and CD) appears to intervene in the mechanism (3) in a second fashion. The maximum CD concentration employed in our experiments (0.045 M) causes large changes in  $\Phi_p$ . Yet, from Table 3 it can be seen that an equivalent molar concentration of the non-complexing

carbohydrate dextrose has no discernible influence on the efficiency of photosubstitution; in the absence of cyanide, even an equal weight concentration of dextrose (about 0.3 M) leaves  $\Phi'_{OH}$  unchanged. However, the same dextrose concentration, in combination with 0.1 M KCN, reduces both  $\Phi'_{OH}$  and  $\Phi'_{CN}$  by a factor of nearly one-half. Since neither  $\Phi'_r$  nor the ratio of 4 to 3 is altered within experimental error, dextrose influences photosubstitution without inhibiting formation of the photoreduction transient and without selective interception of intermediates which lead to 3 and 4; quenching of a species which precedes the  $k_i$  step would reduce both  $\Phi'_r$  and  $\Phi'_p$ . It is reasonable, then, that the influence of CD upon the ratio of 4 to 3 is primarily environmental (and not chemical) in its origin; the reductions in  $\Phi'_{OH}$  and  $\Phi'_{CN}$  experienced on addition of the CD derive from both chemical and environmental factors.

### 3.5. Mechanistic considerations related to specific FA environments

CD complexation of 2-FA may result in dramatic restructuring of water molecules near the mouths of the complex and, therefore, along the approach path taken by a nucleophile. In a related study, we have observed that addition of small amounts of *tert*-butyl alcohol to aqueous solutions of 2- or 4-FA containing cyanide has marked effects on  $\Phi_p$  and the rate constant ratio  $k_{CN}/k_{OH}$  [6] (reactions (3)). Most notably, the ratio *increases* by over one order of magnitude for 2-FA but *decreases* by only a factor of about two for 4-FA upon addition of about 0.08 mol.% *tert*-butyl alcohol to neat water solutions of FA and cyanide.

Several other observations may be germane to understanding the selective effects of CD on FA photochemistry and photophysics. To summarize: (1)  $\beta$ -CD complexation of 2-FA inhibits photohydroxylation more than photocyanation; (2) both photohydroxylation and photocyanation of 2-FA are strongly inhibited by  $\alpha$ -CD; (3) complexation of 4-FA by either  $\alpha$ - or  $\beta$ -CD results in almost complete loss of photoproduct formation; (4) the efficiency of iodide quenching of 2-FA fluorescence is dependent on whether the excited singlets are unbound, bound to  $\alpha$ -CD or bound to  $\beta$ -CD; (5) the efficiency of iodide quenching of 4-FA fluorescence is independent of the location of the excited singlets within the aqueous media; (6) the major process upon irradiation in aqueous 0.1 M KCN is photohydroxylation (giving product 4) from 2-FA and photocyanation (giving product 1) from 4-FA. These results suggest that 2- and 4-FA exhibit intrinsic reactivity differences which are influenced further by their environments. The differing propensities of the FA isomers toward photohydroxylation may be related to their hydrogen bonding to water in which hydrogen bonding of water to the methoxy group would place the nucleophile near the fluorinated carbon of 2-FA but far from that of 4-FA. However, for the purposes of this study, it is more important to discern how different environments will influence such factors.

The lower polarity of a CD interior (when compared with the aqueous bulk) should be sufficient to decrease  $k_i$  and, thereby,  $\Phi_p$  [17]. Since  $\alpha$ -CD

complexation reduces significantly the rate of fluorescence quenching of 2-FA singlets and the ability to form both 3 and 4, we suggest that 2-FA is restrained by  $\alpha$ -CD and that external nucleophiles, quenchers and other 2-FA molecules may be inhibited from approaching the substrate [18]. In order to compare these results more quantitatively with those of 4-FA, it would be useful to know the preferred orientation of 2-FA within a CD torus. We do not have spectroscopic or dynamic information concerning this point. From space-filling models, we are unable to note a preference between 2-FA entering a CD torus from the substituted or unsubstituted end of the ring.

From our spectroscopic evidence, complexation with  $\beta$ -CD appears looser than with  $\alpha$ -CD. Thus, 2-FA in a  $\beta$ -CD torus should be more accessible to incoming nucleophiles. However, if the water molecules near a CD form caps similar in structure to the order of water-rich *tert*-butyl alcohol [19], the selectivity observed in the complexes may, in part, arise from external solvent effects.

In this hypothesis, complexed FA reactivity is the net result of a combination of factors: intrinsic solute photoreactivity, steric and polarity constraints to reactivity imposed on FA by CD, and to special water structure near the FA loci of substitution in CD complexes. Although quite speculative, it accommodates virtually all of the data [1, 6] we have gathered for 2-FA and 4-FA photosubstitutions in aqueous CD solutions. We intend to pursue this work in order to refine our explanation and test its more controversial parts.

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