9 Hz), 2.6–1.1 (m, 5, H-1, -6, -7). Elution with ether afforded **4-cyano-3,*syn*-8-diphenylbicyclo[3.2.1]oct-3-en-*endo*-2-ol (8P-CN),** mp 139–140 °C (from benzene–petroleum ether), 0.120 g (41%); IR ν_{OH} 3545, ν_{CN} 2220 cm^{-1}; ^{1}H NMR δ 7.4 (sharp m, 10, Ph H), 4.2 (d, 1, H-2, J = 10 Hz), 3.4–3.2 (m, 3, H-1, -5, -8), 2.2–0.8 (m, 5, H-6, -7, OH). Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35. Found: C, 83.66; H, 6.40.

The endo alcohol 8P-CN and its exo epimer (85:15, respectively) were also obtained (quantitatively) by heating tosylate 6P-CN in 80% dioxane/20% water at 160 °C for 3 weeks. Oxidation of the alcohol mixture with pyridinium chlorochromate (methylene chloride, 25 °C, 3.5 h), followed by the usual workup,[37] led to **4-cyano-3,*syn*-8-diphenylbicyclo[3.2.1]oct-3-en-2-one (9P-CN),** 65%, mp 154–156 °C (from benzene–petroleum ether); IR ν_{CN} 2250, ν_{CO} 1680 cm^{-1}; ^{1}H NMR δ 7.3–6.87 (m, 10, Ph H), 3.58 (br m, 3, H-1, -5, -8), 2.53–1.77 (m, 4, H-6, -7). Anal. Calcd for $C_{21}H_{17}NO$: C, 84.25; H, 5.72. Found: C, 84.15; H, 5.83.

From tosylate 6T-CN in 80:20 dioxane/water (130 °C, 8 days) was similarly obtained a semisolid mixture of crude endo and exo alcohols 8T-CN (82%). Oxidation of the crude alcohols as before with pyridinium chlorochromate led to **4-cyano-3,*syn*-di-*p*-tolylbicyclo[3.2.1]oct-3-en-2-one (9T-CN),** 80%, mp 176–177 °C from benzene–petroleum ether; IR ν_{CN} 2250, ν_{CO} 1680 cm^{-1}; ^{1}H NMR δ 7.12 (m, 8, Ar H), 3.57 (m, 2, H-1 (or -5), 8), 2.32 (s, 6, Ar CH_3), 2.72–1.73 (m, 5, H-5 (or -1), -6, -7). Anal. Calcd for $C_{23}H_{21}NO$: C, 84.37; H, 6.46. Found: C, 84.39; H, 6.55.

Less material was available in the -Et series, particularly in the *p*-tolyl (T) case. For product analysis, therefore, all the titrated (ampule) material was pooled and processed. Because this material represented reactions carried out at different temperatures, the percentage of each component represents an average over the temperature range used. Removal of the solvent from the solvolysate of 6P-Et and a combination of chromatography of the residue on Florisil, using ether–petroleum ether mixtures (increasingly richer in the former) as eluants, and/or high-pressure liquid chromatography (25-cm Partisil PXS 10/25 column, hexane eluant) gave a series of fractions with the product composition described below (based upon peak area only). Elution with 5% ether in petroleum ether gave **2-ethylidene-3,*syn*-8-diphenylbicyclo[3.2.1]oct-3-ene (10P),** *E* or *Z* nature unknown, 18%, waxy solid, mp 69.5–70 °C; IR $\nu_{C=C}$ 1600 cm^{-1}; ^{1}H NMR δ 7.33–6.77 (m, 10, Ph H), 5.70 (d, 1, H-4, J = ca. 7 Hz), 4.97 (q, 1, =$CHCH_3$, J = ca. 8 Hz), 3.63 (m, 1, H-1(5)), 3.23–2.87 (br m, 2, H-5(1), -8), 2.4–1.17 (br m, 4, H-6, -7), 1.70 (d, 3, CH_3, J = ca. 8 Hz). Anal. Calcd for $C_{22}H_{22}$: C, 92.26; H, 7.74. Found: C, 91.60; H, 7.83. Elution with 10% ether in petroleum ether led to **2-ethyl-4-*endo*-(2,2,2-trifluoroethoxy)-3,*syn*-8-diphenylbicyclo[3.2.1]oct-2-ene (7P-Et),** oil, 14%, only partially characterized; ^{1}H NMR (partial) δ 3.54 (br s, 1, H-4), 3.23 (q, 2, OCH_2CF_3, J = 4.5 Hz). Finally, elution with 25% ether in petroleum ether afforded **4-ethyl-3,*syn*-8-diphenylbicyclo[3.2.1]oct-3-en-*endo*-2-ol (8P-Et),** oil, 68%, only partially characterized; IR ν_{OH} 3585, $\nu_{C=C}$ 1593 cm^{-1}; ^{1}H NMR no vinyl protons.

An analogous product study on the solvolysate from 6T-Et was also performed, although even less material was available. The chromatographic fractions were therefore characterized only by spectra. The results indicated that 6T-Et had solvolyzed to a similar array of products as those mentioned above from 6P-Et.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

Registry No. 1-H, 3391-05-7; 1-HBr_2, 82521-65-1; 1-Br, 82521-66-2; 1-CN, 82521-67-3; 1-COOH, 82521-68-4; 1-COOMe, 82521-69-5; **2P**-CN, 82521-70-8; **2T**-CN, 82536-73-0; **2P**-COOMe, 82521-71-9; **2T**-COOMe, 82521-72-0; **3P**-COOMe, 82521-73-1; **3T**-COOMe, 82521-74-2; **4P**-CN, 82521-75-3; **4T**-CN, 82521-76-4; **4P**-COOMe, 82521-77-5; **4T**-COOMe, 82521-78-6; **4P**-CH_2OH, 82521-79-7; **4P**-CHO, 82521-80-0; **4P**-H, 50522-49-1; **4P**-CH_2NH_2, 82521-81-1; **4P**-CH_2NHTs, 82569-87-7; **4T**-CH_2OH, 82521-82-2; **4T**-CHO, 82536-74-1; **4P**-CH=CH_2, 82521-83-3; **4T**-CH=CH_2, 82521-84-4; **4P**-Et, 82521-85-5; **4T**-Et, 82521-86-6; **5P**-CN, 82521-87-7; **5T**-CN, 82521-88-8; **5P**-Et, 82521-91-3; **5T**-Et, 82521-92-4; **5′**P-Et, 82521-89-9; **5′**T-Et, 82521-90-2; **6P**-CN, 82521-93-5; **6T**-CN, 82521-94-6; **6P**-H, 29266-07-7; **6T**-H, 50522-61-7; **6P**-Et, 82521-95-7; **6T**-Et, 82521-96-8; **7P**-CN, 82521-97-9; **7P**-Et, 82522-02-9; **8P**-CN (isomer 1), 82521-98-0; **8P**-CN (isomer 2), 82522-04-1; **8P**-Et, 82522-03-0; **8T**-CN (isomer 1), 82522-05-2; **8T**-CN (isomer 2), 82522-06-3; **9P**-CN, 82521-99-1; **9T**-CN, 82522-00-7; **10P**, 82522-01-8; Ph_3P=CH_2, 3487-44-3; diphenyldiazomethane, 883-40-9; di-*p*-tolyldiazomethane, 1143-91-5.

Hydration of the Flavylium Ion. 2. The 4′-Hydroxyflavylium Ion

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Received March 15, 1982

An investigation of the transformations undergone by the 4′-hydroxyflavylium ion in aqueous solution is reported. A rapid initial deprotonation of the hydroxy group occurs, resulting in an anhydro base, the pK_a value associated with this ionization being 5.5. A slower transformation follows in which further equilibration occurs with a pseudobase and a ring-opened *cis*-chalcone. The stabilities of the neutral species are very similar, the mixture at equilibrium consisting of 37% pseudobase, 33% neutral chalcone, and 30% anhydro base. This equilibrium is displaced toward flavylium ion in acid solutions (pH <5) and is displaced toward chalcone in base due to the ionization of its phenolic hydroxyl groups. The pseudobase is formed in solutions with pH <8 by hydration of the flavylium ion, while in solutions with pH >8 direct hydration of the anhydro base occurs. In all solutions with pH >4 a very slow further reaction occurs, resulting in the irreversible formation of *trans*-2,4′-dihydroxychalcone, the product of thermodynamic control at all pHs.

Polyhydroxyflavylium ions form the nucleus of the anthocyanin pigments responsible for a large number of plant and flower colors.[1-3] While these highly colored cations are stable in relatively acidic solutions, they undergo a number of structural transformations in less acidic, neutral, and basic solutions, usually with substantial color changes or color disappearance.[1-3] The chemistry associated with these changes has been examined in varying degrees with several naturally occurring anthocyanins and some model flavylium salts.[1-11] We recently reported[12] a detailed study

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(1) Hayashi, K. In "The Chemistry of Flavanoid Compounds"; Geissman, T. A., Ed.; Pergamon Press: Oxford, 1962; pp 248–285.

(2) Jurd, L. In "The Chemistry of Plant Pigments"; Chichester, C. O., Ed.; Academic Press: New York, 1972; p 123.

(3) Jurd, L. *Recent Adv. Phytochem.* **1972**, 135.

(4) Sondheimer, F. *J. Am. Chem. Soc.* **1953**, *75*, 1507.

(5) Jurd, L. *J. Org. Chem.* **1963**, *28*, 987.

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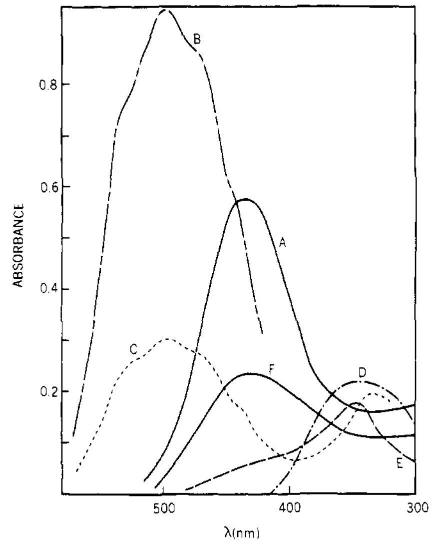
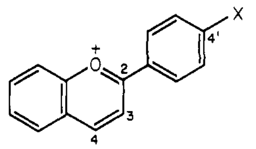


Figure 1. Spectra of 4′-hydroxyflavylium perchlorate (1.2 × 10^5 M): A (—), 0.1 M HCl (flavylium ion); B(- - -), initial spectrum (10 ms) at pH 6.7 (anhydro base); C (- - -), intermediate spectrum (30 min) at pH 6.7 (mixture of anhydro base, pseudobase, and *cis*-chalcone); D (–·–), final spectrum (2 days) at pH 6.7 (*trans*-chalcone); E (— — —), intermediate spectrum (2 min) at pH 12.0 (*cis*-chalcone dianion); F (—), final spectrum at pH 12 (*trans*-chalcone dianion).

involving the parent flavylium ion and its 4′-methyl and 4′-methoxy derivatives. A number of transformations do



occur with these cations, but using various spectral and kinetic methods, we were able to evaluate most of the equilibrium constants and rate constants associated with these, providing a detailed quantitative description of the overall chemistry.

In this paper we report a study of the 4′-hydroxyflavylium cation. This ion can undergo a reaction not available to the three ions of our previous study, the ionization of the hydroxyl group resulting in a species termed an anhydro base. Anhydro bases themselves are highly colored, and their formation with natural anthocyanins is well documented. The simple 4′-hydroxy derivative was chosen so that the importance of the anhydro base could be evaluated in the context of the results obtained in our previous study. We do, in fact, find that the behavior is similar to that of the parent ion, with added pathways involving the hydroxyl ionization. This ion has been studied previously[7,9] in terms of some spectral changes and reduction polarography. Our results and conclusions are in essential agreement, although our analysis provides a much more quantitative description of the system.

Results and Analysis

Our approach is the same as that used previously[12] and involves a combination of stopped-flow and conventional spectroscopic studies. Three distinct spectral changes, which we label i–iii, are observed on addition of the 4′-hydroxyflavylium ion to solutions of pH 4 and greater. The first involves the simple ionization of the hydroxy group to produce the anhydro base. This is followed by a slower transformation (ii), resulting in a complex equilibrium involving several species including the anhydro base. Transformation (iii) is a very slow and irreversible formation of *trans*-2,4′-dihydroxychalcone. The principal data to be used in our analysis are given in Figures 1–3, Figure 1 presenting some typical spectra, Figure 2 some acid base titration curves, and Figure 3 the kinetic behavior associated with transformations ii and iii. A general scheme is presented in Scheme I, where rate and equilibrium constants to be used in our discussion are also defined. Except for the additional pathways involving 4′-hydroxyl ionization, this is the same scheme proposed in our previous study, and where appropriate, the same symbolism has been used here.

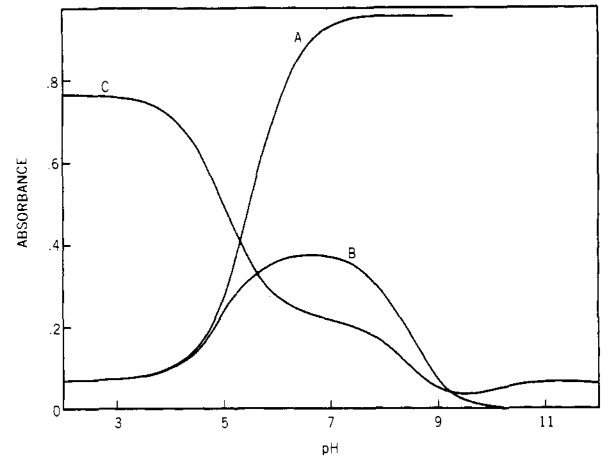


Figure 2. Absorbance vs. pH: A, λ = 500 nm, obtained 5 ms after addition of an acidic solution of 4′-hydroxyflavylium ion; B, λ = 500 nm; C, λ = 440 nm, obtained 30–60 min after addition. Concentration = 1.2 × 10^{-5} M.

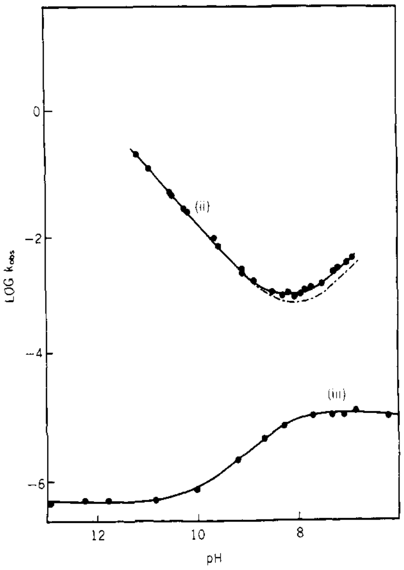


Figure 3. Observed first-order rate constants (s^{-1}, 25 °C) for transformations ii and iii. The dashed portion of curve ii represents rate constants referring to anhydro base disappearance only (see text).

Transformation i. Flavylium Ion–Anhydro Base Equilibration. The 4′-hydroxyflavylium ion has a λ_{max} of 440 nm (curve A of Figure 1). Adjustment to pH 5 or greater results in the formation of a solution with a peak

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(6) Jurd, L.; Geissman, T. A. *J. Org. Chem.* **1963**, *28*, 2394.

(7) Timberlake, C. F.; Bridle, P. *Nature (London)* **1966**, *212*, 518.

(8) Harper, K. A.; Chandler, B. V. *Aust. J. Chem.* **1967**, *20*, 731–744; **1967**, *20*, 745.

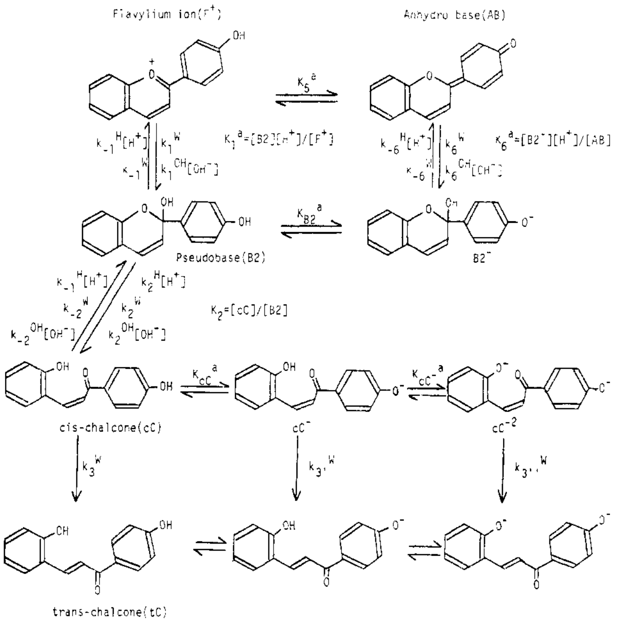
(9) Brouillard, R.; Dubois, J. F. *J. Am. Chem. Soc.* **1977**, *99*, 1359.

(10) Brouillard, R.; Delaporte, B. *J. Am. Chem. Soc.* **1977**, *99*, 8461.

(11) Brouillard, R.; Delaporte, B.; Dubois, J. E. *J. Am. Chem. Soc.* **1978**, *100*, 6202.

(12) McClelland, R. A.; Gedge, S. *J. Am. Chem. Soc.* **1980**, *102*, 5838.

Scheme I



centered at 500 nm which can be assigned to the neutral anhydro base formed by ionization of the hydroxyl group. As with most simple proton transfers,[13] this ionization is very rapid (see later), so that the anhydro base must be the only product initially formed upon neutralization. The anhydro base once formed is not stable, but its spectral characteristics (curve B of Figure 1) can be obtained in a stopped-flow spectrophotometer by recording absorbance values 5–10 ms after adjustment of the pH of an acid solution of the cation. Ionization is complete within this time while the subsequent transformation has yet to commence. A titration curve representing the flavylium ion–anhydro base equilibration was obtained in the same way, by recording absorbance values at the $\lambda_{\max}$ of the anhydro base for different values of pH (curve A of Figure 2). The acidity constant obtained from this curve, defined as $\mathrm{p}K_5^{\mathrm{a}}$ (Scheme I), is 5.53.

Rate constants for the equilibration were obtained by using the temperature-jump technique. A series of solutions were prepared in the pH range 5.3–5.7 where significant quantities of both forms coexist at equilibrium, and these were subjected to a rapid jump from 19 to 23 °C. First-order relaxations are observed, the rate constants for which vary with acidity according to the relationship in eq 1. The two derived rate constants in this expression

$$\tau^{-1}\ (\mathrm{s}^{-1}) = 2.6 \times 10^{4} + 7.7 \times 10^{9}[\mathrm{H}^+] \qquad (1)$$

can be assigned to the constants $k_5^{\mathrm{H_2O}}$ and $k_{-5}^{\mathrm{H_3O^+}}$ of eq 2

$$\mathrm{F}^+ \underset{k_{-5}^{\mathrm{H_3O^+}}}{\overset{k_5^{\mathrm{H_2O}}}{\rightleftharpoons}} \mathrm{AB} + \mathrm{H}^+ \qquad (2)$$

and represent deprotonation of the flavylium ion by a water molecule and its microscopic reverse, protonation by the hydronium ion. The ratio of the two, expressed as a pK value, is 5.47, in good agreement with the spectroscopically determined value of $\mathrm{p}K_{\mathrm{a}}^{5}$.

The value of $k_{-5}^{\mathrm{H_3O^+}}$ shows that the thermodynamically favored protonation reaction is diffusion limited[13] (or at least very near the diffusion limit). This is the normal situation for a proton transfer between oxygen atoms.[13] It does contrast somewhat with the case reported[9] for the naturally occurring anthocyanin malvin and its anhydro base (presumably formed at the 7-position). In this system a value of $k^{\mathrm{H_3O^+}}$ of $1.4 \times 10^{8}\ \mathrm{M^{-1}\ s^{-1}}$ (at 6.5 °C) is obtained.

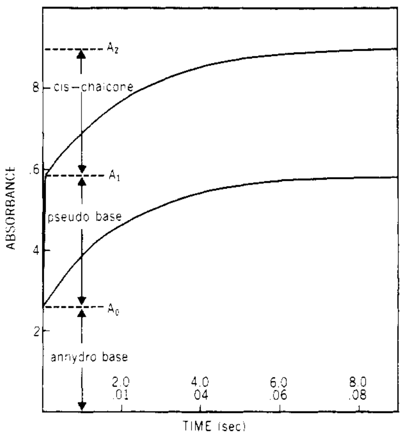
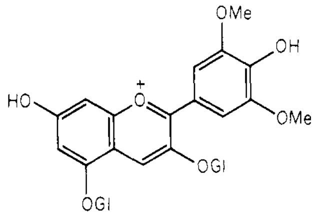


Figure 4. Variation of absorbance at 440 nm with time on acidification to pH 2.7 of a pH 7.2 solution of the 4′-hydroxyflavylium ion: lower curve refers to the lower time scale; upper curve refers to upper time scale.



malvin

Transformation ii. Products. This change follows the initial equilibration of the flavylium ion and anhydro base and results in a new equilibrium mixture. The complex acid–base nature of this new mixture is revealed in curves B and C of Figure 2, which depict the variation with pH of the absorbances at 500 and 440 nm after completion of ii. The 440-nm curve in particular indicates that the system is best described in terms of the ionization of a species with three ionizable protons (eq 3). A curve-fitting

$$\mathrm{AH_3} \overset{K_{\mathrm{a}}^{1}(\mathrm{app})}{\rightleftharpoons} \mathrm{AH_2} \overset{K_{\mathrm{a}}^{2}(\mathrm{app})}{\rightleftharpoons} \mathrm{AH} \overset{K_{\mathrm{a}}^{3}(\mathrm{app})}{\rightleftharpoons} \mathrm{A} \qquad (3)$$

program[14] provides pK values of 5.07, 8.36, and 9.77 for the three ionizations. The 500-nm curve shows only the first two ionizations.[14] The species $\mathrm{AH_3}$ of eq 3 is obviously the flavylium ion itself. $\mathrm{AH_2}$ is therefore some combination of neutral species, including anhydro base, as indicated by the residual absorbance due to this species in solutions near neutrality (see curve C of Figure 1 and curve B of Figure 2). AH is some monoanionic species or combination of these, while A represents a dianion. The most reasonable candidate for this last species is the dianion of the ring-opened *cis*-chalcone, this being the only species with two relatively acidic hydrogens.

The nature of $\mathrm{AH_2}$ was determined in the following way. The basis for the experiment is the reversibility of the equilibria under consideration here and in particular the

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(13) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1.

(14) Absorbance = $(A_3[\mathrm{H}^+]^3 + A_2K_{\mathrm{a}}^{1}[\mathrm{H}^+]^2 + A_1K_{\mathrm{a}}^{1}K_{\mathrm{a}}^{2}[\mathrm{H}^+] + A_0K_{\mathrm{a}}^{1}K_{\mathrm{a}}^{2}K_{\mathrm{a}}^{3})/([\mathrm{H}^+]^3 + K_{\mathrm{a}}^{1}[\mathrm{H}^+] + K_{\mathrm{a}}^{1}K_{\mathrm{a}}^{2}[\mathrm{H}^+] + K_{\mathrm{a}}^{1}K_{\mathrm{a}}^{2}K_{\mathrm{a}}^{3})$, where A_3, A_2, A_1, and A_0 are the absorbance values which would be observed for solutions with only $\mathrm{AH_3}$, $\mathrm{AH_2}$, $\mathrm{AH_1}$, or A, respectively, present. For curve C, A_3 and A_0 were taken to be the observed absorbance values at pH 1 and 13, respectively, and the data were subjected to curve-fitting with A_2, A_1, and the three dissociation constants as unknowns. For curve B, A_3 was taken as the pH 1 absorbance value, A_1 and A_0 were set equal to zero, and curve-fitting yielded A_2, K_{a}^{1}, and K_{a}^{2}.

Table I. Initial, Intermediate, and Final Absorbance Values at 440 nm on Acidification to pH 2·7

initial pH	A_0	A_1	A_2	pseudobase/ anhydro base ratio[a]	*cis*-chalcone/ pseudobase ratio[b]
7.28	0.26	0.58	0.92	1.23	1.06
7.52	0.25	0.57	0.93	1.28	1.13
7.84	0.23	0.49	0.91	1.13	1.62
8.04	0.20	0.45	0.92	1.25	1.88
8.25	0.17	0.37	0.90	1.18	2.65
8.44	0.13	0.30	0.93	1.31	3.71
12.0	0	0	0.96		

[a] $(A_1 = A_0)/A_0$. [b] $(A_2 - A_1)/(A_1 - A_0)$.

quantitative regeneration of flavylium ion when any solution is adjusted to acid pH. The actual experiment involves the performing of this acidification on a stopped-flow apparatus and the monitoring of the appearance of the ion. Traces such as those of Figure 4 are obtained, the key features of which are two quite distinct stages of flavylium ion appearance. Both these phases exhibit first-order kinetics, with the first-order rate constants obeying the relationships of eqs 4 and 5, with $k_{-1}^{H} = 2.5 \times 10^4\ M^{-1}\ s^{-1}$, $k_{-2}^{H} = 73\ M^{-1}\ s^{-1}$, and $k_{-2}^{W} = 0.26\ s^{-1}$.

$$k_{obsd}(\text{fast}) = k_{-1}^{H}[H^+] \tag{4}$$

$$k_{obsd}(\text{slow}) = k_{-2}^{H}[H^+] + k_{-2}^{W} \tag{5}$$

These same two kinetic phases were observed with the three ions of our previous study,[12] and we conclude here that they represent the same situation. That is, the solution, prior to acidification, must contain both pseudobase B2 and *cis*-chalcone cC. The faster of the two phases represents the pseudobase being converted to flavylium ion in a reaction catalyzed by hydronium ion. The slower phase represents *cis*-chalcone being converted to ion. This occurs by way of the pseudobase, with ring closure being rate determining and occurring in H$^+$-catalyzed and pH-independent reactions. The essence of this experiment is that in an acid solution conversion of pseudobase to flavylium ion is a more rapid process than conversion of *cis*-chalcone to pseudobase, so that pseudobase is trapped to form flavylium ion before significant reaction with chalcone.

There is one important difference between the traces obtained with the 4′-hydroxy system and those of the previous study,[15] i.e., the nonzero initial absorbance observed with the 4′-hydroxy system. This can be explained by the additional presence of anhydro base. On acidification the kinetic trace representing conversion of this species to flavylium ion cannot be observed by using the stopped-flow apparatus, since the protonation reaction is so fast that the ion has formed within the dead time of the instrument.

In other words, Figure 4 can be interpreted in terms of three species being present prior to acidification, each of these being converted to flavylium ion at quite different rates. The relative absorbance changes can be taken as a measure of the relative concentrations of the three species (Figure 4). The initial absorbance A_0 represents anhydro base, the difference between this reading and the intermediate reading $(A_1 - A_0)$ represents pseudobase, and the difference between the intermediate reading and the final reading $(A_2 - A_1)$ represents *cis*-chalcone. A set of readings obtained with solutions of different initial pH is given in Table I. The data in this table were all obtained after completion of transformation ii, ensuring therefore that the numbers do represent the equilibrium position prior to acidification.

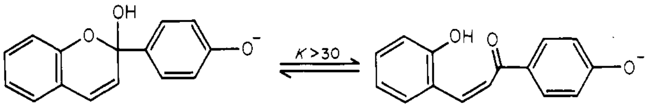
The ratio $(A_1 - A_0)/A_0$ is equal to the ratio [pseudobase]/[anhydro base]. This is reasonably constant with a value of 1.2 and can be taken as the equilibrium constant for interconversions of these two neutral species. In terms of Scheme I this constant is equal to K_1^{a}/K_5^{a}, so that with the value of K_5^{a} previously determined pK_1^{a} can be set equal to 5.45.

The ratio $(A_2 - A_1)/(A_1 - A_0)$ is equal to the ratio [*cis*-chalcone]/[pseudobase]. This does change with pH but the variation can be explained in terms of the ionization of the *cis*-chalcone shifting the equilibrium toward that species. In quantitative terms the relationship in eq 6 can be derived.

$$\frac{A_2 - A_1}{A_1 - A_0} = \frac{[cC] + [cC^-]}{[B2]} = K_2 + \frac{K_2 K_{cC}^{a}}{[H^+]} \tag{6}$$

A plot of $(A_2 - A_1)/(A_1 - A_0)$ vs. $1/[H^+]$ is reasonably linear, furnishing values of $K_2 = 0.9$ and $pK_{cC}^{a} = 7.93$.

A comment can also be made regarding the involvement of the anion of the pseudobase B2$^-$. From the constancy of the value of $(A_1 - A_0)/A_0$ we can conclude that this anion is not present in significant amounts up to pH 8.4; otherwise ionization of the pseudobase would result in an increase in this ratio. Thus we set $pK_{B2} > 9.4$. Coupling this limit with values of K_2 and pK_{cC}^{a}, one can see that the ratio $[cC^-]/[B2^-]$ must be greater than 30 (eq 7).



(7)

Therefore we conclude that the monanion in the equilibrium of eq 3 is principally ionized *cis*-chalcone. This seems reasonable. The phenolic OH in the pseudobase has a para-saturated carbon and should resemble the parent phenol in its ionization, whereas the phenolic OH in the *cis*-chalcone has an electron-withdrawing carbonyl group in the para position and should be considerably more acidic. It is presumably the 4′-hydroxy group which ionizes in this *cis*-chalcone, and not the 2-group. This conclusion is reached on considering that the pK^{a} value of 2-hydroxychalcone is 9.0.[12]

The species present upon completion of transformation ii are summarized in Figure 5. Equation 3 can be rewritten as

$$F^+ \underset{}{\overset{K_a{}^1(\text{app})}{\rightleftharpoons}} \begin{array}{c} AB \\ + \\ B2 \\ + \\ cC \end{array} \overset{K_a{}^2(\text{app})}{\rightleftharpoons} cC^- \overset{K_a{}^3(\text{app})}{\rightleftharpoons} cC^{2-} \tag{8}$$

and

---

(15) Compare this figure to Figure 9 of ref 1.

$$K_a^1(\text{app}) = K_5^a + K_1^a + K_1^aK_2 \tag{9}$$

$$K_a^2(\text{app}) = \frac{K_1^aK_2K_{cC}^a}{K_5^a + K_1^a + K_1^aK_2} \tag{10}$$

$$K_a^3(\text{app}) = K_{cC^-}^a \tag{11}$$

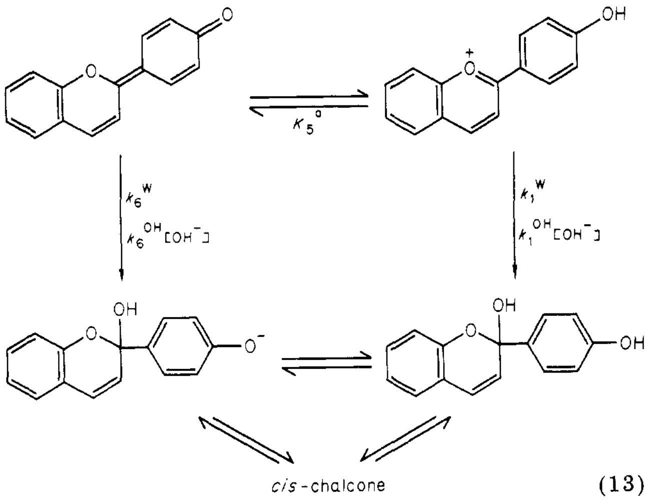
Using values of K_1^a, K_5^a, K_2, and K_{cC}^a derived in our analysis, we calculate values of pK_a^1(app) and pK_a^2(app) as 5.01 and 8.49. These show good agreement with the observed values, pointing to the consistency of the analysis.

Kinetics. The kinetics associated with transformation ii are necessarily complex because of the substantial number of species which can be present in equilibrium upon completion. We have carried out a kinetic study from pH 7 to 10, where little flavylium ion is present either before or after reaction. The kinetics can be conveniently followed by using the decrease in absorbance at 500 nm as anhydro base is converted to the mixture of anhydro base, pseudobase, and *cis*-chalcones. Excellent first-order behavior is observed, and the observed first-order rate constants are presented as a function of pH in Figure 3. These constants do refer to an approach to equilibrium, since a significant amount of anhydro base is still present after complete reaction. By use of values of the equilibrium constants discussed in the previous section, the observed constants were corrected[16] to refer to anhydro base disappearance only, and these are given as the dashed line of Figure 3. These obey the simple relationship

$$k_{\text{dis}} = k_{\text{dis}}^{\text{OH}}[\text{OH}^-] + k_{\text{dis}}^{\text{W}} + k_{\text{dis}}^{\text{H}}[\text{H}^+] \tag{12}$$

with values of $k_{\text{dis}}^{\text{OH}} = 1.5 \times 10^2$ M^{-1} s^{-1}, $k^{\text{W}} = 7 \times 10^{-4}$ s^{-1}, and $k^{\text{H}} = 2.1 \times 10^4$ M^{-1} s^{-1}.

The scheme shown in eq 13 can be proposed to account for this behavior. The constants k_{dis} refer to the conversion of anhydro base to pseudobase, and in our scheme this conversion is proposed to occur with two nucleophiles, water and hydroxide ion, adding to two species, directly to the anhydro base, or to the flavylium ion present in small amounts in equilibrium with this. The pseudobase subsequently equilibrates with *cis*-chalcone, but this process is extremely rapid[12] and does not enter into the kinetic analysis.



(13)

The mechanism of eq 13 yields the eq 14. Comparison

$$k_{\text{dis}} = k_6^{\text{OH}}[\text{OH}^-] + k_6^{\text{W}} + \frac{k_1^{\text{OH}}K^{\text{W}}}{K_5^a} + \frac{k_1^{\text{W}}}{K_5^a}[\text{H}^+] \tag{14}$$

of eq 14 with eq 12 reveals that the $k_{\text{dis}}^{\text{H}}$ term of eq 12 represents the addition of a water molecule to the flavylium ion, the acid catalysis arising from the increase in concentration of this ion with increasing acidity. Consistency in our overall analysis can be noted here. The constant $k_{\text{dis}}^{\text{H}}$ is equal to k_1^{W}/K_5^a, and this yields a value for k_1^{W} of 0.08 s^{-1} by using the previously determined K_5^a. A value for this same constant of 0.09 s^{-1} is calculated as the product of the constants k_{-1}^{H} and K_1^a independently determined in our analysis in the previous section.

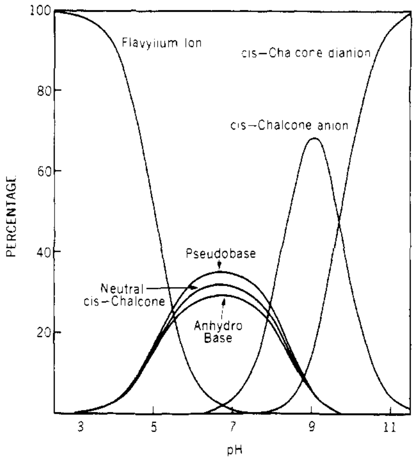


Figure 5. Variation with pH of the species at equilibrium in the hydration of the 4′-hydroxyflavylium ion.

Table II. Rate Constants and Equilibrium Constants for the Transformations of 4-Substituted Flavylium Ions

constant	4′-HO	method of determination (present work)	4′-MeO[12]
pK_5^a	5.53	initial spectra transformation (i)	
pK_1^a	5.45	$K_5^a \times$ B2/AB (Table I)	4.47
k_{-1}^{H}, M^{-1} s^{-1}	2.5×10^4	reacidification (eq 4)	1.38×10^4
k_1^{W}, s^{-1}	0.089	$k_{-1}^{\text{H}}K_1^a$	0.47
K_2	0.9	eq 6	0.5
k_{-2}^{H}, M^{-1} s^{-1}	73	reacidification (eq 5)	39
k_2^{H}, M^{-1} s^{-1}	66	$k_{-2}^{\text{H}}K_2$	20
k_{-2}^{W}, s^{-1}	0.26	reacidification (eq 5)	0.46
k_2^{W}, s^{-1}	0.23	$k_{-2}^{\text{W}}K_2$	0.23
pK_{cC}^a	7.9_3	eq 6	
p$K_{cC^-}^a$	9.7_7	eq 11	9.0_3
k_6^{OH}, M^{-1} s^{-1}	148	$k_{\text{dis}}^{\text{OH}}$ (eq 12)	

No kinetic ambiguity can exist for the hydroxide ion reaction. This must represent hydroxide ion adding directly to the anhydro base, with $k_{\text{dis}}^{\text{OH}} = k_6^{\text{OH}}$. Our observation here that anhydro base can directly convert to pseudobase contrasts with the suggestion of Brouillard and Dubois[9] that only flavylium ion can undertake such a reaction. The latter proposal, however, is based on a study carried out in relatively acidic solutions, where our results also suggest the involvement of flavylium ion, not anhydro base. We would suggest that either species can be involved, depending on the pH.

Kinetic uncertainty does arise with the pH-independent process of eq 12, which is important over a short range of acidity near pH 8. This can represent addition of water to anhydro base or addition of hydroxide ion to flavylium ion. These two possibilities cannot be distinguished on a simple kinetic basis. Estimates of k_6^{W} and k_1^{OH} can be made on the basis that with the 4′-methoxyflavylium ion

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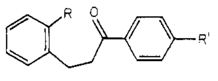
[16] For AB $(k_{\text{dis}}) \rightleftharpoons (k_{\text{for}})$ B2 $\rightleftharpoons$ cC $\rightleftharpoons$ cC$^-$ $\rightleftharpoons$ cC^{2-}, $k_{\text{obsd}} = k_{\text{dis}} + k_{\text{for}}f_{\text{B2}}$, where $f_{\text{B2}} = [\text{B2}]/([\text{B2}] + [\text{cC}] + [\text{cC}^-] + [\text{cC}^{2-}])$ and $k_{\text{dis}}/k_{\text{for}} = k_1^a/K_5^a$.

Table III. Rate Constants (s^{-1}) for Isomerization of *cis*-Chalcones

	$R' = H$[12]	MeO[12]	HO	O^-
R = OH	4.1×10^{-4}	5.8×10^{-5}	3.7×10^{-5} (k_3)	1×10^{-6} (k_3')
$R = O^-$	2.6×10^{-4}	4.6×10^{-5}		5×10^{-7} (k_3'')

the ratio of the rate constants for hydroxide ion addition and water addition to the 2-position is 2.5×10^5. In the present case the rate constant for hydroxide ion addition to the anhydro base is equal to $k_{\mathrm{dis}}^{\mathrm{OH}}$, and if the 2.5×10^5 ratio of reactivities is assumed, k_6^{W} is estimated as 0.0006 s^{-1}, quite close to the observed $k_{\mathrm{dis}}^{\mathrm{W}}$ of 0.0007 s^{-1}. The rate constant for water addition to the flavylium ion is also known; the assumption of the same reactivity difference leads to a value of k_1^{OH} of 2×10^4 M^{-1} s^{-1} and a value of $k_1^{\mathrm{OH}}K_{\mathrm{W}}/K_5^{\mathrm{a}}$ of 0.000 06 s^{-1}. The latter represents the observed constant as it appears in eq 14 and is an order of magnitude smaller. We suggest therefore that water addition to the anhydro base is probably the more important process.

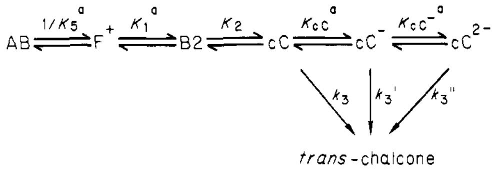
Rate and equilibrium constants determined up to this point in our analysis are summarized in Table II, where they are compared with the same constants obtained with the 4′-methoxyflavylium ion. This comparison reveals that except for the added complication due to the anhydro base, the 4′-hydroxy system behaves similarly. The hydroxy substituent does stabilize the flavylium ion to a somewhat greater extent (see pK_1^{a} values), but this is not unexpected since it is more electron donating.

Transformation iii. Following transformation ii a slow further reaction occurs, resulting in the quantitative formation of *trans*-2,4′-dihydroxychalcone, a species identified by authentic synthesis. This reaction is irreversible, flavylium ion not being regenerated from the *trans*-chalcone in acid. The *trans*-chalcone-forming process occurs at all pHs above 4.5. It may be occurring below this pH as well, but its rate is very slow. A similar process occurs with other 4′-substituted flavylium ions,[12] and we conclude that the simple model flavylium salts all seem to give *trans*-chalcone as the ultimate product of thermodynamic control in all but strongly acidic solutions.

First-order rate constants for the *trans*-chalcone formation are given in Figure 3. As in our previous study,[12] the rate profile can be interpreted in terms of a mechanism involving simple isomerization of *cis*-chalcone species, these species being in equilibrium with pseudobase, anhydro base, and flavylium ion (eq 15). The rate expression here takes the form shown in eq 16, where f_{cC}, $f_{\mathrm{cC^-}}$, and $f_{\mathrm{cC^{2-}}}$ refer

$$k_{\mathrm{obsd}}(\mathrm{tC}) = k_3 f_{\mathrm{cC}} + k_3' f_{\mathrm{cC^-}} + k_3'' f_{\mathrm{cC^{2-}}} \qquad (16)$$

to the fractions of the various forms of the *cis*-chalcone in the equilibrium attained upon completion of transformation ii. Using values for these fractions calculated on the basis of our previous analysis (see Figure 5), we calculated the rate constants k_3, k_3', and k_3'' to provide the best fit to the experimental data. These are summarized in Table III, along with values obtained for *cis*-chalcone isomerization in our previous study. The trend noted there can be seen to be continued; that is, there is a pronounced substituent effect on the isomerization rates, electron-donating substituents in the 4′-position significantly retarding the isomerization. In strongly basic solutions, for example, the *cis*-chalcone dianion of the 4′-hydroxy series is almost three orders of magnitude more stable toward isomerization than the monoanion in the parent series.



(15)

Summary

Addition of the 4′-hydroxyflavylium ion to neutral and base solutions results in three successive transformations.

Transformation i is a very fast deprotonation of the hydroxy group, producing a highly colored anhydro base. This process is a typical proton transfer in that in its thermodynamically protonation-favored direction, reaction occurs near the diffusion limit.

Transformation ii follows this initial deprotonation, with half-lives in the pH 7–10 region ranging from 10 s to 10 min. A complex equilibrium mixture results, consisting of a pseudobase derived by addition of water to the 2-position of the flavylium ion, a ring opened *cis*-chalcone, and some residual anhydro base. The three neutral forms of these species are of about equal stability, an equilibrium mixture consisting of 37% pseudobase, 33% *cis*-chalcone, and 30% anhydro base. This equilibrium is displaced toward the chalcone in base, because of the ionization of its phenolic hydroxyl groups. A solution at pH 12, for example, would consist only of the dianion of this chalcone.

Mechanistically, transformation ii involves the conversion of the anhydro base to the pseudobase followed by rapid equilibration of this species with the chalcone. An acid-catalyzed reaction is seen at pH <8, representing water addition to the flavylium ion which is in equilibrium with the anhydro base. A hydroxide ion reaction is seen at pH >8.5, representing hydroxide ion directly adding to the anhydro base. A pH-independent process also occurs between these limits, probably representing the addition of water to the anhydro base.

Transformation iii occurs at a much slower rate with typical half-lives being 10 h at pH 7 and 400 h at pH 12. This process involves the isomerization of the *cis*-chalcone species present upon completion of ii, resulting in the irreversible formation of *trans*-2,4′-dihydroxychalcone. The latter is formed quantitatively, being the ultimate product of thermodynamic control in all solutions above pH 4.5.

Experimental Section

4′-Hydroxyflavylium perchlorate was synthesized by the method of Michaelidis and Wizinger[17] and purified by recrystallization from 20% perchloric acid. *trans*-2,4′-Dihydroxychalcone was prepared by the base condensation of salicylaldehyde and 4-hydroxyacetophenone, the trans geometry being verified by the 18-Hz vinylic coupling constant. The production of the *trans*-chalcone as the ultimate product of thermodynamic control of hydration of the flavylium ion was verified by comparison with the UV spectrum of the authentic sample. (The *trans*-chalcone has λ_{max} at 350 nm.)

Temperature-jump experiments were carried out by using a Messanlangen Studiengesemschaft Gottingen T-jump spectrometer which was operated under the following conditions: capacitor of 0.05 μF, rise time of 5 μs, discharge voltage of 19 kV, microcell of 0.44-mL heating volume and optical path of 7 mm, bath tem-

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[17] Michaelidis, C.; Wizinger, R. *Helv. Chim. Acta* **1951**, *34*, 1761.

3736 *J. Org. Chem.* **1982**, *47*, 3736-3743

perature of 19.0 °C with a jump of 4.1 °C. The chemical relaxation which occurred after a sudden temperature rise was followed at 500 nm by displaying the photomultiplier output on a Tektronix 549 storage oscilloscope. Relaxation curves were photographed, and the developed negatives traced on a computerized digitizer to calculate relaxation times. At least four determinations of relaxation time were measured for each solution.

All other kinetic and spectroscopic techniques were essentially the same as those described previously.[12] The spectral determination of the flavylium ion–anhydro base equilibrium position (pK_5^a, curve A of Figure 2) was carried out by placing a stock solution (1×10^{-4} M) of the ion in 0.1 M HCl in one syringe of a stopped-flow apparatus and various buffer solutions also containing 0.1 M NaOH in the other syringe. The absorbance value at 500 nm obtained on mixing (5–10 ms) was recorded. Curves B and C of Figure 2 were obtained by recording the absorbance at 500 and 440 nm, respectively, at a time corresponding to 6–8 half-lives of transformation ii (see Figure 3) after adjustment of the pH of the stock flavylium ion solution in 0.1 M HCl. Reacidification experiments were carried out by adding the stock acid solution to a dilute buffer solution also containing 0.1 M NaOH and, after a time corresponding to 6–8 half-lives of transformation ii, by mixing this in the stopped-flow apparatus with an appropriate HCl solution. Rate constants for transformation ii (Figure 3) were obtained by addition of the stock acid solution to an appropriate buffer, observing the decrease in absorbance at 500 nm associated with anhydro base disappearance. Rate constants for transformation iii were obtained at pH <9 by following at 500 nm the further disappearance of anhydro base and at pH >9 by following at 350 nm the appearance of *trans*-chalcone. In all experiments exposure to ambient light was kept at a minimum. The cis → trans isomerization is greatly accelerated even by room light.

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Registry No. F^+, 15896-53-4; AB, 15896-55-6; BZ, 82522-50-7; cC, 82522-51-8; tC, 82522-52-9; cC^-, 82522-53-0; BZ^-, 82522-54-1.

Frontier-Controlled Pericyclic Reactions of a Powerful Electron-Attracting Fused-Ring Cyclopentadienone

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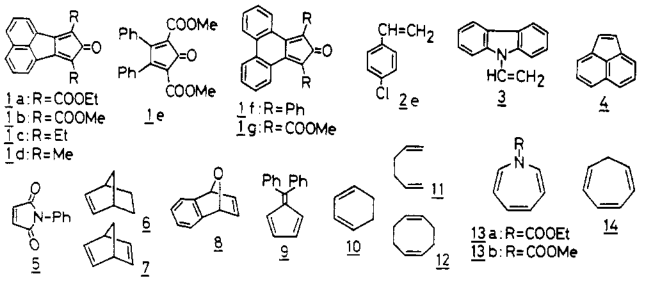
2-Oxo-1,3-bis(ethoxycarbonyl)-2*H*-cyclopenta[*i*]acenaphthylene (**1a**) reacts readily with dienophile to give [4 + 2] π cycloadducts that lose carbon monoxide spontaneously to afford tetrasubstituted 1,3-cyclohexadiene derivatives. The cycloadducts with conjugated cyclic olefins undergo facile Cope rearrangement. Adducts with nonconjugated olefins are transformed into intramolecular double Diels–Alder adducts on heating. A proposed pathway for the pericyclic reaction of **1a** with cycloheptatriene is supported by an X-ray crystallographic study of the structure of the syn-endo [2 + 4] π cycloadduct. The cycloaddition reactions of **1a** are discussed in terms of frontier molecular orbital (FMO) theory. Molecular mechanics calculations indicate that strain release in the norbornen-7-one system fused to the acenaphthylene ring is important in the decarbonylation reaction and the Cope rearrangement of the primary Diels–Alder adducts of **1a**.

Interest in the chemistry of cycloaddition has led to a continuing search for new reactive components that can be used in carbon skeleton construction. Previously, we have studied pericyclic reactions of cyclopentadienones, such as 2,5-bis(methoxycarbonyl)-3,4-diphenylcyclopentadienone (**1e**)[1] and phencyclone (**1f**),[2] with cyclic unsaturated compounds (Chart I). We have recently found that 2-oxo-1,3-bis(ethoxycarbonyl)-2*H*-cyclopenta[*i*]acenaphthylene (**1a**)[3a] undergoes cycloaddition to cyclooctatetraene to give an endo [4 + 6] π cycloadduct,[2c] which is the first example of an isolable cycloadduct derived from cyclooctatetraene. There are few reports of cycloaddition reactions of acecyclone derivatives such as **1a–d**, except for the synthetic interest[3b] in polycyclic aromatic hydrocarbons with the acenaphthylene skeleton. We here report on some cycloadditions of **1a**, discussed in terms of frontier molecular orbital (FMO) theory,[4] based on kinetics, MO calculations, force-field calculations, and X-ray crystallographic data.

Chart I



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(1) (a) Harano, K.; Yasuda, M.; Ban, T.; Kanematsu, K. *J. Org. Chem.* **1980**, *45*, 4455–4462. (b) Mori, M.; Hayamizu, A.; Kanematsu, K. *J. Chem. Soc., Perkin Trans 1* **1981**, 1259–1272. (c) Harano, K.; Ban, T.; Yasuda, M.; Kanematsu, K. *J. Am. Chem. Soc.* **1981**, *103*, 2310–2317.

(2) (a) Yasuda, M.; Harano, K.; Kanematsu, K. *J. Org. Chem.* **1980**, *45*, 659–664. (b) *Ibid.* **1980**, *45*, 2368–2372. (c) *J. Am. Chem. Soc.* **1981**, *103*, 3120–3126. (d) *J. Org. Chem.* **1981**, *46*, 3836–3841.

(3) (a) Allen, C. H. F.; Allan, J. V. *J. Org. Chem.* **1952**, *17*, 845–854. (b) Fray, G. I.; Geen, G. R.; Mackenzie, K.; Williams-Smith, D. L. *Tetrahedron* **1979**, *35*, 1173–1175. Atkins, R. J.; Fray, G. I. *Ibid.* **1979**, *35*, 1177–1181.

(4) (a) Fujimoto, H.; Fukui, K. "Chemical Reactivity and Reactions"; Wiley: New York, 1974. (b) Houk, K. N. "Pericyclic Reactions"; Academic Press: New York, 1977; pp 248–255.