Stereochemistry of the Photoinduced and Michael Addition of Methanol to Seven- and Eight-Membered 2-Cycloalkenones

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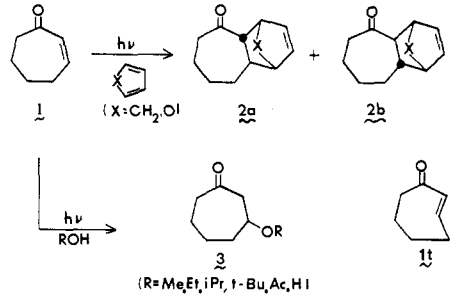
Abstract: The stereochemistry of the photoinduced addition of methanol to 2-cycloheptenone (**1**), 2-cyclooctenone (**11**), and 2,3-benzo-2,6-cycloheptadienone (**4**) was studied using CH_3OD. In each case, the methoxyl and deuterium in the resulting 3-methoxycycloalkanones (**3d**, **12d**, and **6d**, respectively) were trans. A two-step mechanism is proposed to explain the observed results: (a) photoisomerization of the cis cycloalkenone to a trans cycloalkenone, and (b) regiospecific and stereospecific nucleophilic syn addition of methanol to the highly polarized, strained trans double bond. The addition exhibits a large positive isotope effect (4.3 for **1**, and 5.7 for **11**, at 29 °C). The base-catalyzed (0.01 N CH_3ONa) Michael addition of CH_3OD to the cis enones **1**, **4**, and **11** proceeds in a stereospecific trans manner. Base-catalyzed deuterium exchange in the 3-methoxycycloalkanones **3**, **6**, and **12** at the methylene carbon between the carbonyl group and the methoxyl-bearing carbon is also highly stereoselective, exchange being much faster for the proton trans to the methoxyl than for the corresponding cis proton. These results may be explained by a reversible base-catalyzed elimination and addition of methanol, via a transition state in which the methoxyl and hydrogen undergoing elimination or addition are in an antiperiplanar arrangement. In contrast, the acid-catalyzed addition of CH_3OD to 2-cycloheptenone was found to be stereorandom, the enol intermediate being protonated approximately equally at each face.

Irradiation of seven- and eight-membered-ring 2-cycloalkenones results in isomerization to the corresponding trans isomers. These highly strained, reactive photoproducts have been trapped with dienes or nucleophiles.[1-4] For example, irradiation of 2-cycloheptenone (**1**) in the presence of cyclo-



pentadiene or furan gave the trans adducts **2**,[1] whereas alcohols and other nucleophiles gave Michael-type adducts **3**.[3] The *trans*-2-cycloheptenone intermediate (**1t**) in these reactions has been identified in a rigid glass at low temperature[1] and more recently by flash photolysis.[5]

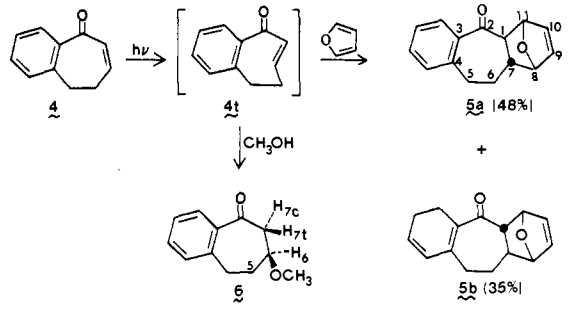
With 2-cyclooctenone, Noyori[3b,4] clearly demonstrated that alcohol addition is a dark reaction of the trans isomer. Evidence that such additions involve ground state intermediates even with the more strained seven-membered-ring enones (i.e., **1t**) was obtained with the stronger nucleophile, diethylamine.[3b] Similar photoinduced polar additions have been reported for 2,6-cycloheptadienone,[6] 2,4-cyclooctadienone,[7] 2,6-cyclooctadienone,[7a,8] 2,7-cyclooctadienone,[9] 2-cyclononenone,[3b] and a variety of other α,β-unsaturated ketones.[10]

By using ROD in place of ROH, we have studied and report here the stereochemistry of photoinduced nucleophilic additions exemplified by **1** → **3**.[11] For comparison, we also studied the stereochemistry of the base-catalyzed (and in one instance, the acid-catalyzed) Michael addition of methanol to the same enones. Finally, we studied the stereochemistry of deuterium exchange in the resulting 3-methoxycycloalkanones (e.g., **3**). The high degree of stereospecificity observed has important mechanistic implications.

Results

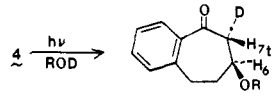
Photoinduced Additions to 2,3-Benzo-2,6-cycloheptadienone (4). Enone **4** was selected for initial study as a consequence of our interest in the photodimerization and other photoreactions of benzocycloheptadienones.[12] As it turned out, the choice was fortunate because of the simplicity and ease with which the NMR spectrum of the addition product **6** could be interpreted.[13]

Irradiation of **4**[14] in furan (Uranium glass filter, >350 nm) gave the crystalline trans adducts **5a** and **5b** in 83% yield. Their



stereochemistry was established from a careful analysis of their NMR spectra.[15] From this result we infer that **4** photoisomerizes to **4t** which is trapped by furan.[16]

Irradiation of **4** in methanol gave the methyl ether **6** in high yield. No addition occurred in the dark. The NMR spectrum of **6** showed that the trans and cis coupling constants between H_6 and H_{7t} or H_{7c} were different (7.5 and 5.0 Hz, respectively, in $CDCl_3$, and 7.0 and 4.0 Hz with added $Eu(fod)_3$)[13] and could be used to assign stereochemistry.[17] Consequently **4** was irradiated in CH_3OD. In the resulting **6d**, the only observable



H_6,H_7 coupling constant was 8 Hz,[18] clearly establishing that the protons were trans to one another. NMR spectra of the crude photolysis product with added $Eu(fod)_3$ gave little evidence for the formation of the other isomer. The photoinduced addition of AcOD to **4** gave **7d** in an analogous manner.[11]

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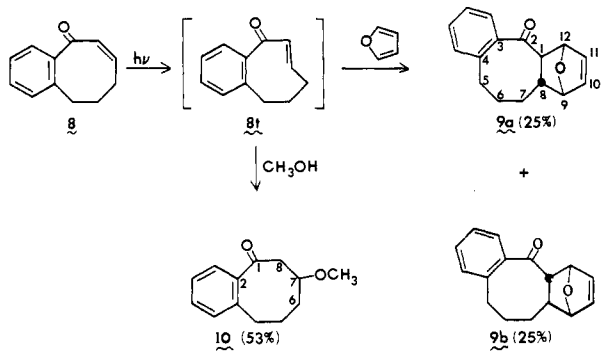
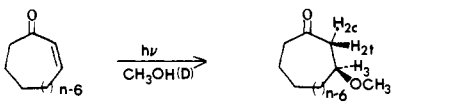
Photoinduced Additions to 2,3-Benzo-2,7-cyclooctadienone (8). Irradiation of **8** in furan gave the trans adducts **9a** and **9b**, and in methanol **10** was obtained. These reactions presumably involve the trans intermediate **8t**. Unfortunately, there was no difference between the coupling constants of H_7 with H_{8t} or



H_{8c} in **10**; indeed, H_7 appeared as a quintet, being coupled almost identically with all four of its neighbors (J = 6.5 Hz). Furthermore, shift reagent did not separate the signals well enough to identify H_{8t} and H_{8c}. Consequently, it was not possible to study the stereochemistry of methanol addition to **8**.

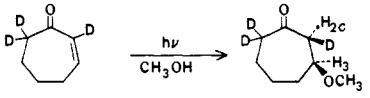
Photoinduced Addition of CH_3OD to 2-Cycloheptenone and 2-Cyclooctenone. Irradiation of **1** and **11** in CH_3OD were carried out as described by Noyori[3b,4] for ordinary methanol.



1 (n=7)
11 (n=8)
3 (n=7), 3d (H2c=D)
12 (n=8), 12d (H2c=D)

In each case a single product was obtained, with the methoxyl group and deuterium trans to one another. There was no dark reaction.

The stereochemical assignments of **3d** and **12d** are based on their NMR spectra. In **3**, the coupling constants of H_3 with the trans and cis protons H_{2t} and H_{2c} were quite different, being 6.5 and 4.0 Hz, respectively, in $CDCl_3$ and 7.8 and 2.0 Hz in the Eu(fod)$_3$-shifted spectrum.[13] The product obtained by irradiating **1** in CH_3OD showed only one such coupling, J = 8.0 Hz[18] (H_{2t}, H_3), consistent only with structure **3d**. As a check, we prepared **13** and irradiated it in ordinary methanol. The



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NMR spectrum was consistent with the reverse stereochemistry (shown in **14**), with protons H_3 and H_2 cis to one another.

It was not possible to use the NMR spectrum of **12** directly to assign stereochemistry, since the coupling constants for H_3 with trans and cis H_2 were identical (7.0 Hz in $CDCl_3$). However in the Eu(fod)$_3$-shifted spectrum of **12**, these coupling constants changed to 8.0 and 3.0 Hz, respectively.[13] In the product from the irradiation of **11** in CH_3OD the observed J_{H_2,H_3} was 10 Hz[18] (8 Hz in the Eu(fod)$_3$-shifted spectrum), consistent only with trans geometry for the protons (i.e., **12d**).

To summarize, the stereochemistry of the photoinduced addition of CH_3OD to **1**, **4**, and **11** is identical; in each case, addition is stereospecific with the methoxyl and deuterium being trans in the addition product.

Isotope Effects. Cycloalkenones **1** and **11** were irradiated in mixtures of CH_3OH/CH_3OD to determine the magnitude of the isotope effect for the photoinduced addition. Preliminary experiments with a 1:1 mol ratio of CH_3OH/CH_3OD gave almost entirely the protio product, showing that the isotope effect was substantial. To increase accuracy, ~1:6 mol ratio of CH_3OH/CH_3OD was used. Calibrated low voltage mass spectra enabled us to determine the ratio of **3**/**3d** and **12**/**12d** produced, and the calculated isotope effects at several temperatures are given in Table I.

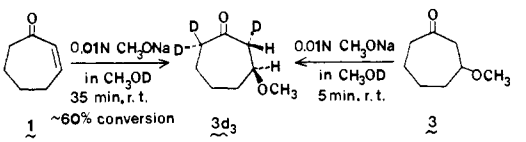
Table I. Isotope Effects for the Photoinduced Addition of Methanol to **1** and **11** (CH_3OH/CH_3OD)

Temp, °C	1[a]	11[a]	11[b]
8	4.9	6.7	6.9
18.5	4.4	6.2	6.6
29	4.3	5.7	6.2

[a] By mass spectrometric analysis. [b] By NMR.

It was also possible to measure the ratio of **12**/**12d** by an NMR method. Addition of sufficient Eu(fod)$_3$ to mixtures of **12** and **12d** resulted in two distinct methoxyl peaks, with that for **12d** being at lower field. This is a consequence of the dissociation constant for the substrate-shift reagent complex being less for the deuterio compound than for its protio analogue.[19] Measurement of the two methoxyl peak heights allowed the isotope effect to be calculated, and the results (Table I) are in reasonable agreement with the mass spectrometric results. The separation of the methoxyl peaks also was observable with **3** and **3d**, but insufficient to be analytically useful.

Base-Catalyzed Michael Addition of CH_3OD. For mechanistic reasons (vide infra) it was desirable to examine the stereochemistry of the base-catalyzed Michael addition of methanol to 2-cycloalkenones. Fortunately, the base-catalyzed addition of methanol to **1** and **11** is known to have a highly favorable equilibrium constant (>100).[20] Consequently it was possible to study the stereochemistry of this addition using CH_3OD with very dilute base and short reaction times. For example, allowing an ~0.1 N solution of **1** in CH_3OD which was also 0.01 N in CH_3ONa to stand at room temperature for 35 min gave a 60% conversion to 3-methoxycycloheptanone labeled as shown (**3**-d_3).[21] No addition whatever was detect-



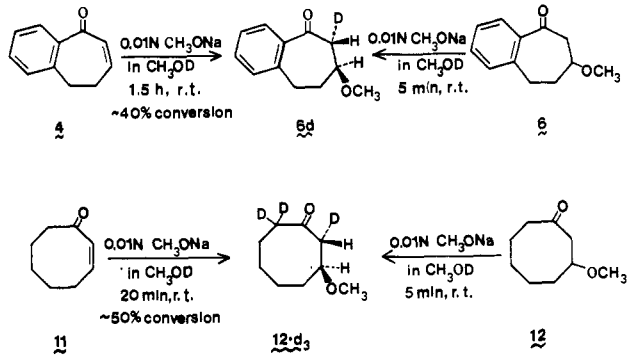
1 ~60% conversion 3d3 3

able if the 0.01 N base was omitted. It is not known whether exchange at C_7 occurs before or after methanol addition.

Since the addition product 3-methoxycycloheptanone could undergo base-catalyzed deuterium exchange, that reaction was studied independently. Brief (5 min) treatment of **3** (~0.1 N) with 0.01 N CH_3ONa in CH_3OD at room temperature resulted in rapid exchange of three of the four α protons: exchange of the C_2 proton cis to the methoxyl was slow. Longer reaction times (2 h) resulted eventually in exchange of the remaining C_2 proton. If the base was omitted, no detectable exchange occurred.

Similar results were obtained for the base-catalyzed addition of CH_3OD to **4**[22] and **11**, and the base-catalyzed exchange of **6** and **12**.

Acid-Catalyzed Addition of CH_3OD to 2-Cycloheptenone. For comparison with the base-catalyzed results, the acid-catalyzed Michael addition of CH_3OD to **1** was briefly studied. A CH_3OD solution 0.18 N in **1** and 0.01 N in D_2SO_4 gave, after standing for 20 min at room temperature a 53% yield of the adduct **3**. In contrast with the base-catalyzed reaction (vide supra), NMR analysis showed that the deuterium at C_2 was

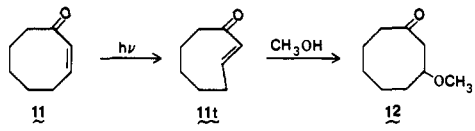


equally distributed cis and trans to the methoxyl at C_3.

In the converse experiment, treatment of **3** with 0.10 N D_2SO_4 in CH_3OD for as long as 20 min at room temperature resulted in only a modest amount of exchange, and this occurred predominantly at C_7 rather than C_2.

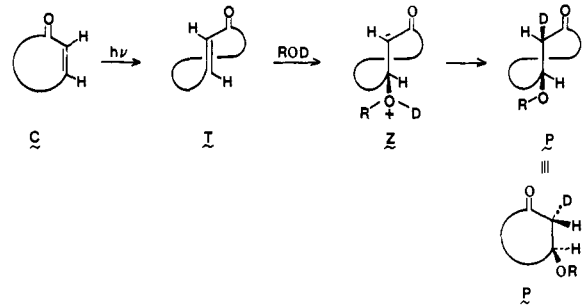
Discussion

The photoinduced addition of methanol to 2-cyclooctenone involves two discrete steps. The first is photoisomerization of **11** to the trans isomer **11t,** and the second is a thermal reaction of the ground-state trans enone with methanol. Thus, irradiation of **11** in 2-methyltetrahydrofuran at −78 °C, followed by removal of the light source and subsequent addition of methanol and warming, gave the adduct **12.**[3b] Polar addition to a photoexcited state of the enone was shown to be insignificant.[3b]

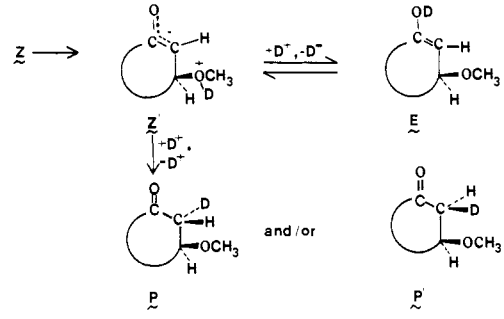


The two-step mechanism is applicable with somewhat less certainty to the seven-membered-ring enones. Experiments such as those just described were only partially successful with 2-cycloheptenone (**1**). When **1** was irradiated in EPA at −196 °C, followed by removal of the light source, subsequent addition of methanol at −78 °C, and gradual warming to room temperature, only cyclo dimers were formed.[3b] No methanol adduct could be detected. However, with the more efficient nucleophile diethylamine, the corresponding Michael-type amine adduct could be isolated in modest yield.[3b] Apparently the trans intermediate **1t** is formed, but is so much more strained and reactive than **11t** that on warming it dimerizes more rapidly than it reacts with the relatively weak nucleophile methanol. The stronger nucleophile diethylamine can, however, compete with the dimerization. Thus it seems likely that here too the photoinduced addition involves two discrete steps.[23] Furthermore, the second step involves *nucleophilic* attack on the trans enone, since it proceeds faster with diethylamine than with methanol. This result argues strongly *against* a mechanism in which the strained trans double bond is first protonated by the methanol (i.e., electrophilic attack), followed by capture of the resulting carbocation by the nucleophilic solvent.[5] Such a mechanism, which is reasonable for the photoinduced addition of protic solvents to six- and seven-membered-ring alkenes,[24] cannot be extended to the cycloalkenones, as it is inconsistent with the observation that diethylamine (a weak acid) is a more effective addend than is methanol (a stronger acid).

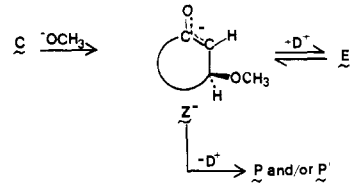
Our stereochemical results for the photo-induced addition of CH_3OD to **1, 4,** and **11** can be explained by a regio- and stereospecific syn addition to a photochemically produced trans intermediate T. In the resulting product P, the components of the addend (RO and D) are trans to one another. The double bond in the intermediate T is less conjugated with the carbonyl group than in the starting cis ketone C,[1,2,3b] but is probably more polarizable because of strain, and is consequently strongly polarized inductively by the electron-withdrawing carbonyl group. Therefore nucleophiles attack regiospecifically at C_3 to give initially the dipolar intermediate Z. Deuterium transfer must occur to the same, unblocked face of the double bond, to account for the observed stereochemistry. This transfer could occur intramolecularly, in which case the conversion T → Z → P can be regarded as a synchronous four-centered process, or the transfer could come from another solvent molecule.[25] The large observed isotope effects (Table I) are consistent with proton transfer being important in the rate-determining step. The larger isotope effect for the eight-membered-ring enone than for the seven-membered-ring enone can be rationalized, since the intermediate in the former case is less strained, less reactive, and therefore presumably more discriminating between protium and deuterium.[26] The twisted geometry of Z permits only poor overlap between the filled, "anionic" orbital at C_2 and the π orbital of the carbonyl group. Protonation at C_2 may therefore occur extremely rapidly. In this event, the only possible product is P, since one face of C_2 is blocked from protonation by the methylene chain.



Another alternative is that Z relaxes conformationally to permit delocalization of charge to the carbonyl oxygen, giving Z′. Protonation (deuteronation) can then occur at either face of C_2 to give P and/or P′, or on oxygen to give the enol E which can subsequently ketonize.[27] To account for the observed stereochemistry (i.e., the formation of P, not P′) one would have to assume that for some reason Z′ is protonated exclusively trans to the methoxyl group.

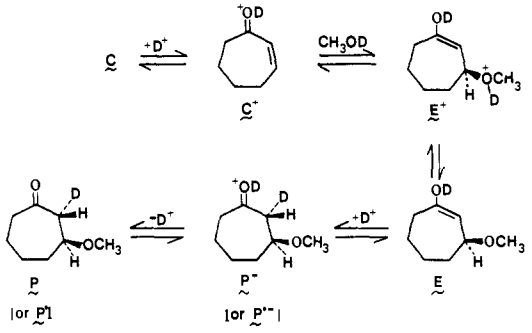


To test this possibility, we studied the stereochemistry of the base-catalyzed Michael addition of methanol to the cis cycloalkenones **1, 4,** and **11.** The first intermediate in these reactions should be very similar to Z′, but an anion rather than a dipolar ion (i.e., Z^-). This anion could add a deuteron at oxygen to give E, or at carbon to give in principle P and/or P′. In fact the experimental results in every case were consistent



with highly selective protonation trans to the methoxyl group (that is, **1** → **3**-d_3, **4** → **6d** and **11** → **12**-d_3). Consistent with this result, the 3-methoxycycloalkanones **3, 6,** and **12,** when subjected to base-catalyzed deuterium exchange, were selectively deprotonated and protonated at the C_2 methylene proton trans to the methoxyl group (in the case of **3** and **12,** exchange of both methylene protons at C_7 or C_8, respectively, also occurred rapidly). Consequently we cannot, on the basis of stereospecificity alone, rule out Z′ as a possible intermediate in the photochemical reaction.

We also examined briefly the acid-catalyzed addition of methanol to **1** and deuterium exchange of **3.** In this case, the scheme for addition and exchange should involve the protonated intermediates C^+, E^+, and P^+ (or P'^+). The experimental

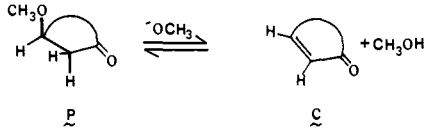


results were that the addition is *not* stereospecific; the product was an ~1:1 mixture of P and P′. We conclude that the protonation of E is not highly stereoselective. The acid-catalyzed deuterium exchange of **3** was slow and occurred predominantly at C_7; we could not draw any conclusion about its stereoselectivity at C_2.

To summarize, the photoinduced and the base-catalyzed Michael addition of methanol to seven- and eight-membered-ring cycloalkenones proceeds with the same overall stereochemical consequence; in each case, the methoxyl group and the proton of the methanol end up trans to one another in the resulting 3-methoxycycloalkanone. Nevertheless the reactions must proceed by different mechanisms. The photoinduced addition involves two steps: (a) photoisomerization to the highly strained, trans cycloalkenone, and (b) nucleophilic regiospecific and stereospecific syn addition of methanol to the highly polarized double bond of the trans enone. The large deuterium isotope effect and the way the isotope effect changes with ring size suggests that the process T → Z → P is essentially synchronous. The base-catalyzed Michael reaction involves a regiospecific anti addition of methanol to the cis enone.

We must now rationalize the high stereoselectivity of the base-catalyzed Michael addition to the cis cycloalkenones and of the base-catalyzed exchange of the 3-methoxycycloalkanones, with the lack of stereoselectivity in the corresponding acid-catalyzed reactions. The acid-catalyzed addition and exchange must involve, as the step which determines stereochemistry, the protonation of E or deprotonation of P^+. These reactions do not occur with any appreciable stereoselectivity. If these processes are stereorandom, it is difficult to see why the protonation of Z^- or deprotonation of P should be stereospecific (the structures of E and Z^- and of P^+ and P are very similar).[28] Yet this is precisely what we would be forced to postulate, to explain the experimentally observed sterospecificity of the base-catalyzed reactions.

One way out of the dilemma is to avoid the intermediates. The base-catalyzed exchange at C_2 in the 3-methoxycycloalkanones may occur to a considerable extent by a reversible base-catalyzed elimination and addition of methanol. The preferred geometry for such an E2-type elimination should have the departing methoxyl and hydrogen in an antiperiplanar arrangement, and of course the addition would simply be the microscopic reverse of this process. This mechanism accounts



nicely for the observed results, in which methanol adds in a trans manner to the cis double bond in C, and the methylene proton at C_2 that is trans to the C_3 methoxyl undergoes selective exchange. The extent to which exchange by the elimination–addition mechanism competes with exchange by the more conventional enolate anion mechanism undoubtedly depends on the particular structural features of the system, and studies designed to evaluate the factors involved are being undertaken.[29]

Experimental Section

2,3-Benzo-2,6-cycloheptadienone (4). This ketone was prepared by the following modification of a published procedure.[14] A solution of benzsuberone (15 g, 0.093 mol) in 100 mL of ether was brominated at 0 °C with 1 equiv of bromine in 30 mL of chloroform–ether (1:2). After a faint bromine color persisted, the solution was stirred for 1 h. Ice and sodium bicarbonate were added, and the product was extracted with ether and dried (Na_2SO_4) and the solvent was evaporated. The resulting crude α-bromobenzsuberone was refluxed under nitrogen for 3 h with freshly fused lithium chloride (10 g) in dry dimethylformamide (350 mL). Most of the solvent was removed at 1 Torr and the residue was poured into water and extracted with ether. After solvent removal, the dark oily residue was chromatographed on silica gel (100 g, Merck EM 60) with dichloromethane–hexane (1:1). The partially purified product was rechromatographed, this time with an eluent ratio of 1:5. The yield of pure **4** was 5.2 g (35%): IR (neat) $\nu_{C=O}$ 1650 cm^{-1} (sh, 1625 cm^{-1}); UV λ_{max} (cyclohexane) 293 nm (ε 700, sh), 266 (5530), 229 (5820); NMR (CCl_4) δ 2.3–2.7 (m, 2 H, H_5), 2.8–3.1 (m, 2 H, H_4), 6.01 (dt, 1 H, J = 12, 1.5 Hz, H_7), 6.50 (dt, 1 H, J = 12, 4.5 Hz, H_6), 6.9–7.6 (m, 4 H, arom); mass spectrum *m/e* (rel intensity) 158 (33), 130 (100), 129 (76), 128 (45), 104 (49). The compound is sensitive, must be refrigerated if stored, and darkens on standing. It can be distilled (Kugelrohr) at 140–150 °C (0.5 Torr), but with some decomposition. An analytical sample was obtained by GLC (6 ft × 0.25 in. column, 15% SE-30 on Chromosorb W, 80–100 mesh, 180 °C). Anal.[30] Calcd for $C_{11}H_{10}O$: C, 83.51; H, 6.37. Found: C, 83.39; H, 6.47.

Irradiation of 4 in Furan. A nitrogen-flushed solution containing 395 mg (2.5 mmol) of **4** in 50 mL of furan was irradiated with a Hanovia Type L 450-W lamp through a Uranium glass filter for 8 h. After removal of the solvent in vacuo, the residue was chromatographed on 55 g silica gel (Merck EM 60) with dichloromethane–ethyl acetate (49:1). The separation was very difficult. Fraction A (104 mg) was enriched **5a,** fraction B (330 mg) was a 1:1 mixture of **5a** and **5b,** (NMR) and fraction C (32 mg) was enriched **5b.** The calculated yields (NMR) were 48 and 35% for **5a** and **5b,** respectively. Partial separation could also be achieved by fractional crystallization from hexane, **5a** being less soluble than **5b.** In this way, enriched fractions A and C gave pure **5a,** mp 126–127 °C, and pure **5b,** mp 128–130 °C.

5a: IR (Nujol) $\nu_{C=O}$ 1675 cm^{-1}; NMR ($CDCl_3$) δ 1.11–2.4 (m, 4H, H_1, H_6, and H_7),[31] 2.8–3.1 (m, 2 H, H_5), 4.81 (dd, 1 H, J = 3, 1.5 Hz, H_8), 5.40 (d, 1 H, J = 1.5 Hz, H_{11}, 6.26 (dd, 1 H, J = 5.5, 1.5 Hz, H_9), 6.55 (dd, 1 H, J = 5.5, 1.5 Hz, H_{10}), 7.05–7.97 (m, 4 H, arom); the LIS relative slopes, using Eu(fod)$_3$, were 2.2, 1.1, 1.0, and 4.9 for H_8–H_{11}, respectively; mass spectrum *m/e* (rel intensity) 226 (12), 158 (58), 130 (77), 81 (100), 68 (54). An analytical sample was prepared by sublimation at 125–130 °C, 0.5 Torr. Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.57; H, 6.15.

5b: IR (Nujol) $\nu_{C=O}$ 1670 cm^{-1}; NMR ($CDCl_3$) δ 1.5–2.3 (m, 3 H, H_6 and H_7),[31] 3.17 (dd, 1 H, J = 6, 4 Hz, H_1), 2.9–3.2 (m, 2 H, H_5), 4.58 (d, 1 H, J = 1 Hz, H_8), 5.23 (d, 1 H, J = 4 Hz, H_{11}), 6.35 (br s, 2 H, H_9 and H_{10}), 7.00–7.88 (m, 4 H, arom); the LIS relative slopes, using Eu(fod)$_3$, were 2.1, 2.4, 1.0, 1.0, and 2.2 for H_1 and H_8–H_{11}) respectively; mass spectrum *m/e* (rel intensity) 226 (8), 158 (25), 130 (55), 81 (100), 68 (70). An analytical sample was prepared by sublimation at 120–125 °C, 0.4 Torr. Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.63; H, 6.24.

Irradiations in Methanol. All irradiations were carried out with ntirogen-flushed solutions using a Hanovia Type L 450-W lamp through Pyrex (except **4**, which was irradiated through a Uranium glass filter). Analytical grade methanol (Mallinckrodt) and 99% methanol-d_1 (Stohler or Aldrich) were used as solvents, and the reactions were monitored by GLC (5 ft × 0.25 in. column, 10% SE-30 on Chromosorb W). Conversions of 70–90% were obtained after 3–7-h irradiation. Products were obtained by solvent removal in vacuo and analyzed (NMR and/or mass spectrum) directly or after purification, either by column chromatography (**6**, silica gel, dichloromethane eluent) or GLC (**3** and **12**, 5 ft × 0.25 in. column, 6% SE-30 on Chromosorb W, 120–130 °C).

Irradiation of 4 in Methanol. Irradiation of 316 mg (2 mmol) of **4** in 30 mL of methanol for 6.5 h gave, after workup, 55 mg (17%) of recovered **4** and 232 mg (73% based on reacted **4**) of methanol adduct **6**:[32] IR (neat) $\nu_{C=O}$ 1680 cm^{-1}; NMR;[13] mass spectrum *m/e* (rel intensity) 190 (5), 158 (75), 130 (100), 129 (79), 128 (58), 115 (56). An analytical sample was prepared by GLC (5 ft × 0.25 in. column, 20% SE-30 on Chromosorb W, 210 °C). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.73; H, 7.49.

Irradiation of 4 in CH_3OD. Irradiation of 158 mg (1 mmol) of **4** in 20 mL of methanol-*d* (CH_3OD) for 7 h gave over 90% conversion to **6d** (by NMR analysis of the crude product mixture). Attempts to purify **6d** by GLC caused epimerization of the hydrogen and deuterium at C_7. Consequently, the following data were obtained on the crude product. **6d:** NMR ($CDCl_3$) δ 2.02 (q, 2 H, J = 5/] Hz, C_5 methylene), 2.70–3.15 (m, 3 H, C_7 proton and C_4 methylene), 3.28 (s, 3 H, methoxyl), 3.68 (dt, 1 H, J = 8.0, 5.0 Hz, C_6 methine), 7.0–7.8 (m, 4 H, arom) (irradiation at δ 2.02 collapsed the signal at 3.68 to a doublet, J = 8.0 Hz; addition of Eu(fod)$_3$-shift reagent permitted the C_7 proton to be separated from the C_4 methylene;[13] a $CDCl_3$ solution containing 18 mg (0.095 mmol) of **6d** and 167 mg (0.16 mmol) of Eu(fod)$_3$ showed only one C_7 proton peak, a broad doublet at δ 13.60 (J = 7 Hz) and the C_6 methine proton as a multiplet at 9.10; irradiation at δ 6.80 (C_5 methylene) collapsed the C_6 proton to a doublet, J = 7 Hz; the peak corresponding to the C_7 proton cis to the C_6 proton, which should have appeared at about δ 13.0 in the shifted spectrum, was essentially absent); mass spectrum *m/e* (rel intensity) with inlet at room temperature, 191 (40, M^+), 159 (100, $M^+ - CH_3OH$), and 158 (67, $M^+ - CH_3OD$), with inlet at 150 °C, 191 (17), 159 (100), and 158 (25).

Irradiation of 4 in Acetic Acid. Irradiation of 948 mg (6 mmol) of **4** in 100 mL of glacial acetic acid through a Uranium glass filter for 15 h gave 175 mg (18%) of recovered **4** and 675 mg (63% based on reacted **4**) of the adduct **7**. The product was purified by column chromatography on silica gel (Merck EM-60) using first hexane–dichloromethane (1:1) to elute **4** and then dichloromethane to elute **7**: IR (neat) $\nu_{C=O}$ 1735, 1680 cm^{-1}; NMR ($CDCl_3$) δ 1.95 (s, 3 H, acetyl methyl), 1.9–2.4 (m, 2 H, C_5 methylene), 2.8–3.2 (m, 4 H, C_4 and C_7 methylenes), 5.21 (quintet, 1 H, J = 6 Hz, C_6 methine), 7.0–7.8 (m, 4 H, arom) (irradiation at δ 2.25 (C_5 methylene) caused the quintet at δ 5.21 to collapse to a triplet); mass spectrum *m/e* (rel intensity) 218 (0.5), 158 (100), 130 (95). An analytical sample was prepared by GLC (5 ft × 0.25 in. column, 20% SE-30 on Chromosorb W, 180 °C; about half of the sample is recovered, the rest is converted to acetic acid and **4**). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.49; H, 6.70.

When the above irradiation was carried out in CH_3COOD, the resulting **7d** showed the following NMR changes: the peak at δ 2.8–3.2 was reduced in area to 3 H and the peak at δ 5.21 was a quartet, J = 7 Hz. At higher resolution, this peak was seen to be a doublet of triplets, J = 7.45 and 6.0, and on irradiation at δ 2.25 (C_5 methylene) it collapsed to a doublet, J = 7.5 Hz. The mass spectrum *m/e* (rel intensity) of **7d:** inlet at room temperature, 219 (<0.5, M^+), 159 (54, $M^+ - HOAc$), 158 (55, $M^+ - DOAc$), 130 (100); inlet at 150 °C, 219 (0.2), 159 (100), 158 (38); inlet at 160 °C, 219 (0.2), 159 (100), 158 (27).

2,3-Benzo-2,7-cyclooctadienone (8). To a solution of 2,3-benzo-2-cyclooctenone[33] (5.22 g, 30 mmol) in 50 mL of ether was added at 0 °C a solution of 2 mL of bromine in 5 mL of chloroform, and the mixture was stirred for 45 min. Ice and sodium bicarbonate were added, and the product was extracted with ether and dried (Na_2SO_4). The crude bromo ketone obtained on removal of the solvent was dehydrobrominated by 3-h reflux with anhydrous lithium chloride (5 g) in dimethylformamide (200 mL). Most of the solvent was removed in vacuo, and the residue was poured into water and extracted with ether. Combined ether layers were washed with water, dried (Na_2SO_4), and evaporated. The residue was purified by chromatography on 150 g of silica gel (Merck EM-60) with dichloromethane eluent followed by Kugelrohr distillation at 150–160 °C and 0.8 Torr to give 1.6 g (30%) of **8:** IR (neat) $\nu_{C=O}$ 1637 cm^{-1}; UV λ_{max} (cyclohexane) 287 nm (ϵ 1190, sh), 250 (7100, sh), 242 (8200), 214 (6150); NMR ($CDCl_3$) δ 1.58 –2.25 (m, 4 H, C_5 and C_6 methylenes), 2.80 (t, 2 H, J = 6 Hz, C_4 methylene), 6.25–6.60 (m, 2 H, vinyl), 6.90–7.65 (m, 4 H, arom); mass spectrum *m/e* (rel intensity) 172 (80), 144 (21), 131 (100), 81 (75). An analytical sample was prepared by GLC (5 ft × 0.25 in. column, 20% SE-30 on Chromosorb W, 180 °C). Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.58; H, 7.16.

Irradiation of 8 in Furan. A solution containing 258 mg (1.5 mmol) of **8** in 30 mL of furan was irradiated through Pyrex for 7 h, at which time TLC showed no remaining starting material. The solvent was removed and the residue chromatographed on 50 g of silica gel (Merck EM-60) with chloroform as eluent. A fraction was obtained (180 mg, 50%) which was shown by NMR to consist of an ~1:1 mixture of two stereoisomers. Fractional crystallization from hexane and mechanical separation gave one isomer, **9a,** in pure form, mp 111–113 °C (after sublimation at 100–110 °C and 0.1 Torr). **9a:** IR (Nujol) $\nu_{C=O}$ 1670 cm^{-1}; NMR ($CDCl_3$)[31] δ 1.0–2.3 (m, 5 H), 2.55 (d, 1 H, J = 5 Hz, H_1), 2.72–2.98 (m, 2H, C_5 methylenes), 4.67 (dd, 1 H, J = 4.5, 1.5 Hz, H_9), 5.56 (d, 1 H, J = 1.5 Hz, H_{12}), 6.34 (dd, 1 H, J = 6, 1.5 Hz, H_{10}), 6.44 (dd, 1 H, J = 6, 1.5 Hz, H_{11}), 6.95–7.7 (m, 4 H, arom); mass spectrum *m/e* (rel intensity) 240 (26), 172 (50), 144 (40), 131 (100), 115 (32), 81 (77), 68 (72). Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.05; H, 6.56.

The NMR spectrum ($CDCl_3$) of **9b** was deduced from an enriched sample:[31] δ 1.0–2.5 (m, 5 H), 2.7–3.0 (m, 2 H, C_5 methylene), 3.42 (t, 1 H, J = 4.5 Hz, H_1), 4.43 (d, 1 H, J = 1.5 Hz, H_9), 5.31 (dd, 1 H, J = 4.5, 1.5 Hz, H_{12}), 6.18 (dd, 1 H, J = 6, 1.5 Hz, H_{10}), 6.36 (dd, 1 H, J = 6, 1.5 Hz, H_{11}), 6.9–7.5 (m, 4 H, arom).

Irradiation of 8 in Methanol. A solution containing 172 mg (1 mmol) of **8** in 20 mL of methanol was irradiated through Pyrex for 26 h. Chromatography on 30 g of silica gel (Merck EM-60) with dichloromethane as eluent gave 46 mg (27%) of recovered **8** and 80 mg (53%) of methanol adduct **10:** IR (neat) 1670 cm^{-1}; NMR ($CDCl_3$)[31] δ 1.3–2.4 (m, 4 H, C_5 and C_6 methylenes), 2.9–3.25 (m, 4 H, C_4 and C_8 methylenes], 3.28 (s, 3 H, methoxyl), 3.45–3.72 (m, 1 H, C_7 methine), 6.9–7.4 (m, 3 H, arom), 7.82 (dd, 1 H, J = 7.2 Hz, arom ortho to carbonyl) (the multiplet for the C_7 methine had the approximate appearance of a quintet and was converted to a distinct triplet, J = 6.5 Hz, on irradiation at δ 1.60 (C_6 methylene)); mass spectrum *m/e* (rel intensity) 204 (19), 172 (57), 131 (100), 118 (57), 71 (76). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.44; H, 7.96.

Use of CH_3OD in place of ordinary methanol in the above irradiation afforded **10d:** mass spectrum *m/e* (rel intensity), inlet at 175 °C, 205 (37), 204 (3), 173 (45), 172 (12), 131 (100), 118 (55), 71 (57).

Irradiation of 8 in Acetic Acid. A solution containing 129 mg (0.75 mmol) of **8** in 15 mL of acetic acid was irradiated through Pyrex for 29 h. Most of the solvent was removed in vacuo and the residue (~1:2 starting material–product by NMR) was chromatographed on silica gel (Merck EM-60) using dichloromethane as eluent to give 53 mg (30%) of 7-acetoxy-2,3-benzocyclooctenone (**10**-OAc), ~85% pure, contaminated with starting material. A pure sample of **10**-OAc was obtained by GLC (5 ft × 0.25 in. column, 20% SE-30 on Chromosorb W, 200 °C). Some elimination to **8** (identified by IR) occurs during GLC. **10**-OAc: IR (neat) $\nu_{C=O}$ 1738, 1670 cm^{-1}; NMR ($CDCl_3$) δ 1.5–2.0 (m, 4 H, C_5 and C_6 methylenes), 2.01 (s, 3 H, acetyl), 2.9–3.32 (m, 4H, C_4 and C_8 methylenes), 5.12 (quintet, 1 H, J = 6 Hz, C_7 methine), 6.95–7.40 (m, 3 H, arom), 7.80 (dd, 1 H, J = 7, 2 Hz, arom ortho to the carbonyl); mass spectrum *m/e* (rel intensity) 232 (<1), 172 (80), 144 (25), 131 (100), 81 (75). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.44; H, 6.99.

Irradiation of 2-Cycloheptenone in CH_3OD. A solution of 2-cycloheptenone[34] (440 mg, 4 mmol) in 15 mL of CH_3OD was irradiated for 3 h after which addition was complete (the reaction was followed by GLC; 5 ft × 0.25 in. column, 20% SE-30 on Chromosorb W, 140 °C).[3b] The yield of crude product obtained by removal of the solvent in vacuo was 515 mg (90%), and the NMR spectra of crude and GLC purified product were identical.[32] **3d:** NMR ($CDCl_3$)[13] δ 1.5–2.06 (m, 6 H, C_4, C_5, and C_6 methylenes), 2.33–2.54 (m, 2H, C_7 methylene),

2.76 (dt, 1 H, J = 8, 2 Hz, C_2 methine), 3.26 (s, 3 H, methoxyl), 3.34–3.56 (m, 1 H, C_3 methine) (irradiation of the C_4 methylene at δ 2.00 caused the C_3 proton to collapse to a sharp doublet, J = 8 Hz; the second coupling constant for the C_2 methine proton is due to geminal deuterium coupling). The following Eu(fod)$_3$-shifted spectrum[35] was obtained with a solution containing 19 mg (0.142 mmol) of **3d** and 88 mg (0.085 mmol) of Eu(fod)$_3$: δ 3.5–4.9 (m, 6 H, C_4, C_5, and C_6 methylenes), 5.50 (s, 3 H, methoxyl), 7.38–7.62 (m, 1 H, C_3 methine), 8.6–9.3 (m, 2H, C_7 methylene), 10.6 (br d, 1 H, J = 8 Hz, C_2 methine) (irradiation at C_3 (δ 7.50) caused the peak at δ 10.6 to collapse to a broad singlet; irradiation at C_2 (δ 10.6) changed the C_3 multiplet to a doublet of doublets, J = 7.5 and 7 Hz;[36] irradiation of C_4 (δ 4.70) converted the C_3 multiplet to a doublet, J = 8 Hz).

In a control experiment, 50 mg of 3-methoxycycloheptanone in 3 mL of CH_3OD was irradiated for 2.5 h. NMR examination of the crude product showed that there was almost no deuterium exchange at the α positions and that such exchange as might have occurred was not selective.

2,7,7-Trideuterio-2-cycloheptenone (13). Cycloheptanone was exchanged with sodium methoxide in D_2O–CH_3OD until the NMR spectrum showed that all of the α protons had exchanged. The resulting 2,2,7,7-tetradeuteriocycloheptanone (2 g) was treated with 0.9 mL of bromine in 20 mL of CH_3OD at 10–15 °C and then worked up[24] by adding successively 40 mL of pentane, 5 g of sodium carbonate, and 20 mL of D_2O, stirring (15 min) and separating layers. The water layer was extracted (3×) with pentane, and the combined organic layers were dried (Na_2SO_4) and evaporated. The residue, which consisted of a mixture of mono- and dibrominated products, was dehydrobrominated directly by reflux (60 h) with NaOD prepared by dissolving 1.45 g of sodium in a mixture of 12 mL of CH_3OD and 1.1 mL of D_2O. The reaction mixture was diluted with 5 mL of D_2O and extracted with pentane. After removal of the solvent, the residue (acetal) was hydrolyzed by stirring with 5 mL of 3% D_2SO_4 in D_2O for 10 min. Ether extraction, drying, and evaporation of the solvent gave crude product which on GLC (6 ft × 0.25 in. column, XF-1150, 130 °C) gave 80 mg (4%) of the desired **13:** NMR (CCl_4) δ 1.7–1.9 (m, 4 H, C_5 and C_6 methylenes), 2.1–2.5 (m, 2 H, C_4 methylene), 6.1–6.4 (m, 1 H, vinyl); mass spectrum *m/e* (rel intensity) 113 (45), 112 (20), 83 (80), 82 (100). The material was ~70% deuterated as desired.

Irradiation of 13 in methanol. The procedure was as described for the irradiation of **1** in CH_3OD. In the Eu(fod)$_3$-shifted spectrum of the product, the main H_2 peak appeared as a broadened singlet with a slope identical with that for the proton trans to the methoxyl in **3.**[13] A small peak was discernible for the other H_2 proton (cis to the methoxyl) with an area corresponding to the amount of nondeuterated material in the starting compound.

Irradiation of 2-Cyclooctenone in CH_3OD. A solution of 2-cyclooctenone[37] (124 mg, 1 mmol) in 5 mL of CH_3OD was irradiated for 5 h to give 140 mg (89%) of **12d.**[32] The NMR spectra of crude and GLC purified material were virtually identical. **12d:** δ 1.0–2.1 (m, 8 H, C_4–C_7 methylenes), 2.20–2.45 (m, 2 H, C_8 methylene), 2.68 (br d, 1 H, J = 10 Hz, C_2 methine), 3.30 (s, 3 H, methoxyl), 3.40 (dt, 1 H, J = 10, 4 Hz, C_3 methine) (irradiation at δ 1.95 (C_4) caused collapse of the C_3 signal to a doublet, J = 10 Hz). The following Eu(fod)$_3$-shifted spectrum[35] was obtained with a solution containing 18 mg (0.115 mmol) of **12d** and 54 mg (0.052 mmol) of Eu(fod)$_3$: δ 3–6.5 (m, 10 H, C_4–C_8 methylenes; at 100 MHz this peak was resolved into four distinct multiplets), 7.0 (s, 3 H, methoxyl), 9.7 (dt, 1 H, J = 8, 3 Hz, C_3 methine), 10.7 (br d, 1 H, J = 8 Hz, C_2 methine) (irradiation at δ 9.7 caused the peaks at δ 10.7 to collapse to a broad singlet; irradiation at δ 10.7 converted the C_3 methine signal to a doublet of doublets, J = 8, 3 Hz; irradiation at δ 6.0 (the C_4 proton trans to the C_3 proton) converted the C_3 methine signal to a broad doublet, J = 8 Hz; and irradiation at δ 5.10 (the C_4 proton cis to the C_3 proton) converted the C_3 methine signal to a triplet, J = 8 Hz).[38]

Isotope Effect Measurements. Enones **1** (55 mg, 0.5 mmol) or **11** (62 mg, 0.5 mmol) in a mixture of 1.8 mL of CH_3OD and 0.3 mL of CH_3OH were irradiated without a nitrogen purge at constant temperature (LAUDA K-2/R thermostat, ±1 °C) up to 60–70% conversion (7–8 h) for **1** and up to 80–90% conversion (5–6 h) for **11.** Each experiment was performed at least twice. The solvent was removed in vacuo and the crude product mixtures were analyzed by mass spectrometry and, for **11,** also by NMR.

In the mass spectra, the ratios of M^+ (**3d**)/M^+ (**3**) and M^+ (**12d**)/M^+ (**12**) were measured with the help of calibration curves. Known mixtures of GLC-purified **3** and **3d** or **12** and **12d** were prepared and submitted to mass spectrometry at 15 eV (sample inlet at 90 °C). Corrected weight ratios were used because **3d** contained 8–9% **3,** and **12d** contained 12–13% **12.** The mass spectral peak-height ratios were accurate because the natural abundance (for **3** and **12**) was approximately equal to the amount of **3** in **3d** and **12** in **12d.** The corrected weight ratios plotted against the mass peak ratios gave a straight line for each pair (**3**/**3d** and **12**/**12d**). In each case the deuterio compounds fragmented less than the protio compounds. The solvent ratio was also corrected for the fact that the CH_3OD contained 1% CH_3OH.

The ratio of **12d**/**12** was also determined by NMR, with the help of Eu(fod)$_3$. The methoxy singlets of **12** and **12d** were clearly separable with shift reagent, that for **12d** being downfield as expected.[19] The peak height ratios (average of four–six runs; area integration was inaccurate because the signals were not sufficiently separated) gave isotope effects comparable with those obtained from mass spectrometry. The separation of the methoxyl singlets on adding shift reagent to mixtures of **3** and **3d** was visible but insufficient for analytical use.

Base-Catalyzed Addition and Exchange Studies. All reactions were carried out by dissolving the enone (addition) or methoxy ketone (exchange) in CH_3OD and adding 0.1 N CH_3ONa in CH_3OD until the concentration of base in the reaction mixture was 0.01 N. The reaction mixtures were allowed to stand at room temperature for various times and then were quenched to pH 7 with sodium acetate in CH_3CO_2D.[20] Most of the solvent was removed in vacuo, water was added, and the methoxy ketone was extracted with ether, washed with aqueous sodium bicarbonate, and dried (Na_2SO_4). The products were analyzed directly by NMR, both normal and with added Eu(fod)$_3$.

Control experiments on the addition reaction showed that no detectable methoxy ketone was formed when either **1, 4,** or **11** was allowed to stand at 18.5 °C for 7 h in methanol (0.25 mmol of enone in 1 mL of methanol) in the absence of sodium methoxide.

Acid-Catalyzed Addition of CH_3OD to 1. To a solution containing 100 mg of **1** in 4.5 mL of CH_3OD was added 0.5 mL of 0.1 N D_2SO_4 in CH_3OD. After 21 min at room temperature, the reaction was quenched with aqueous sodium bicarbonate. Workup as in the base-catalyzed additions gave 70 mg (53%) of 3-methoxycycloheptanone. NMR analysis with the aid of Eu(fod)$_3$[13] showed that at C_2 the deuterium was equally cis and trans to the methoxyl at C_3 (by area integration against the methoxyl singlet).

Acid-Catalyzed Exchange of 3 in CH_3OD. To a solution containing 100 mg of **3** in 5 mL of CH_3OD was added 0.5 mL of 0.1 N D_2SO_4 in CH_3OD. After 10 min at room temperature the mixture was quenched with aqueous sodium bicarbonate and worked up. Very little exchange was observable by NMR, and what exchange had occurred involved mainly C_7. A mass spectrum showed *m/e* (rel intensity) 144 (2 D, 7), 143 (1 D, 44), 142 (no D, 100). An identical experiment but for 20 min showed (NMR) very little exchange at C_2 but some at C_7; a mass spectrum showed *m/e* (rel intensity) 146 (4 D, trace), 145 (3 D, trace), 144 (2 D, 11), 143 (1 D, 51), 142 (no D, 100).

Acknowledgment. We are indebted to the National Science Foundation (GP-43659X) and the National Institutes of Health (GM 15997) for financial support of this work.

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(21) Analyzed by NMR using the same methods as for the photoinduced additions. NMR integration, using the methoxyl protons as a reference, showed that a small fraction of the C_2 proton cis to the methoxyl was exchanged, but the product is mainly **3**-d_3.
(22) In this case, ~50% of the C_7 proton cis to the methoxyl is also exchanged, owing to the slowness of the addition and the prolonged opportunity for the product to exchange.
(23) One cannot, however, strictly rule out the possibility that some fraction of the reaction of **1** with methanol may proceed by polar addition to a photoexcited state.
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(28) The same is true for Z', another reason why we favor the synchronous addition, T → Z → P.
(29) The stereochemistry of Michael additions has not been studied in detail, but examples of syn addition, anti addition, and nonstereoselective addition are known. For brief discussions, see S. Patai and Z. Rappoport in "The Chemistry of Alkenes", S. Patai, Ed., Wiley-Interscience, New York, N.Y., 1964, p 464; see also R. A. Abramovitch, M. M. Rogić, S. S. Singer, and N. Venkatesevaran, *J. Org. Chem.*, 37, 3577 (1972), and references therein.
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(31) For numbering, see structure in the text. Spectra were determined on a Varian HA 100 instrument, and all assignments were confirmed by decoupling.
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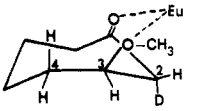
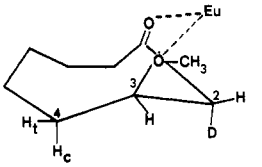
(35) Many such spectra were recorded, with varying ratios of substrate to shift reagent.
(36) These results are consistent with a rigid geometry for the europium complex,[13] with large trans coupling constants for J_{H_2,H_3} = 8.0 Hz and $J_{H_3,H_{4t}}$ = 7.5 Hz and a small cis coupling constant, $J_{H_3,H_{4c}}$ = 2.0 Hz. Consistent



with this, J_{H_{2c},H_3} in the unlabeled complex is small (2.0 Hz).[13]
(37) H. Houp and G. H. Whitham, *J. Chem. Soc. B*, 164 (1966).
(38) These results are consistent with a rigid geometry for the europium complex, [13] with large trans coupling constants, J_{H_2,H_3} = 8.0 Hz and $J_{H_3,H_{4t}}$ =



8.0 Hz, and a small cis coupling constant, $J_{H_3,H_{4c}}$ = 3.0 Hz. Consistent with this conclusion is the small value (3.0 Hz) observed for J_{H_{2c},H_3} in the unlabeled ketone.[13]

Substituted Acetophenones. Importance of Activation Energies in Mixed State Models of Photoreactivity

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Abstract: The photoabstraction and phosphorescence of triplet acetophenones requires a mixing between zero-order n,π^* and π,π^* states with interaction energies $\geq$100 cm^{-1}. The extent of mixing (b^2) and the energy separation (ΔE) of the resultant states are fundamental properties of the molecule and are independent of the phenomena being observed. However, the best expressions for the radiative rate constants (eq 1) and for the reaction rate constants (eq 6) differ since no activation energies are involved in the former while there are substantial barriers to reaction in the latter. Variations in photoreactivity between compounds are then mainly manifested as activation energy differences and the reactivity of a given compound changes significantly with temperature. On the other hand the radiative rate constants show essentially no temperature dependence although they do differ widely from compound to compound.

Introduction

Considerable experimental and theoretical activity has gone into trying to determine the factors which influence the photoreactivity of carbonyls with respect to hydrogen abstraction (k_a), >C=O* + RH → >COH + R·. Yang and co-workers[1-3] have shown that the variations in the reactivities

0002-7863/78/1500-5147$01.00/0