yl)phosphine. The tubes were opened, and VPC analyses confirmed these results.

Reactions of Di-*tert*-butylphosphine with Methyl Vinyl Ether, with and without AIBN. Two NMR tubes, one containing 0.05 g of AIBN (0.3 mmol), were charged with 0.3 g of di-*tert*-butylphosphine (2.1 mmol) and about 0.4 mL of methyl vinyl ether (9 mmol) was condensed into each. The contents were freeze–thaw–degassed and the tubes were sealed under vacuum. Both were heated at 80 °C for 5 h; no reaction was observed by NMR. The temperature was then raised to 140 °C, and after 4 h at this level a reaction was beginning in the tube without AIBN. After 18 h more, this reaction had gone to completion, yielding di-*tert*-butyl(1-methoxyethyl)phosphine. The reaction in the other tube was also yielding the same product, but was less than 50% complete. A reaction at 140 °C with di-*tert*-butyl peroxide in place of AIBN gave similar results.

Di-*tert*-butyl(1-methoxyethyl)phosphine. An excess of methyl vinyl ether (4 mL, 90 mmol) was condensed into a heavy-walled glass tube containing a mixture of 4.0 g of di-*tert*-butylphosphine (27 m moles) and 0.1 mL of trifluoroacetic acid (0.6 mmol). The contents were frozen and the tube was flame-sealed under vacuum, then heated to 130 °C for 1.5 h. The contents were distilled (bp 54–56 °C (0.4 mm)) to give 3.38 g (60%) of the product: ^1H NMR (neat) δ 1.15 (d, $^3J_{PH}$ = 10.5 Hz, 9 H, $C(CH_3)_3$), 1.22 (d, $^3J_{PH}$ = 10.5 Hz, 9 H, $C(CH_3)_3$, diastereotopic *tert*-butyl groups), 1.45 (d of d, $^3J_{HH}$ = 7 Hz, $^3J_{PH}$ = 15 Hz, 3 H, CH_3), 3.20 (s, 3 H, OCH_3), 3.72 (q of d, $^3J_{HH}$ = 7 Hz, $^2J_{PH}$ = 3 Hz, 1 H, CH).

Diethyl(1-methoxyethyl)phosphine. Excess methyl vinyl ether (4 mL, 90 mmol) was condensed onto a mixture of 2.0 g of diethylphosphine (22 mmol) and 0.05 mL of CF_3CO_2H (0.3 mmol) in a heavy-walled glass tube. The tube was then sealed, heated at 130 °C for 3 h, cooled, and opened. Vacuum distillation (bp 90–93 °C (40 mm)) gave 2.3 g (70%) of the product: ^1H NMR ($CDCl_3$) δ 0.7–1.7 (m, 13 H, CH_2CH_3 and CH_3), 3.38 (s, 3 H, OCH_3), 3.55 (m, 1 H, CH).

Di-*tert*-butyl(2-methoxyethyl)phosphine. A solution of $[(CH_3)_3C]_2PLi$[13] in 120 mL of THF (distilled from $LiAlH_4$) was prepared from 7.85 g of di-*tert*-butylphosphine (53.8 mmol) and 37 mL of 1.8 M phenyllithium solution (66 mmol). To this was added 6.5 g (69 mmol) of 2-chloroethyl methyl ether[14] (prepared from 2-methoxyethanol, thionyl chloride, and pyridine) in 50 mL of THF. The mixture was stirred for 1 h, and then 5 mL of methanol was added. Solvents were removed by distillation at atmospheric pressure, leaving a thick mixture. About 30 mL of ethyl ether was added; the suspension was filtered, washed with 100 mL of H_2O, and dried over $MgSO_4$. Vacuum distillation (bp 65–70 °C (0.15 mm)) gave 6.55 g (60%) of the product: ^1H NMR ($CDCl_3$) δ 1.22 (d, $^3J_{PH}$ = 11 Hz, 18 H, $(CH_3)_3C$), 1.70 (m, 2 H, PCH_2), 3.30 (s, 3 H, OCH_3), 3.50 (m, 2 H, OCH_2).

Diethyl(2-methoxyethyl)phosphine. Excess methyl vinyl ether (1.5 mL, 34 mmol) was condensed into a mixture of 0.95 g of diethylphosphine (11 mmol) and 0.10 g of AIBN (0.6 mmol) in a heavy-walled glass tube. The tube was sealed and heated at 80 °C for 2 h. Vacuum distillation (bp 96–99 °C (40 mm)) of the contents gave 0.98 g (64%) of the product: ^1H NMR ($CDCl_3$) δ 0.7–1.5 (m, 10 H, CH_2CH_3), 1.6 (m, 2 H, PCH_2), 3.35 (s, 3 H, OCH_3), 3.50 (overlapping triplets, $^3J_{HH}$ and $^3J_{PH}$ = 8 Hz, 2 H, OCH_2).

Acknowledgments are made to Dr. R. L. Pruett for his encouragement and support and to Dr. L. Kaplan for helpful discussions.

Registry No.—Di-*tert*-butylphosphine, 819-19-2; methyl vinyl ether, 107-25-5; di-*tert*-butyl(1-methoxyethyl)phosphine, 66792-96-9; diethyl(1-methoxyethyl)phosphine, 66792-97-0; diethyl phosphine, 627-49-6; di-*tert*-butyl(2-methoxyethyl)phosphine, 66792-98-1; *t*-Bu_2PLi, 19966-86-0; 2-chloroethyl methyl ether, 627-42-9; diethyl(2-methoxyethyl)phosphine, 66792-99-2.

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Stereochemistry of the Photoinduced Addition of Methanol to Pummerer's Ketone, a 2-Cyclohexenone

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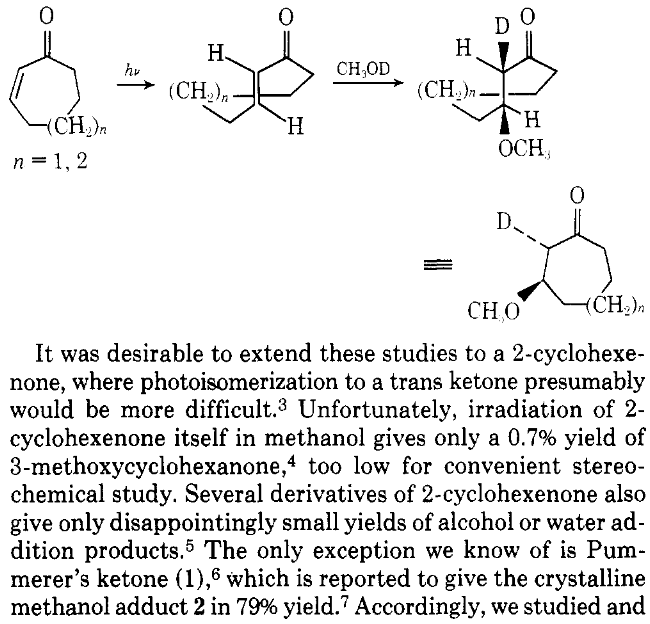
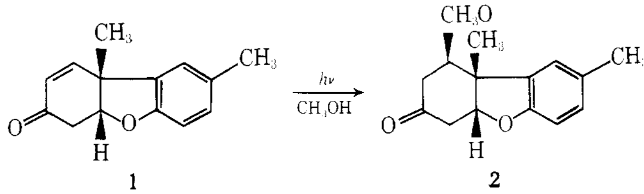
By using methanol-*d*, we recently showed that the photoinduced addition of methanol to 2-cycloheptenone, 2-cyclooctenone, and related compounds involves two steps: (a) photoisomerization to the *trans*-cycloalkenone, and (b) regio- and stereospecific syn addition of methanol to the ground state trans ketone.[1,2]



$n = 1, 2$

It was desirable to extend these studies to a 2-cyclohexenone, where photoisomerization to a trans ketone presumably would be more difficult.[3] Unfortunately, irradiation of 2-cyclohexenone itself in methanol gives only a 0.7% yield of 3-methoxycyclohexanone,[4] too low for convenient stereochemical study. Several derivatives of 2-cyclohexenone also give only disappointingly small yields of alcohol or water addition products.[5] The only exception we know of is Pummerer's ketone (**1**),[6] which is reported to give the crystalline methanol adduct **2** in 79% yield.[7] Accordingly, we studied and



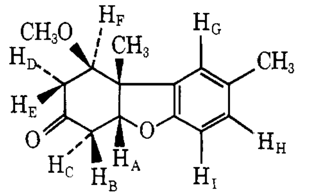
1 2

report here the stereochemistry of this reaction with CH_3OD, and also the isotope effect for the addition.

Results

Although we confirm the overall stereochemical assignment[7] of the methoxyl and angular methyl in **2** as being cis, we find some discrepancies in the previous[7] proton NMR assigments. Since the correct assignments, particularly those for H_D and H_E, were essential for establishing the stereochemistry of CH_3OD addition, we examined the 180 MHz proton spectrum of **2** in detail. The results, with the previous and new assignments, are given in Table I. The previous assignments of H_D and H_E should be reversed, as should those

Table I. The ^{1}H NMR Assignments of 2

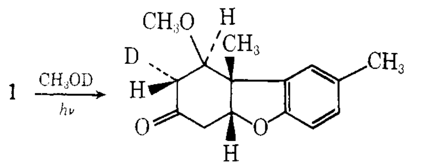


proton	assignment, δ^{a} previous	present[c]	coupling constants, Hz (CDCl3)	previous[7]	present[c]
H_A	4.47 (t)	4.69 (t)	AB	3.5	3.5
H_B	2.87 (q)	2.59 (dd)	AC	3.5	3.5
H_C	2.59 (q)	2.93 (dd)	BC	17.0	16.7
H_D	1.96 (q)	2.67 (dd)	DE	17.5	17.2
H_E	2.60 (q)	1.99 (dd)	DF	3.5	3.5
H_F	3.51 (q)	3.49 (dd)	EF	12.0	12.1
H_G	6.5–7.2	7.10 (bs)	HI		7.5
H_H	6.5–7.2	6.96 (bd)			
H_I	6.5–7.2	6.64 (d)			
OCH_3	3.37 (s)	3.41 (s)			
CH_3(arom)	2.3 (s)	2.33 (s)			
CH_3(ang)	(s)[b]	1.58 (s)			

[a] Peak multiplicities are represented by s (singlet), d (doublet), t (triplet), and q (quartet). [b] Not specified, but between δ 1.22 and 1.60. [c] Determined on a Bruker WH 180 spectrometer.

of H_B and H_C. All other assignments are correct. H_D and H_E were identified by their coupling constants with H_F (cis, J = 3.5 Hz, and trans, J = 12.1 Hz, respectively). Evidence regarding the assignments of H_B and H_C comes from the Eu(fod)$_3$-shifted spectrum of **2d** (vide infra.)[8]

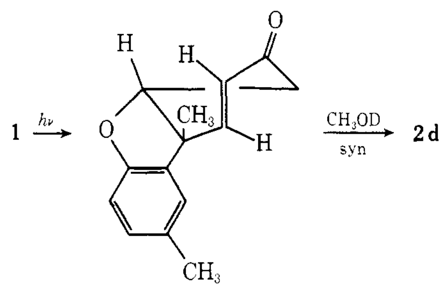
Irradiation of 1 in CH_3OD gave a single methanol adduct, assigned structure **2d**. The NMR spectrum of **2d** was modified



2d

from that of 2 only in the following ways. The peak at δ 2.67 (H_D) was absent, and H_E appeared as a broad doublet at δ 1.95, J = 12.5 Hz, coupled with H_F, which was a doublet at δ 3.47. Irradiation at H_A, H_E, and H_F verified the various coupling constants. A Eu(fod)$_3$ shift study showed that coordination occurs mainly with the carbonyl oxygen. The Δ values (extrapolated shift for 1:1 mol ratio of shift reagent/substrate) for H_B and H_E were nearly equal (6.8 and 6.5, respectively). The larger Δ value for H_C (7.7) than for H_B is consistent with H_C being in a pseudo-equatorial position, closer to the carbonyl oxygen.

These results show that the photoinduced addition of methanol to Pummerer's ketone occurs in a stereospecific trans manner. Since the ring juncture between the aliphatic five- and six-membered rings is cis, it is not surprising that methanol attacks from the exo (or β) face, so that the methoxyl and methyl groups end up cis to one another. It was quite surprising, however, that protonation occurred from the underneath (or α) face of the molecule. One possible explanation is that irradiation of 1 results in an excited state or intermediate in which the carbon–carbon double bond is twisted more than 90°. In this event, only syn addition to that "trans" double bond would be possible, since one face of the double bond would be blocked by the ring. The double bond can only twist in the sense shown, since a twist in the opposite direction would move the double bond into the face of the aryl and dihydrofuran rings. Consequently, the angular methyl and methoxyl must be cis to one another, with the deuterium trans



to the methoxyl. A short-lived intermediate has recently been detected in the flash photolysis of 2-cyclohexenone, and the authors suggest that it may be a "trans" isomer.[3b]

By irradiating 1 in a mixture of CH_3OH/CH_3OD and measuring the ratio of **2/2d** formed (by mass spectrometry) we find an isotope effect of 4.3 ± 0.5 in favor of protio addition. This effect is comparable to that observed for the addition of methanol to *trans*-cycloheptenone (4.3) and *trans*-2-cyclooctenone (5.7)[2] although we expected a much smaller effect for 1, reasoning that the "trans" intermediate should be more strained, hence less selective than for larger rings.

Experimental Section

Irradiation of 1 in CH_3OD. A solution containing 171 mg (0.8 mmol) of Pummerer's ketone 1[6] in 20 mL of CH_3OD was irradiated through Pyrex under nitrogen with a Hanovia Type L 450 W lamp for 24 to 65 h. The reaction was followed by TLC (silica gel; 30% ether–hexane eluent). The solvent was removed in vacuo and the residue was recrystallized from methanol-pentane, mp 104–106 °C (lit. value[7] for 2, 106–107 °C). For the NMR spectrum, see text. Mass spectrum, *m/e* (rel intensity): for **2**, 246 (29), 214 (2.5), 160 (14), 159 (61), 146 (100), 145 (40), 100 (12); for **2d**, 247 (28), 215 (3), 214 (3.5), 160 (15), 159 (59), 146 (100), 145 (33), 101 (10).[9]

Isotope Effects. A linear calibration plot of *m/e* 246/247 was obtained from known mixtures of **2** and **2d**. Irradiations of 1 with mixtures of CH_3OH/CH_3OD ranging from 1:5 to 1:1.1 were carried out at 25 °C using about 90 mg of 1 and 6–10 mL of methanol, usually for 22–24 h. Solvent was removed and the residue was analyzed directly by mass spectrometry (Hitachi Perkin-Elmer RMU-6). The value of 4.3 ± 0.5 is the average of four experiments at different CH_3OH/CH_3OD ratios, with duplicate analyses of each run.

Acknowledgment. We are indebted to the National Science Foundation (CHE-05956) and the National Institutes of Health (GM 15997) for research grants and to the National

Science Foundation (CHE76-08534) for an equipment grant for the Bruker WH 180 NMR spectrometer.

Registry No.—1, 15413-34-0; 2, 66702-00-9; 2d, 66674-96-2; methanol, 67-56-1.

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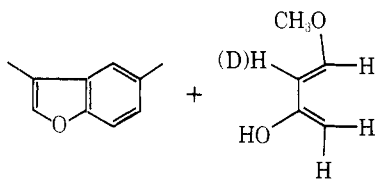
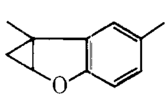
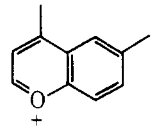


m/e 146 *m/e* 100 (101)

accounting for the same base peak in **2** and **2d**. The peaks at *m/e* 160 and 159 in both compounds may arise from α-carbonyl and benzylic cleavage to give


and


m/e 160 *m/e* 159

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Determination of p*K* Values for the Bisulfite Adducts of Cytidine 5′-Monophosphate by Carbon-13 Nuclear Magnetic Resonance

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Addition of bisulfite to carbon 6 of biologically important pyrimidines is a well-studied reaction,[1–3] having been investigated for nucleosides,[4] nucleotides,[5] and nucleic acids.[6] From a bioorganic standpoint the most intriguing event is the bisulfite-catalyzed deamination of cytidine to form uridine, the biological implications of which have been previously demonstrated.[7,8] Shapiro et al.[9] have advanced a mechanistic rationale (Scheme I) which includes both the protonated and nonprotonated cytidine–bisulfite adducts. In this mechanism the assumption was made that there is only one adduct formed. The present communication characterizes the two diastereomeric bisulfite adducts of cytidine 5′-monophosphate (CMP, 4) (Scheme II) and reports the p*K* values for the N-3 proton dissociation of these two adducts.

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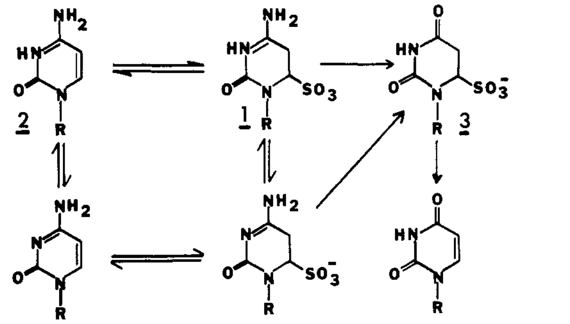
Scheme I



^{13}C NMR spectroscopy of an aqueous solution of CMP (**4**) yields a nine-line spectrum (Table I). Upon addition of bisulfite, a spectrum is obtained which is a composite of the original spectrum and those of two new compounds (Table I). Significantly, the signals corresponding to the sp^2 carbons of CMP (C-6, 142.7 ppm, and C-5, 97.3 ppm) are diminished. The CMP–bisulfite adducts (**5A** and **5B**) each display a set of signals of unequal intensity which includes carbon 2, carbon 4, and the sugar carbons. Based on their relative intensities, the signals can be grouped into two sets (CMP/HSO_3^- A and CMP/HSO_3^- B) and assigned to the appropriate carbons of the adducts[10] (Table I). In addition, two new sets of signals corresponding to the sp^3 carbons at positions 5 and 6 of the adducts are observed at 28.8 and 28.5 ppm (C-5) and 68.1 and 66.1 ppm (C-6). These are readily assigned by analogy with the known spectra for the bisulfite adducts of uracil and uridine.[4,11] When the sample is allowed to stand for longer periods (24 h), two more nine-line spectra are observed. The new carbon signals are assigned (Table I) as the diastereomeric bisulfite adducts of uridine monophosphate (**6A** and **6B**, Scheme II). This assignment is made on the basis of data previously reported from our laboratories in which uridine[4] and uracil[11] were substrates of similar bisulfite addition.

Shapiro et al.[9] reported a p*K* value of 5.3 for the N-3 proton dissociation in the cytidine–bisulfite adduct. This value was determined by ^1H NMR spectroscopy with deuterium oxide as the solvent. Thus, corrections were made to account for the effect of the deuterated solvent on the observed pH values. In light of the evidence for the existence of two diastereomeric bisulfite adducts of CMP, and because one of the parameters in the kinetically derived mechanism is the p*K* of these species, we were prompted to determine the p*K* values for each adduct.

The system under study using ^{13}C NMR spectroscopy initially consists of an aqueous solution containing only CMP (**4**) and its bisulfite adducts (**5A** and **5B**). However, after 24 h it was found to contain five discrete chemical species (Scheme II): CMP, its two diastereomeric bisulfite adducts (**5A** and **5B**), and two diastereomeric bisulfite adducts of uridine 5′-monophosphate (UMP) (**6A** and **6B**). These five species have a total of 18 possible p*K* values. Theoretically it is possible,

Scheme II