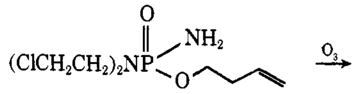
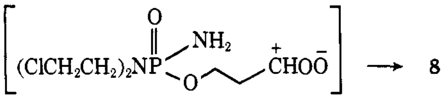
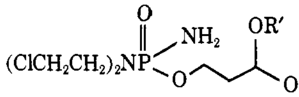
Ozonization of **6** in a mixture of acetone and H_2O (2:1) at 0° with a slight excess of O_3 gave 2-[bis(2-chloroethyl)amino]-4-hydroperoxytetrahydro-2*H*-1,3,2-oxazaphosphorine 2-oxide (**8**)[8] (4-hydroperoxycyclophosphamide) in *ca.* 10% yield, mp 107–108°; $\text{ir}_{\text{max}}^{\text{Nujol}}$ (cm^{-1}): 3310, 3080, 1237, 1210, 1035, 926, 840; $\text{nmr}_{\text{TMS}}^{\text{DMSO-}d_6}$: δ 1.92 (2 H, m, C_5–H_2), 3.01–4.02 (8 H, m), 4.21 (2 H, m, C_6–H_2), 4.71–5.11 (1 H, d of m, $J_{\text{H,P}} = 24.5$, $J_{\text{H,NH}} = 5.0$, $J_{\text{H,CH}} = 3.0$ Hz, C_4–H), 5.81[9] (1 H, d of d, $J_{\text{H,P}} = 7.0$ Hz, NH), 11.51[9] (1 H, s, OOH). The structure assignment for **8** was based on the spectral properties cited and on the following chemical behavior: **8** readily oxidizes KI to I_2, and it gives 4-ketocyclophosphamide (**2**) in good yield on treatment with $SOCl_2$–pyridine. It can be rationalized that **8** is produced by intramolecular cyclization of Criegee's zwitterion[10] intermediate **7** which was intercepted by adduct formation with alcohols (*vide infra*). The yield of **8** was markedly increased (50–60%) when excess of hydrogen peroxide or *tert*-butyl hydroperoxide was added to the ozonization reaction mixture.[11] Deoxygenation of **8** by triphenylphosphine in CH_2Cl_2 at 0° afforded 4-hydroxycyclophosphamide (**3**)[8] as labile crystals in 40% yield, mp 47.5–48.5°; $\text{ir}_{\text{max}}^{\text{Nujol}}$ (cm^{-1}): 3240, 3180, 1240, 1215, 1195, 1053, 980; $\text{nmr}_{\text{TMS}}^{\text{DMSO-}d_6}$: δ 1.80 (2 H, m, C_5–H_2), 3.00–3.87 (8 H, m), 4.20 (2 H, m, C_6–H_2), 4.90 (1 H, d of m, $J_{\text{H,P}} = 21$ Hz, C_4–H), 5.15[9] (2 H, m, NH, OH). Action of hydrogen peroxide upon **3** regenerated **8** in good yield.



6



7



9, R = Et; R′ = OH
10, R = $CH_2C_6H_5$; R′ = OH
13, R = R′ = Et

When the ozonolysis of **6** was carried out in the presence of alcohol, the zwitterion **7** could be captured as the open-chain hemiacetal hydroperoxide. Thus, ozonization of **6** in CH_2Cl_2 containing an excess amount of EtOH gave *O*-(3-ethoxy-3-hydroperoxy) *N*,*N*-bis(2-chloroethyl)propylphosphorodiamidate (**9**)[8,12] in 50% yield. Similarly, in the presence of benzyl alcohol, **6** gave **10**.[8,12] On treatment with $SOCl_2$–pyridine, **9** and **10** afforded the corresponding esters **11**[1] and **12**[1] in good yield. Deoxygenation of **9** by triphenylphosphine yielded an unstable mixture[13] from which no characterizable product could be isolated in a pure state. An alternative attempt to obtain **5** by acid hydrolysis of **13**, which was prepared by the reaction of *N*,*N*-bis(2-chloroethyl)aminophosphorodichloridate[14] with γ-hydroxypropionaldehyde diethylacetal followed by treatment with NH_3, was unsuccessful because of facile elimination of the C_3 unit of **5** to give acrolein.

As expected, 4-hydroxycyclophosphamide (**3**) exhibited high cytostatic activity in the preliminary bioassay. For example, it inhibited the growth of Yoshida sarcoma in rats (inoculated at 10^7 cells/rat) by over 95% (determined by tumor weight after 7 days) at 5 mg/kg (iv) administration. For L1210 leukemia in BDF_1 mice (inoculated at 4 × 10^4 cells/mouse), 50 mg/kg (iv) gave a 100% ILS (per cent increase in lifespan over control).[15] The most striking activity shown by **3** was its *in vitro* activity against B-HeLa cells (ED_{50} 0.6 μg/ml).[16] 4-Hydroperoxycyclophosphamide (**8**) also exhibited high cytostatic activity in both *in vivo* and *in vitro* experiments with almost equal potency, which indicates that **8** can be readily converted into **3** by biological reduction. Both **3** and **8** were shown to be metabolized into **2** and **4** by isolating these metabolites from the urine of rabbits.[17]

The results presented so far give confirmatory support to the previous proposal that the first step of the activation of cyclophosphamide involves C_4-hydroxylation of its oxazaphosphorine ring.

Acknowledgment. The authors are indebted to Mr. Shoji Sakai and Mr. Itsuo Makino for their technical assistance.

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Flash Photolysis of Michler's Ketone in Solution. Rate Constants for Decay and Triplet Excimer Formation[1]

Sir:

The relationship between the electronic configuration of the lowest lying triplet state (n,π^*, π,π^*, or charge transfer) and the photochemical reactivity of ketones has been a question of great interest in photochemistry.[2–4] In a classic study, Porter and his coworkers[2] proposed, based on absorption and emission spectroscopy and solvent shifts, that for benzophenones with substituents

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[9] Signal assignment was made on the basis of deuterium exchange.

[10] R. Criegee and G. Wenner, *Justus Liebigs Ann. Chem.*, **564**, 9 (1946).

[11] The role of the added hydroperoxides is to prevent dimerization or decomposition of **8**.

[12] Obtained as a rather unstable oil, but purifiable by column chromatography (silica gel).

[13] The mixture gives typical aldehyde reactions and the following spectral properties: $\text{ir}_{\text{max}}^{\text{film}}$ 1720 cm^{-1}; $\text{nmr}_{\text{TMS}}^{\text{CDCl}_3}$ δ 9.8 (t, J = 1.2 Hz), which differed slightly from the reported data for **5** (R. F. Struck and D. L. Hill, *Proc. Amer. Ass. Cancer Res.*, **13**, 50 (1972)).

[14] O. M. Friedman and A. M. Seligman, *J. Amer. Chem. Soc.*, **76**, 655 (1954).

[15] The LD_{50} of **3** was 240 mg/kg in DS mice, which was slightly increased as compared to **1** (LD_{50} 380 mg/kg).

[16] Recently, Hill and coworkers reported on the possible enzymatic conversion of cyclophosphamide to **3** or **5** which showed also the remarkable *in vitro* activity (D. L. Hill, W. R. Laster, Jr., and R. F. Struck, *Cancer Res.*, **32**, 658 (1972)).

[17] The isolated amount of **2** and **4** was approximately the same as produced from **1**.

[1] Photochemistry of Ketones in Solution. XXXVII. Part XXXVI: D. I. Schuster, T. M. Weil, and A. M. Halpern, *J. Amer. Chem. Soc.*, **94**, 8248 (1972).

[2] G. Porter and P. Suppan, *Trans. Faraday Soc.*, **61**, 1664 (1965); **62**, 3375 (1966); *Pure Appl. Chem.*, **9**, 499 (1964).

[3] P. Suppan, *Ber. Bunsenges. Phys. Chem.*, **72**, 321 (1968).

[4] J. N. Pitts, Jr., H. W. Johnson, Jr., and T. Kuwana, *J. Phys. Chem.*, **66**, 2456 (1962).

such as $-NH_2$ and $-NMe_2$ there was a reversal of the ordering of the lowest triplet states in polar ($^3\pi,\pi^*$ or ^{3}CT) and nonpolar ($^3n,\pi^*$) solvents. This proposal was offered as an explanation for the low quantum yield for disappearance of Michler's ketone (p,p'-bis(dimethylamino)benzophenone) (MK) in 2-propanol (Φ = 0.00) compared with its reactivity in cyclohexane (Φ = 0.2–0.6).[2,3] The differences observed in the lifetimes of typical π,π^* or CT triplets (such as MK) and typical n,π^* triplets (such as benzophenone) in various glasses at 77°K were found to be consistent with these configurational assignments.[2-4] If these observations and rationalizations could be extended to systems in fluid solution at room temperature, it would be expected that: (1) the natural triplet lifetime τ_0 of MK should be significantly longer than that of benzophenone, at least in inert solvents, and (2) the triplet lifetime τ_0 of MK should be markedly solvent dependent.

Recently, observations have been reported which led to an alternative explanation for the effect of solvent on photochemical reactivity of MK, which does not require a reversal in configuration of the lowest triplet state of MK in polar *vs.* nonpolar solvents.[5] Prior to this report, we had initiated a flash photolysis study of MK in solution, and now report results relevant to the proposal of Koch and Jones.[5]

We have directly determined by flash photolysis the rate constants for decay of MK triplets in a number of solvents at room temperature. Triplet lifetimes were determined in most solvents by monitoring the emission at an appropriate wavelength, using an FP-2R flash photolysis apparatus supplied by Northern Precision Co., Ltd., London, using two argon-filled flash lamps. A cobalt sulfate filter solution surrounded the cylindrical solution cell to eliminate scattered light from the flash lamps. In cyclohexane, the triplet lifetime was determined by the time-correlated single photon counting technique.[1,6]

The phosphorescence decay was cleanly first order in all cases. However, the rate of decay was dependent on MK concentration, providing unequivocal evidence for direct interaction of MK triplets and ground-state molecules to give a triplet excimer, which had been suggested earlier[5] on the basis of exchange reactions in benzene in the presence of ethanethiol-*S-d*. Using the general relationship in eq 1, values of τ_0, the triplet

$$1/\tau_{\text{obsd}} = 1/\tau_0 + k_e[\text{MK}] \qquad (1)$$

lifetimes at infinite dilution, and k_e, rate constants for excimer formation, were obtained in several solvents (see Tables I and II). Our directly determined value of $k_e = 1.25 \times 10^8$ l. mol^{-1} sec^{-1} in benzene is in general agreement with the value of 1×10^9 l. mol^{-1} sec^{-1} calculated by Koch and Jones[5] from the kinetics of quenching of the deuterium exchange process by 1,3-cyclohexadiene.

Table I. Triplet Lifetimes (τ_0) of Benzophenone and Michler's Ketone

Ketone	Temp, °K	Triplet lifetimes, sec × 10^6 C_6H_{12}	i-C_3H_7OH	C_6H_6	CCl_4
MK	~300	$3^{a,e}$	$27,^{a,f}$ 70^g	$27^{a,h}$	$30^{a,f}$
Ph_2CO	~300	0.300^b	0.046^b	10^c	120^d
MK	77	$41{,}000^i$	$106{,}000^i$		
Ph_2CO	77	5100^i	5400^i		

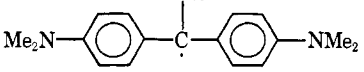
[a] This work. [b] G. Porter and M. R. Topp, *Proc. Roy. Soc., Ser. A*, **315**, 163 (1970). [c] Reference 1. [d] D. I. Schuster and T. M. Weil, *Mol. Photochem.*, **4**, 447 (1972). [e] Measured using a time-correlated single photon counting technique. [f] Decay of emission after flash excitation, monitored at 470 nm. [g] Reference 7. [h] Decay of emission after flash excitation, monitored at 480 nm. [i] Reference 2.

Table II. Rate Constants (k_e) for Excimer Formation from Michler's Ketone Triplets[a]

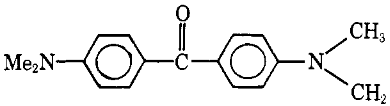
Solvent	k_e, l. mol^{-1} sec^{-1}
Benzene	$1.25 \pm 0.22 \times 10^8$
Isopropyl alcohol	$1.96 \pm 0.41 \times 10^7$ [b]
Carbon tetrachloride	$7.61 \pm 0.87 \times 10^7$

[a] From eq 1. [b] Reference 7 gives 8×10^6 as a lower limit for the rate constant for exciplex formation between ^{3}MK and benzophenone in isopropyl alcohol.

Absorption flash photolysis studies in benzene over a concentration range of 10^{-3}–10^{-5} *M* from λ 425 to 625 nm demonstrate strong transient absorption, but the decay of the absorption is not cleanly first or second order, presumably because of absorption by radicals such as **1** and **2** in addition to MK triplets.[7,8] However, at wavelengths between 500 and 550 nm in benzene and at 535 nm in CCl_4 at very dilute MK concentrations (10^{-5} *M*), a very weak long-lived transient is observed which decays cleanly by first-order kinetics, $k_d = 1.7 \times 10^3$ sec^{-1} in benzene and 1.8×10^2 sec^{-1} in CCl_4. We tentatively ascribe this absorption to the triplet excimer of MK.



1



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The short lifetime of $^3Ph_2CO^*$ in 2-propanol is obviously to be ascribed to rapid H abstraction from the solvent by the $^3n,\pi^*$ state of benzophenone. The relatively long limiting lifetime τ_0 of ^{3}MK* in this solvent (500 times longer than $^3Ph_2CO^*$) indicates that this reaction is inhibited, consistent with a $^3\pi,\pi^*$ or ^{3}CT* configuration for ^{3}MK* in 2-propanol.[2-4] Since the limiting triplet lifetime τ_0 of MK at room temperature decreases in cyclohexane by only one order of magnitude, one might conclude that the electronic configuration of the lowest triplet state of MK does not change in any important way when going from a polar to a nonpolar solvent and is still $^3\pi,\pi^*$ or ^{3}CT*. However, one can examine these results from another perspective by comparing the relative lifetimes of MK and Ph_2CO at 77 and ~300°K (Table I). At room temperature in C_6H_{12}, ^{3}MK* is only one order of magnitude longer lived

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(5) T. H. Koch and A. H. Jones, *J. Amer. Chem. Soc.*, **92**, 7503 (1970).

(6) For a description of the apparatus, see A. M. Halpern and W. R. Ware, *J. Chem. Phys.*, **54**, 1271 (1971); W. R. Ware in "Creation and Detection of the Excited State," A. A. Lamola, Ed., Marcel Dekker, New York, N. Y., 1971.

(7) C. C. Wamser, G. S. Hammond, C. T. Chang, and C. Baylor, Jr., *J. Amer. Chem. Soc.*, **92**, 6362 (1970).

(8) I. H. Leaver, *Tetrahedron Lett.*, **25**, 2333 (1971).

than $^3Ph_2CO^*$, exactly paralleling the situation at 77°K, leading to precisely the opposite conclusion, namely that $^3MK^*$ has an $^3n,\pi^*$ configuration in cyclohexane. In fact, in CCl_4, τ_0 for MK is even less than for Ph_2CO! Thus, no firm conclusion about the electronic configuration of $^3MK^*$ in nonpolar solvents can be made on the basis of the available evidence, and we must await further investigation into the individual decay modes (radiative, nonradiative, reversible, and irreversible reaction) which determine τ_0.

The fact that self-quenching of MK is observed is not in itself inconsistent with an n,π^* configuration of the triplet, since recent studies indicate that self-quenching is a general process for ketone triplets and is not restricted to π,π^* triplets.[9-11] Self-quenching is particularly significant kinetically in solvents such as benzene, CCl_4, and water where ketone triplet lifetimes tend to be long at room temperature, compared with lifetimes in solvents such as 2-propanol and cyclohexane. Comparison of reactivities (*e.g.*, quantum yields) of ketones in different solvents must take into account such concentration dependencies. Consequently, it is necessary to reevaluate such data[2-4] already in the literature.

In any event, these results indicate that one must be wary about making extrapolations concerning the relationship of triplet lifetimes and electronic configurations of substituted benzophenones and presumably other ketones in fluid solution at room temperature, on the basis of experimental observations in glasses at 77°K. In addition, it would appear that τ_0 may not be sensitive to changes in electronic configuration at room temperature and thus may not be suitable as a probe for determining electronic configuration.

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[9] D. R. Kemp and P. de Mayo, *J. Chem. Soc., Chem. Commun.*, 233 (1972).

[10] D. I. Schuster and T. M. Weil, unpublished results.

[11] O. L. Chapman and G. Wampfler, *J. Amer. Chem. Soc.*, **91**, 5390 (1969); see also P. S. Engel and B. M. Monroe, *Advan. Photochem.*, **8**, 245 (1971).

Additions and Corrections

The Mechanism of the Reaction of Silver Nitrite with Alkyl Halides. The Contrasting Reactions of Silver and Alkali Metal Salts with Alkyl Halides. The Alkylation of Ambident Anions [*J. Amer. Chem. Soc.*, 77, 6269 (1955)]. By NATHAN KORNBLUM,* ROBERT A. SMILEY, ROBERT K. BLACKWOOD, and DON C. IFFLAND, Department of Chemistry, Purdue University, Lafayette, Indiana 47907.

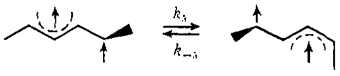
In column 1, line 38, of page 6278, "20 g of silver nitrite" read "120 g of silver nitrite."

On the Kinetics and Mechanism of the Perkow Reaction [*J. Amer. Chem. Soc.*, **94**, 1623 (1973)]. By IRVING J. BOROWITZ,* STEVEN FIRSTENBERG, GRACE B. BOROWITZ, and DAVID SCHUESSLER, Department of Chemistry, Belfer Graduate School of Science, Yeshiva University, New York, New York 10033, and Upsala College, East Orange, New Jersey 07019.

The fourth sentence of the abstract read: "ρ values for the two series are 2.37 and 1.89, respectively."

Temperature and Viscosity Effects on the Decay Characteristics of *s-trans*-1,3-Diene Triplets [*J. Amer. Chem. Soc.*, **94**, 5903 (1972)]. By JACK SALTIEL,* ALAN D. ROUSSEAU, and ALAN SYKES, Department of Chemistry, Florida State University, Tallahassee, Florida 32306.

Equation 5 is incorrect and should read



^{3}tp ^{3}cp (5)

On page 5905, line 9, read "10^{-8}" instead of "10^8." On the same page, line 14 read "faster" instead of "slower."

An Electron Spin Resonance Study of the Reaction of *tert*-Butoxy Radicals with Triphenylarsine [*J. Amer. Chem. Soc.*, **94**, 5932 (1972)]. By E. FURIMSKY, J. A. HOWARD,* and J. R. MORTON, Division of Chemistry, National Research Council of Canada, Ottawa, Canada K1 A OR9.

The second line of the ninth paragraph on page 5932 should read. "The rates were first-order in the radical concentration and independent of the triphenylarsine concentration and steady-state radical concentrations were proportional to the intensity of the initiating light."

Oxidation of Cobalt(I) Carbonyl Complexes and Cobalt(I)-Catalyzed Oxidation of Carbon Monoxide [*J. Amer. Chem. Soc.*, **94**, 6534 (1972)]. By JOHN E. BERCAW, LAI-YOONG GOH, and JACK HALPERN,* Department of Chemistry, The University of Chicago, Chicago, Illinois 60637.

The formula of **5** in Scheme 1 should read $[YCo(CN)_2(PEt_3)_2(CO_2)]^{5-}$. *Formally*, this corresponds to a CO_2 complex of cobalt(I).

Degenerate Thermal Rearrangement of Bicyclo[5.3.0^{4,8}]deca-2,5,9-triene (Lumibullvalene) [*J. Amer. Chem. Soc.*,