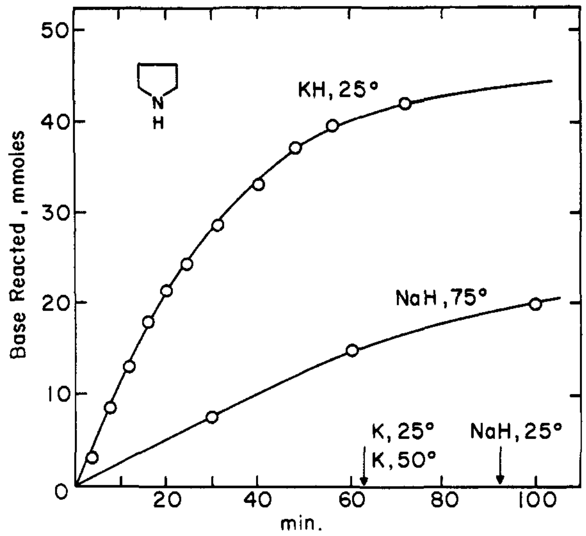

Figure 1. Reaction of strong metalating agents with pyrrolidine.

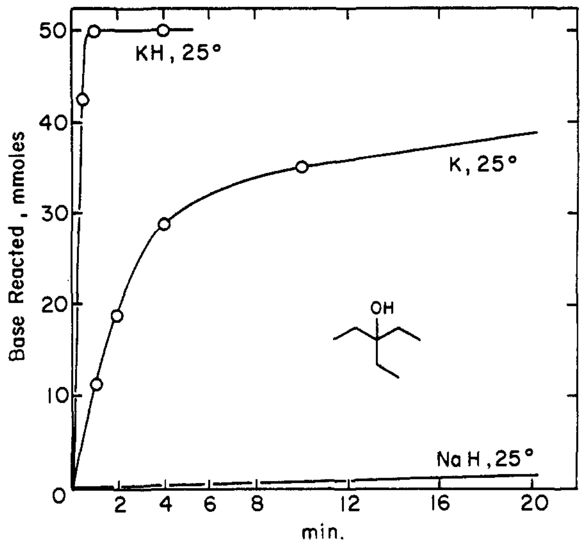

Figure 2. Reaction of strong metalating agents with triethylcarbinol.

The KH and NaH[11,12] employed in this study are prepared by hydrogenation of the molten metal dispersed in mineral oil at 200°. No current data are available regarding surface area or aggregation; however, the particle size appeared to be similar. Both hydrides appear to be totally insoluble in the common ethereal solvents; no H^- activity appears in the centrifuged supernatant liquid after prolonged stirring. KH appears to be a very poor reducing agent, although methyl iodide is attacked slowly at 50° in tetrahydrofuran (THF). In THF, alcohols react vigorously with KH to yield the alkoxide; however, pretreatment of the KH with trimethylchlorosilane inhibits or poisons the surface, possible through formation of insoluble KCl.

At present, insufficient data are available to explain the high reactivity of KH; however, it is interesting to note that reactivity increases (LiH[13] $<$ NaH $<$ KH) while lattice energies[14] of the saline hydrides fall (LiH $>$ NaH $>$ KH).[15]

In the few cases where comparisons exist, the reactivity of bases varies with the cation in the order $K \gg Na > Li$.[2,16a,b] This order is also observed for dissociation of "dimsyl" salts.[16c] Nonetheless, lithium salts of very weak acids are far more generally used[17] due to ease of formation *via* available organolithium compounds; no comparable route to potassium analogs has existed. Kaliation with KH[18] now provides strong potassium bases with unprecedented ease. The new mono- and dialkylamides of potassium appear to be the most reactive bases both soluble in and stable toward moderately polar organic solvents. Preliminary results indicate that they will open new avenues in synthetic chemistry and proton transfer studies.

Further studies on the reactions of KH with organic, organometallic, and inorganic compounds as well as exploitations of the new amide "superbases" are in progress. It is also hoped that the high observed reactivity of KH will stimulate investigations of KH surface reactions beyond the scope of our laboratory.

Acknowledgment. Financial assistance by the Research Corporation and by E. I. Dupont, Inc. (Young Faculty Grants Program administered by the Cornell Chemistry Department) is gratefully acknowledged.

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(11) Obtained from Alfa Products, Division of Ventron Corp.

(12) (a) Highly reactive NaH has been prepared by hydrogenation of sodium naphthalene.[12b,c] The potassium naphthalene complex fails to hydrogenate under similar circumstances; however, other more reactive radical anions of potassium may be suitable. (b) S. Bank and T. A. Lois, *J. Amer. Chem Soc.*, **90**, 4505 (1968); (c) E. E. van Tamelen and R. B. Fechter, *ibid.*, **90**, 6854 (1968).

(13) (a) LiH has been reported less reactive than NaH toward DMSO,[4a] weak Lewis acids,[12b] and amides;[12c] (b) H. C. Brown, private communication; (c) R. Schlessinger, private communication.

(14) (a) S. R. Gunn and L. G. Green, *J. Amer. Chem. Soc.*, **80**, 4782 (1958); (b) L. Dass and S. C. Saxena, *J. Chem. Phys.*, **43**, 1747 (1965).

(15) (a) The ionic radius of H^-, calculated from lattice constants and alkali metal Pauling radii, increases substantially from LiH to KH. After KH, the calculated H^- radius is constant. Possibly this reflects either some covalency of M–H or compression of H^- in LiH and NaH, which might be expected to hinder the H^- H^+ reaction. (b) The reactions of weak acids with KH should present a useful entry into reactions at crystal faces; unlike common metathetical reactions, the reaction liberating H_2 is essentially irreversible.

(16) (a) S. Bank, A. Schriesheim, and C. A. Rowe, Jr., *J. Amer. Chem. Soc.*, **87**, 3244 (1965); (b) A. Schriesheim, address to the New York Academy of Sciences, Oct 10, 1968; (c) E. C. Steiner, R. O. Trucks, J. D. Starkey, and J. G. Exner, *Amer. Chem. Soc. Polym. Prepr.*, **9**, 1135 (1968).

(17) (a) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, New York, N. Y., 1972, Chapters 9 and 10; (b) see ref 17a, p 547, and references therein.

(18) Potassium hydride in oil reacts slowly with moist air and is best handled under nitrogen or argon. It reacts very vigorously with water, smoking and sputtering in a manner similar to sodium metal. We normally handle the oil dispersion with a wide mouth (*ca.* 2 mm) medicine dropper. Droppers and stirrers are washed with kerosine; the kerosine–KH residue should be disposed of in a manner analogous to $LiAlH_4$, Na metal, etc. If desired, the oil may be removed by washing the dispersion with *dry* pentane, benzene, ether, etc. KH which has been separated from the oil by washing should *never* be allowed to contact air.

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Photoionization of Pyrene in Polar Solvents. The Role of the Triplet State

Sir:

Pyrene, when excited by light in the wavelength range of its visible and uv absorption spectrum, undergoes a

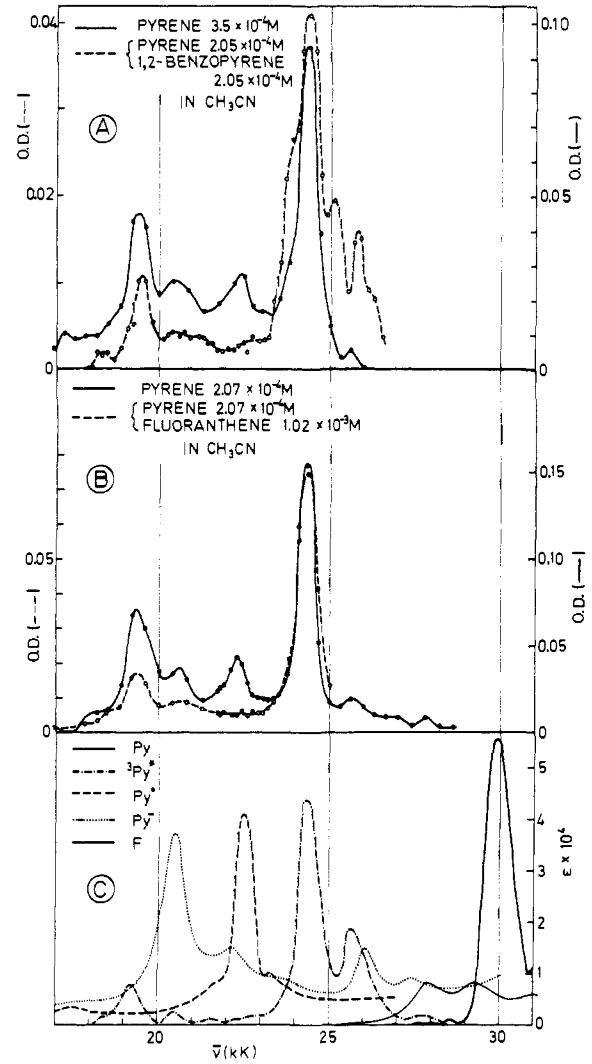

Figure 1. (A) Transient absorption spectrum obtained on flashing pyrene in acetonitrile (—); transient absorption spectrum obtained on flashing a mixture of pyrene and 1,2-benzopyrene in acetonitrile (- - -). (B) Transient absorption spectrum obtained on flashing pyrene in acetonitrile (—); transient absorption spectrum obtained on flashing a mixture of pyrene and fluoranthene in acetonitrile (- - -). (C) Comparison spectra, taken from the literature. The triplet-triplet absorption spectrum (W. Heinzelmann and H. Labhart, *Chem. Phys. Lett.*, **4**, 20 (1969)) was drawn using the extinction coefficient determined by Brinen (J. S. Brinen in "Molecular Luminescence," E. C. Lim, Ed., W. A. Benjamin, New York, N. Y., 1969, p 333); the spectra of the pyrene radical cation and the pyrene radical anion come from W. I. Aalbersberg, G. J. Hoijtink, E. L. Mackor, and W. P. Weijland, *J. Chem. Soc.*, 3049 (1959). The symbols Py and F represent pyrene and fluoranthene, respectively.

photoionization process yielding conducting species. The first evidence that such a process occurs in solution was obtained by Jarnagin and coworkers,[1] who examined the photoconductivity of THF solutions of pyrene. They concluded from their experiments that radical cations and anions of pyrene are produced by a triplet–triplet annihilation process; substantially the same conclusion was reached by other groups,[2] who, however, suggested that the species responsible for the ion formation is not the same as the precursor of the delayed fluorescence.

According to the mechanism postulated by these authors the pyrene triplet state plays a decisive role in the production of charge carriers; however, the only positive evidence for its involvement is based on the rather complicated kinetics observed in the earlier flash conductivity work.[1] In fact, the photoionization of another polynuclear aromatic hydrocarbon, perylene, has been shown to proceed by two mechanisms, neither of which involves the triplet state,[3] and it seemed that this aspect of the pyrene photoionization was worth closer study. This note reports the result of an investigation in which we have used sensitization experiments to explore the details of the photoionization mechanism.

The solid curve in Figure 1A shows the transient spectrum observed on flashing an acetonitrile solution of pyrene (recrystallized and zone-refined; further experimental details are described elsewhere[4]); for comparison, spectra of the triplet, radical cation, and radical anion, drawn to the same wave number scale, have been included in Figure 1C. It can be seen that peaks due to the pyrene triplet (at 19.3, 20.5, 24.6, and 25.8 kK) and to the pyrene radical cation (at 22.4 kK) are present in the experimental flash spectrum; it is difficult to say whether the increased absorption around 20 kK and to lower wave numbers is due to formation of the pyrene radical anion, solvated electrons, or both.

The results of this experiment differ from the earlier photoconductivity measurements in two important respects. (a) The quantum yield of ion formation observed in our experiments (about 0.07 for the pyrene radical cation, using a value of 0.3 for the triplet quantum yield) is very much higher than that observed by Jarnagin and coworkers (approximately 10^{-3}) in their photoconductivity experiments. (b) The pyrene radical cation is formed, in our experiments, within the lifetime of the flash (about 20 μsec), whereas the photoconductivity observed by the earlier workers[1] builds up with a half-rise time of 0.3 msec.

These results seem to cast some doubt on the triplet–triplet annihilation mechanism of ion production. However, the differences mentioned above could be due to the differences in polarity between THF (D (dielectric constant) = 7.39) and acetonitrile (D = 37.5), a common mechanism (triplet–triplet annihilation) operating in both cases. To clarify this point we carried out an experiment where a solution of pyrene and 1,2-benzopyrene (which has a triplet state lying energetically about 0.2 eV above the pyrene triplet) was flashed in acetonitrile under conditions where only 1,2-benzopyrene absorbed the exciting light. This was checked by running a blank experiment with the same filters on a solution containing pyrene alone; no pyrene triplet formation under these conditions could be detected. The result of the sensitization experiment is shown as the dashed spectrum in Figure 1A; the pyrene triplet is, in fact, formed by triplet–triplet energy transfer from the initially excited 1,2-benzopyrene, but this time *no* pyrene radical cation can be detected.

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[1] L. P. Gary, K. De Groot, and R. C. Jarnagin, *J. Chem. Phys.*, **49**, 1577 (1968).

[2] S. D. Babenko and V. A. Bendersky, *Opt. Spektrosk.*, **28**, 616 (1970); **29**, 45, 106 (1970); S. D. Babenko, V. A. Bendersky, and V. I. Gol'dansky, *JETP Lett.*, **10**, 129 (1969).

[3] K. H. Grellmann and A. R. Watkins, *Chem. Phys. Lett.*, **9**, 439 (1971).

[4] K. H. Grellmann, A. R. Watkins, and A. Weller, *J. Lumin.*, **1**, 678 (1970).

One possible explanation for the nonappearance of the pyrene radical cation in the sensitization experiment lies in the bimolecular nature of the proposed photoionization mechanism; the efficiency of the production of ions from the triplet–triplet annihilation will be given by

$$\varphi = \frac{\gamma}{1 + (1/[^3\mathrm{Py}^*])(k_1/k_2)}$$

where γ is the probability of a triplet–triplet annihilation leading to ion formation, k_1 and k_2 are rate constants for the disappearance of the pyrene triplets by all first-order and by all second-order processes, and $[^3\mathrm{Py}^*]$ is the initial concentration of triplets produced by the flash. Obviously, as $[^3\mathrm{Py}^*]$ becomes smaller, φ will decrease, perhaps to the point where ion production falls below the detection limit of our instrument.

To settle this question we repeated the experiment with a sensitizer with a more favorable absorption spectrum, fluoranthene (the triplet of which also lies about 0.2 eV above the pyrene triplet). This enabled us to produce approximately the same concentration of triplets by sensitization as was obtained by direct excitation in Figure 1. Since the buildup and decay kinetics of the triplets were approximately the same in both cases, we could assume that the maximum triplet concentration (not measurable because of scattered flash light) was the same in both cases. The result is shown in Figure 1B. As before, the pyrene radical cation is produced only when direct excitation is used (solid curve in Figure 1B) and not when the pyrene triplet is produced *via* excitation of the added sensitizer fluoranthene (dashed curve), in spite of the fact that the concentration of sensitized triplets has increased by a factor of 2. The possibility that initially formed radical cations of pyrene disappear by an electron-transfer reaction with the sensitizer can be ruled out, since 1,2-benzopyrene and fluoranthene have larger oxidation potentials in acetonitrile (1.25 and 1.45 V *vs.* sce, respectively) than pyrene (1.20 V).

The nonoccurrence of the photoionization when the triplets are produced indirectly is thus not a result of the dependence of φ on the triplet concentration, but rather indicates that the contribution of the triplet–triplet annihilation mechanism, or indeed of any mechanism involving the triplet state, is negligible. The same conclusion has been reached by Richards, *et al.*,[5] in a laser study of the pyrene photoionization in ethanol. We are planning further experiments with the aim of obtaining more information about this photoionization reaction.

Acknowledgments. Thanks are due to Mrs. S. Reiche and Miss U. Heine for valuable assistance with the flash experiments.

[5] J. T. Richards, G. West, and J. K. Thomas, *J. Phys. Chem.*, **74**, 4137 (1970).

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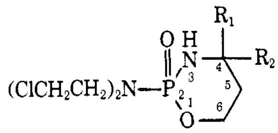
Studies on Cyclophosphamide Metabolites and Their Related Compounds. II.[1] Preparation of an Active Species of Cyclophosphamide and Some Related Compounds

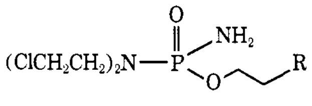
Sir:

The mechanism of the *in vivo* activation of cyclophosphamide (**1**) to the cytostatically effective species has been a matter of considerable interest in recent years.[2] In 1963, Brock and Hohorst[3] found that liver microsomal oxidation is responsible for the activation process. Hill and coworkers,[4,5] and also the authors,[1] isolated 4-ketocyclophosphamide (**2**) and its ring-opened carboxylic acid **4** as the urinary metabolites of animals treated with cyclophosphamide, which indicates that the metabolic reaction of cyclophosphamide involves mainly oxidation at the C-4 position on the oxazaphosphorine ring. However, these oxidized metabolites were found to be cytostatically less active than cyclophosphamide in *in vivo* experiments[1,6,7] indicating that the activation of cyclophosphamide occurs in an earlier phase of the oxidation. Thus, 4-hydroxycyclophosphamide (**3**) or the ring-opened aldehyde **5** have recently been proposed as the active species.[6]

We now report the preparation of 4-hydroxycyclophosphamide (**3**) and some related compounds which exhibit pronounced cytostatic activities in both *in vivo* and *in vitro* experiments, confirming that C-4 hydroxylation is indeed responsible for the activation of cyclophosphamide.



1, $R_1 = R_2 = H$
2, $R_1, R_2 = O$
3, $R_1 = H;\ R_2 = OH$
8, $R_1 = H;\ R_2 = OOH$



4, $R = COOH$
5, $R = CHO$
11, $R = COOEt$
12, $R = COOCH_2C_6H_5$

Reaction of $POCl_3$ with 3-buten-1-ol in CH_2Cl_2 at −10° for 4 hr, followed by treatment with *N,N*-bis(2-chloroethyl)amine hydrochloride and NEt_3 at −5 to −10° for 3 hr, and finally with NH_3 at 0° for 2 hr, afforded *O*-3-butenyl *N,N*-bis(2-chloroethyl) phosphorodiamidate (**6**),[8] mp 20°, in 73% overall yield. Attempts to prepare the aldehyde **5** or its ring-closed equivalent **3** by ozonolysis of the olefin **6** under various conditions were unsuccessful, the corresponding peroxygenated product being obtained instead as follows.

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[1] Part I: A. Takamizawa, Y. Tochino, Y. Hamashima, and T. Iwata, *Chem. Pharm. Bull.*, **20**, 1612 (1972).

[2] For example, see (a) H. Arnold, F. Bourseaux, and N. Brock, *Naturwissenschaften*, **45**, 64 (1958); (b) H. M. Rauen and K. Norpoth, *ibid.*, **52**, 477 (1965); (c) G. E. Foley, O. M. Friedman, and B. P. Drolet, *Cancer Res.*, **21**, 57 (1961); (d) H. Arnold and F. Bourseaux, *Arzneim. Forsch.*, **13**, 927 (1963); (e) H. M. Rauen and K. Norpoth, *ibid.*, **17**, 599 (1967); (f) J. L. Cohen and J. Y. Jao, *Proc. Amer. Ass. Cancer Res.*, **10**, 14 (1969); (g) N. Brock and H.-J. Hohorst, *Cancer (Philadelphia)*, **20**, 900 (1967).

[3] N. Brock and H.-J. Hohorst, *Arzneim. Forsch.*, **13**, 1021 (1963).

[4] D. L. Hill, M. C. Kirk, and R. Struck, *J. Amer. Chem. Soc.*, **92**, 3207 (1970).

[5] R. F. Struck, M. C. Kirk, L. B. Mellett, S. El Dareer, and D. L. Hill, *Mol. Pharmacol.*, **7**, 519 (1971).

[6] H.-J. Hohorst, A. Ziemann, and N. Brock, *Arzneim. Forsch.*, **21**, 1254 (1971).

[7] K. Norpoth, E. Golovinsky, and H. M. Rauen, *Hoppe-Seyler's Z. Physiol. Chem.*, **351**, 377 (1970).

[8] Elemental analysis and molecular weight determination are consistent with the assigned structure.