(22) H. O. House and P. D. Weeks, *J. Am. Chem. Soc.*, **97**, 2785 (1975).
(23) R. D. Bates, L. M. Kroposki, and D. E. Potter, *J. Org. Chem.*, **37**, 560 (1972).
(24) J. Malek, M. Cerny, and R. Rericha, *Collect. Czech. Chem. Commun.*, **39**, 2656 (1974).
(25) M. Cerny and J. Malek, *Collect. Czech. Chem. Commun.*, **39**, 842 (1974).
(26) G. LeGuillanton, *Bull. Soc. Chim. Fr.*, 627 (1974).
(27) N. Kornblum, *Angew. Chem., Int. Ed. Engl.*, **14**, 734 (1975).
(28) I. Granoth, L. Gradovski, and R. Alkabets, *J. Org. Chem.*, **40**, 2304 (1975).
(29) H. Normant, *Adv. Org. Chem.*, **2**, 1 (1960).
(30) I. Granoth, J. B. Levy, and C. Symmes, Jr., *J. Chem. Soc., Perkin Trans. 2*, 697 (1972).
(31) J. L. Kice and F. Taymoorian, *J. Am. Chem. Soc.*, **81**, 3405 (1959).
(32) S. C. W. Hook and B. Saville, *J. Chem. Soc., Perkin Trans. 2*, 589 (1975).
(33) D. S. Hoffenberg, E. M. Smolina, and K. Matsuda, *J. Chem. Eng. Data*, **9**, 104 (1964).
(34) M. Vinatoru, M. Elian, and E. Cioranescu, *Org. Prep. Proced. Int.*, **7**, 98 (1975).
(35) E. Grovenstein, Jr., and L. P. Williams, Jr., *J. Am. Chem. Soc.*, **83**, 2537 (1961).
(36) A. Klages and S. Heilmann, *Ber.*, **37**, 1447 (1904).
(37) V. N. Ipatieff, H. R. Appell, and H. Pines, *J. Am. Chem. Soc.*, **73**, 5507 (1951).

Photoinduced Rearrangement and Related Reactions of Ethyl *N*-Phenylcarbamate

Divakar Masilamani and Robert O. Hutchins*

Department of Chemistry, Drexel University, Philadelphia, Pennsylvania 19104

Jack Ohr

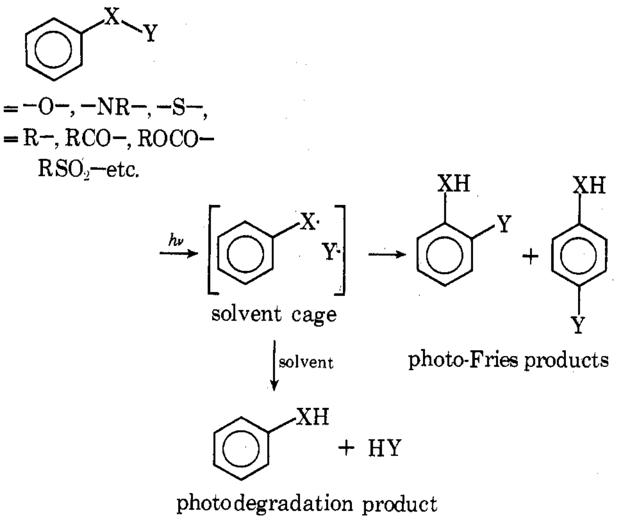
Aero Materials Laboratory, Naval Air Development Center, Warminster, Pennsylvania 18974

Received July 22, 1975

The photoinduced transformation of ethyl *N*-phenylcarbamate (**1**) to ethyl *o*-aminobenzoate (**2**), ethyl *p*-aminobenzoate (**3**), and aniline (**4**) is concentration dependent. At low concentrations, aniline is the exclusive nonpolymeric product. At higher concentrations of **1**, all three products are observed with **2** predominant, but the photoyield is reduced. The results are attributed to the formation of hydrogen-bonded aggregations at higher concentrations which favors similar rearrangement as observed in photo-Fries reactions and to the photolability of **3** and **4**.

Since the initial discovery of the photo-Fries rearrangement by Anderson and Reese in 1960,[1] similar reactions are found to be fairly general for aromatic systems linked to a carbonyl or sulfonyl group through a heteroatom, particularly O, N, or S. Scheme I depicts the overall reaction types observed along with the generally accepted mechanism involving initial light induced homolytic cleavage of the X–Y bond followed by rearrangement of the resulting biradical to the observed ortho and para products. In addition, cleavage products resulting from hydrogen atom abstraction by the intermediate radicals usually accompany the rearrangement products. However, the absence of crossover products[2c] has led to the suggestion[2a] that the rearrangements proceed by intramolecular 1,3 and 1,5 sigmatropic shifts, but this interpretation has been questioned.[3] On the other hand, the absence of crossover products from radicals may be explained if such intermediates are trapped in a solvent cage.[4] The degradation products resulting from hydrogen abstraction evidently result from escape of the radicals from the cage. This is consistent with the observation that the ratio of rearrangement to degradation products is enhanced in viscous solvents in which the cage should be more efficient.[5,6] In fact, no degradation products were observed at all in a polyethylene matrix.[7]

Scheme I

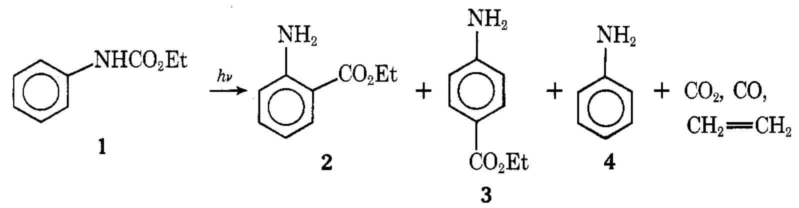


Our interest in the photodegradation of polyurethanes prompted this present investigation of the photochemistry of ethyl *N*-phenylcarbamate (**1**) as a model representative. Irradiation of **1** under a variety of conditions has been previously reported[8–12] to afford a combination of photoinduced rearrangements and photodegradation products as summarized in Table I. As seen, the percent conversion of **1** is consistently low and the ratio of degradation to rearrangement products appears to be nearly independent of solvent viscosity and irradiation time.

Recently, Schwetlick and co-workers[11,13,14] have examined the photoproducts carefully for a variety of *N*-phenylcarbamates and measured the quantum yields in different solvents. Their results were ascribed to a combination of N–C bond cleavage (Scheme I) and C–O bond cleavage which affords an amido radical which further dissociates to the anilino radical and carbon monoxide; the former eventually gives aniline and/or polymers.

A systematic analysis of the concentration dependence of the carbamates on the overall photoyields and relative ratios of the photoproducts has not been attempted. Such an investigation should provide clues as to the nature of the intermediates and whether the process is concerted or one involving biradical intermediates. Secondly, the photostabilities of the products have not been investigated. Recent work[16] on

Table I. Irradiation of Ethyl *N*-Phenylcarbamate (1)



Irradn source[a]	Time, h (temp, °C)	Concn of 1	% convn	% yields[b] 2	3	4	Others	Ref
B	96 (25)	0.25 M (*t*-BuOH)	5	53	14	10		8
A	95 (65)	0.066 M (C_2H_5OH)	14	37	8	30		9
A	48 (60)	Molten, under O_2	7	37	3	34	Azo compd	10
B	6 (20)	1.5×10^{-2} (several solvents)	17–30	24–43	16–34	5–19		11
C	8 (25)	10^{-2} (*i*-PrOH)	8	23	29	24		12

[a] Source A, low-pressure Hg lamp; source B, medium-pressure Hg lamp; source C, high-pressure Hg lamp. [b] The percent yields were determined by GLC.

Table II. Photolysis[a] of Ethyl *N*-Phenylcarbamate (1)

Entry	Solvent	Concn, M	Time, h	% conversion of 1	Yield, %[b] 2	3	4	% loss[c] of 1	Solvent dimers 5, 6 (mole ratio)[d]
				A. Neutral Medium					
1	Ethanol	10^{-3}	3	99	0	0	Tr	99	5 (9)
2	Ethanol	10^{-3}	24	99	0	0	0	99	5 (9)
3	Ethanol	2×10^{-3}	10	56.7	0	0	Tr	56.7	5 (9)
4	Ethanol	$3.5(10^{-3})$	24	60	0	0	Tr	60	5 (9)
5	Ethanol	6×10^{-3}	24	45	2.5	0.5	1	41	
6	Ethanol	10^{-2}	36	29	2.5	1.5	1	13	
7	Ethanol	10^{-2}	24	20	3	3	1	13	5 (9)
8	Ethanol	5×10^{-2}	24	7					
9	Cyclohexane	10^{-3}	24	99	0	0	0	99	6 (0.5)
10	Cyclohexane	$2.5(10^{-3})$	24	74	21	16	4	33	6 (0.5)
11	Cyclohexane	5×10^{-3}	24	55	10	7	2	36	6 (0.5)
12	Cyclohexane	10^{-2}	24	32	7	4	1	20	6 (0.4)
13	Cyclohexane	2×10^{-2}	24	18	4	3	2	8	6
14	Cyclohexane	5×10^{-2}	24	8	2	2	2	2	6
				B. Acid Medium					
15	Ethanol	$3.3(10^{-2})$	72	7	2	0.8	2	2	
16	Ethanol	8×10^{-2}	72	4	0.8	0.2	1	2	
17	Cyclohexane	5×10^{-3}	72	16	2.3	1	7.5	5	
18	Cyclohexane	5×10^{-3}	72	15	4	0	6	5	

[a] Photolysis was carried out in cell of 100-ml capacity under nitrogen. A Hanovia low-pressure mercury lamp (90% emission at 2537 Å) was used and the temperature varied from 42 to 48 °C. [b] Based on the internal standard used during GLC analysis. (See Experimental Section.) [c] Percent loss is the difference between the percent conversion of 1 and the combined percentage yields of 2, 3, and 4 and it is indicative of the polymeric material formed from 1. [d] Mole ratio refers to the number of moles of *meso*- and *dl*-2,3-butanediol (5) or cyclohexylcyclohexane (6) formed per mole of 1 converted.

the photolysis of aniline has demonstrated a two-electron ionization process giving rise to anilinium ion and solvated electrons.

In order to gain further insight into the above questions, a systematic investigation of the photolysis of 1 was undertaken in the polar protic solvent ethanol and the nonpolar aprotic solvent cyclohexane.

Results and Discussion

As a initial probe, a 5×10^{-5} M solution of 1 in ethanol was irradiated at 2537 Å using uv spectroscopy to monitor the disappearance of starting material. Surprisingly, in contrast to reports of others, at 42 °C the half-life for conversion of 1 was only ca. 2.5 h. Even more unexpectedly, the photorearranged products 2 and 3 were completely absent as evident from the lack of characteristic absorptions at 330 and 290 nm, respectively. Concentration of the reaction solution and subsequent analysis by GLC indicated trace amounts of aniline (4) but no evidence for 2 and 3. The bulk of the products appeared to be nonvolatile, colored, polymeric materials which could not be characterized.

In view of the divergence of the above results from those previously reported, the concentration dependence of the conversion of 1 was followed by GLC and the results summarized in Table II. In 10^{-3} to 3.5×10^{-3} M ethanolic solutions, 1 was completely consumed within 24 h but only aniline (4) was produced and only in trace quantities with no evidence for rearrangement products 2 and 3. However, significant amounts of *meso*- and *dl*-2,3-butanediol (5) were detected, apparently arising from dimerization of solvent (vide infra). As the concentration of 1 in ethanol was increased (to 6×10^{-3} M), photoinduced rearrangement products began to appear with the ortho (2) predominating. As the concentration of 1 was further increased, the yield of the para product 3 improved; however, the yield of aniline was essentially constant at about 1%. In addition, the percent conversion of 1 dra-

Table III. Relative Photostabilities[a] of Aromatic Amines

Entry	Amine	Solvent	Concn, M	% lost[b]	Solvent dimer (mole ratio)[c]
1	**2**	Ethanol	5×10^{-3}	12	**5** (trace)
2	**2**	Cyclohexane	10^{-2}	2	None
3	**3**	Ethanol	5×10^{-3}	86	**5** (3.0)
4	**3**	Cyclohexane	10^{-2}	43	**6** (0.2)
5	**4**	Ethanol	10^{-2}	100	**5** (1.9)
6	**4**	Cyclohexane	10^{-2}	90	**6** (0.025)
7	**1**			97	
	2	Ethanol	4×10^{-3}	9	
	3		each	65	
	4			99	
8	**2**			1	
	3	Cyclo-	4×10^{-3}	16	
	4	hexane	each	63	

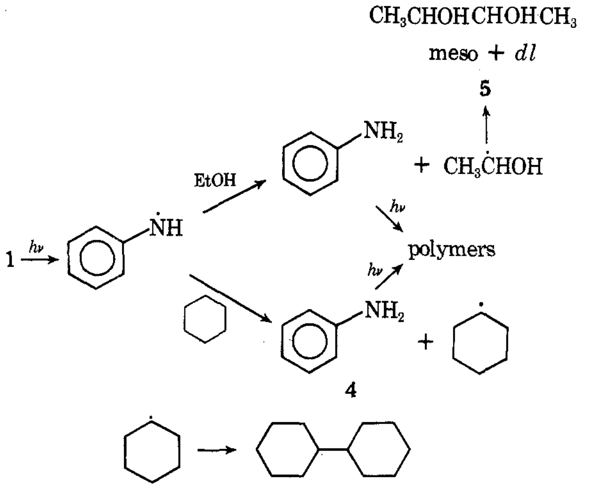
[a] Photolysis was carried out in a cell of 100-ml capacity under nitrogen for 24 h. A Hanovia low-pressure mercury lamp (90% emission at 2537 Å) was used. The temperature varied from 42 to 48 °C. [b] Based on the internal standard used during GLC analysis. (See Experimental Section.) [c] Mole ratio refers to the number of moles of *meso*- and *dl*-2,3-butanediol (**5**) or cyclohexylcyclohexane (**6**) formed per mole of amine destroyed.

matically dropped as photo-Fries products **2** and **3** began to appear.

In cyclohexane, similar results were obtained except that photoproducts **2** and **3** began to appear at lower concentrations (2.5×10^{-3}); solvent dimer [cyclohexylcyclohexane (**6**)] was also produced.

Ostensibly, the formation of dimeric products **5** and **6** is indicative of hydrogen abstraction from ethanol and cyclohexane, respectively. Photoinduced rearrangement products do not involve hydrogen abstraction from solvent, but the formation of aniline from anilino radicals does. The miniscule amounts of aniline produced implies that it is probably consumed in a subsequent polymerization step as illustrated in Scheme II.

Scheme II



Indeed, under identical photolytic conditions, aniline in ethanol was completely destroyed forming polymeric products and 2,3-butanediols (**5**); 2 mol of **5** were produced per mole of **4** (Table III, entry 5). In cyclohexane, the disappearance of aniline occurred more slowly and **6** was produced only in small quantities (Table III, entry 6). Ethyl *p*-aminobenzoate (**3**) also reacted under photolysis (entries 3 and 4, Table III). However, the ortho isomer **2** was quite stable with only ca. 2 and 12% losses of **2** observed in cyclohexane and ethanol, respectively (Table III, entries 1 and 2). Similarly, irradiation of a mixture of **1**, **2**, **3**, and **4** resulted in the complete destruction of **4** in ethanol (64% in cyclohexane) and, again, the least affected compound was the ortho derivative **2** (entries 7 and 8, Table III). From these observations, it appears that the photoinduced rearrangement products previously reported are not the primary products of photolysis and further, the predominance of the ortho isomer **2** is evidently an artifact, arising from selective destruction of the para product and of aniline. The mechanism for the photodestruction of aniline in ethanol (at 77 K) has been investigated by Alfimov[15] and appears to involve a two-quanta photoionization process to yield anilinium ions and solvated electrons. The latter, upon warming, produced $CH_3\dot{C}HOH$ radicals which were identified by EPR. In our case, these radicals evidently dimerize to observed *meso*- and *dl*-butanediols (**5**). Ethyl *p*-aminobenzoate (**3**) probably undergoes a similar reaction, but is considerably deactivated by the electron-withdrawing ester group. The unusual photostability of **2** can be accounted for in terms of a mechanism involving prototropy rather than ionization as with **3** and **4**. Photolysis of **2** may result in the transfer of a proton from the amine nitrogen to the carbonyl oxygen giving rise to the unstable imino enol which spontaneously reverses back to **2** in a thermal process. Similar processes are well known in a number of ortho-substituted aromatic systems.[16]

Photostability of **2** also provides a handle for estimating the lower concentration limit for **1** at which the rearrangement pathway begins to operate (ca. 6×10^{-3} M in ethanol and ca. 2.5×10^{-3} M in cyclohexane). Since **2** is absent at lower concentrations, a concerted sigmatropic mechanism for photoinduced rearrangement may be ruled out since intramolecular process should be quite competitive at low concentrations.

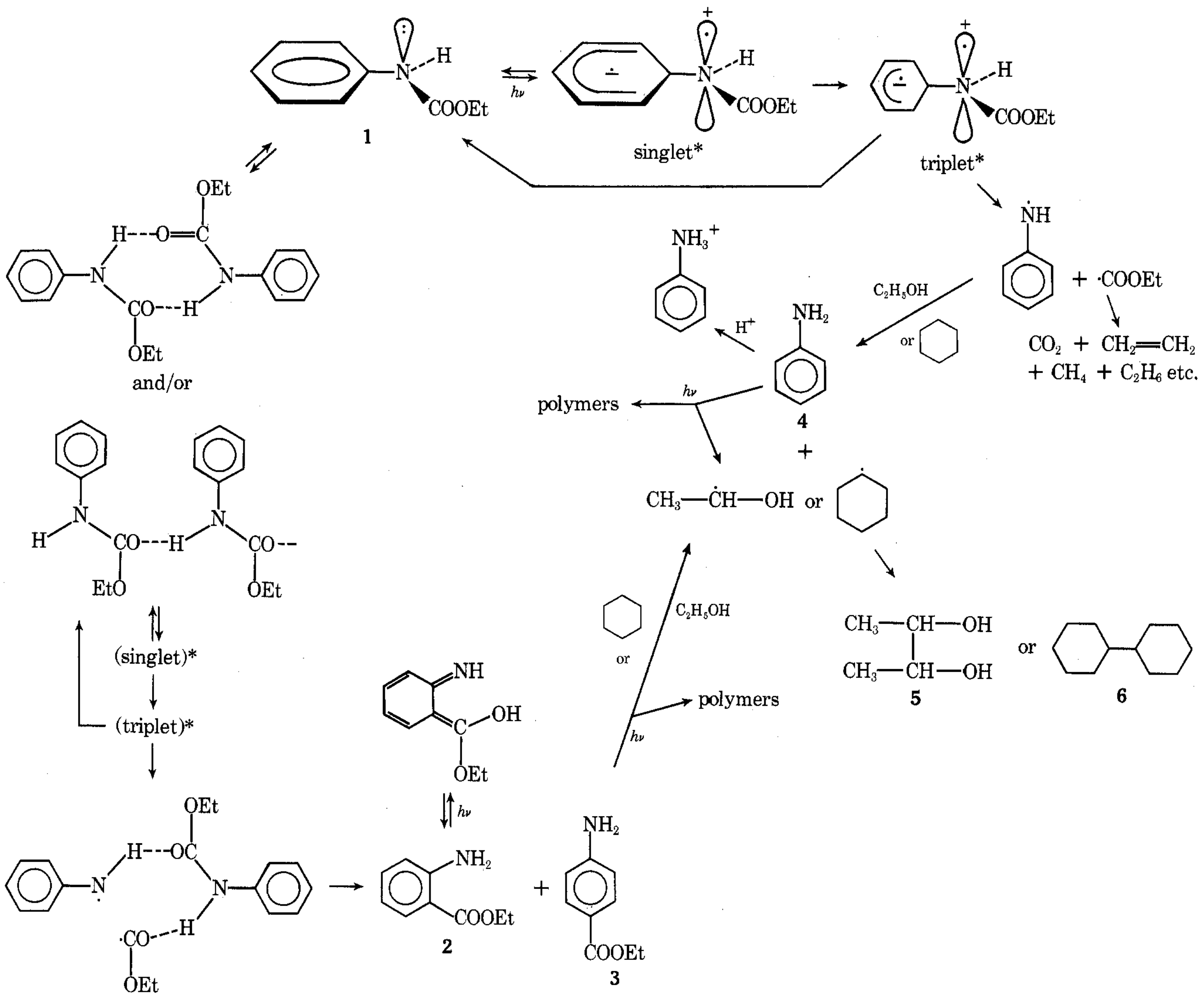
The direct formation of aniline from **1** at low concentrations was demonstrated by trapping the primary photolysis products in the presence of HCl as the amine salts which prevents subsequent decay. As expected, aniline is the major product during the photolysis of **1** in ethanol in the presence of HCl even in concentration ranges as high as 3.3×10^{-2} and 8.0×10^{-2} M (Table II, entries 15 and 16). In cyclohexane, in the same concentration ranges, rearrangement competes more efficiently with photodegradation to aniline (Table II, entries 17 and 18).

The low yields of photoproducts at higher concentrations of **1** may arise from self-quenching of a triplet excited state. Such a state has been implicated by Beachell and Chang[10] on the basis that the oxygen absorption rate of **1** during photolysis was enhanced by triplet sensitizers.[10b] In fact, the photoreaction of **1** was suppressed in the presence of a triplet quencher (naphthalene) even at low dilution. The theoretical rationale for triplet state participation in the photo-Fries rearrangement has been provided recently by Dauben, Salem, and Turro.[17]

In N-substituted anilines, the rate of formation as well as the lifetime of the triplet states[18] is increased compared to those in aniline. In **1**, a triplet excited state geometry will aid in weakening the N–C bond through hyperconjugative effect of the π electrons of the benzene ring. (See Scheme III.) Such a bond weakening is not possible in the singlet excited state. However, the longer lifetime also makes the triplet state vulnerable to possible self-quenching by other nonexcited molecules of **1**. The amine products **2**, **3**, and **4** should also be efficient as triplet quenchers.[19]

At low concentrations (10^{-3} M) the reactant molecules are solvent separated and the efficiency of a bimolecular

Scheme III



quenching process will decrease accordingly. The bond cleavage at N–CO bond can now occur producing the anilino and ethyl carboxylate radicals. The anilino radical may abstract a hydrogen from the solvent forming aniline while the carboxylate radical probably undergoes further cleavage producing carbon dioxide and ethyl radicals. This process is exothermic by 7 kcal/mol[11] (activation energy of ca. 1 kcal/mol[20]). The ethyl radical is converted principally to ethylene, hydrogen, and methane.[11]

At higher concentration, 1 forms cyclic hydrogen-bonded dimers as well as chain polymers. This aspect has been studied in detail by Zharkov and Rudnevskii.[21]

In hydrogen-bonded aggregates there is greater scope for photo-Fries type rearrangement; however, there is also an increased possibility for self-quenching. Thus, the appearance of the photorearrangement products is accompanied by a corresponding decrease in photoyields (Table II). Further, 1 will form hydrogen-bonded clusters at a lower concentration in apolar solvents such as cyclohexane than in the polar protic solvent ethanol. Thus, rearrangement products should appear at lower concentration levels in cyclohexane than in ethanol and this is indeed observed.

The above mechanistic details are presented in Scheme III. The results seem best accommodated by the assumption that an equilibrium exists between the monomers and hydrogen-bonded polymers of 1 which controls the product distribution. Viscosity seems to play a minor role. At low concentrations monomers predominate. The number of photons per mole of 1 is high and the percentage conversion of 1 is also substantial.[23] Aniline is the only product formed in substantial quantities but it is destroyed in a subsequent photochemical step. As the concentration of 1 increases, the equilibrium shifts in favor of hydrogen-bonded clusters and photo-Fries products begin to form. However, bimolecular quenching also becomes efficient and the photoyield goes down; the number of photons per mole of 1 also decreases. Such a decrease not only cuts down the yield of products but also their subsequent photodestruction. (See Table III, entries 7 and 8.) At long exposure times, the percentage of the ortho isomer 2 will increase relative to 3 and 4 because of its optical stability. A steady state mechanism will operate maintaining the concentrations of 3 and 4 at a constant level.

Summary. Among compounds undergoing photoinduced rearrangement, ethyl *N*-phenylcarbamate (1) is apparently a special case. The extent of photoconversion is concentration dependent possibly because of the involvement of a triplet excited state. At low concentrations, only aniline (4) is formed through hydrogen abstraction from surrounding solvent molecules. At higher concentrations, 1 forms hydrogen-bonded clusters which undergo essentially photo-Fries type rearrangement; however, these clusters are also vulnerable to self-quenching and hence the photoyields are low. Unless protonated by an acid, aniline is completely decomposed to polymeric material in a subsequent photoionization process. Ethyl *p*-aminobenzoate (3) is also degraded, but to a smaller extent. The ortho isomer 2 is however stable probably because

of its conversion to a conjugated imino enol which cannot undergo photoionization. It is unlikely that **2** and **3** are formed in concerted sigmatropic rearrangements.

Experimental Section

Commercial ethyl *N*-phenylcarbamate was decolorized by activated carbon in refluxing ethanol and purified by sublimation, mp 52 °C (lit.[10] 52 °C). Aniline and ethyl *o*-aminobenzoate was distilled before use and ethyl *p*-aminobenzoate was purified by crystallization in ethanol. A mixture of *meso*- and *dl*-2,3-butanediol was prepared by the reduction of 2,3-butanedione with lithium aluminum hydride in refluxing ether.

Photochemical Apparatus. A 100-ml photocell was employed which was provided with a 24/40 joint for inserting a Hanovia low-pressure mercury lamp (2.5 W) emitting 90% of radiations of 2537 Å. The cell was provided with an air-tight condenser and flushed with nitrogen before and during photolysis. The solution in the cell was stirred magnetically. The cell was wrapped in aluminum foil.

After photolysis, the solution was concentrated[24] on a rotary evaporator and was directly analyzed in a gas chromatograph using a 6-ft 20% Carbowax (20M) column (0.125 in. diameter) operating between 170 and 210 °C. Sulfolane was used as an internal standard whenever necessary and the response ratios were evaluated from pure authentic samples. The experimental results are summarized in Table II. When photolyzed in the presence of an acid (usually HCl, 10^{-1} M) the photoproducts were basified and extracted with ether. The ether solution was dried ($MgSO_4$), concentrated, and analyzed as before.

Kinetic Runs. The photocell was similar to the one described above. A 5×10^{-5} solution of **1** in ethanol was taken in the flask and photolyzed over a period of 24 h. Samples (5 ml) were withdrawn periodically by means of a syringe and the uv spectrum recorded for each sample. From the change in the absorbance at 2340–2350 Å, the rate of disappearance of I was evaluated to be $4.587 \pm 0.178 \times 10^{-3}$ min^{-1} corresponding to a half-life of 2.5 h.

The output of the lamp was determined with an uranyl oxalate actinometry according to the method of McLaren and Schugar.[22] The quantum yield was of the order of 0.45.

Acknowledgment. The authors wish to express their thanks to the Aero Materials Laboratory, Naval Air Development Center, Warminster, Pa., for support of this research.

Registry No.—**1**, 101-99-5; **2**, 87-25-2; **3**, 94-09-7; **4**, 62-53-3.

References and Notes

(1) J. C. Anderson and C. B. Reese, *Proc. Chem. Soc., London,* 217 (1960).

(2) A large body of literature including two review articles listed below are available. (a) D. Bellus, *Adv. Photochem.,* **8,** 109 (1971); (b) V. I. Stenberg, *Org. Photochem.,* **1,** 127 (1967); (c) R. A. Finnegan and J. J. Mattice, *Tetrahedron,* **21,** 1015 (1965).

(3) C. E. Kalmus and D. M. Hercules, *J. Am. Chem. Soc.,* **96,** 449 (1974).

(4) H. Kobsa, Abstracts, 148th National Meeting of the American Chemical Society, Chicago, Ill., August 1964, No. 12E.

(5) M. R. Sandner, E. Hedaya, and D. J. Trecker, *J. Am. Chem. Soc.,* **90,** 7249 (1968).

(6) M. R. Sandner and D. J. Trecker, *J. Am. Chem. Soc.,* **89,** 5725 (1967).

(7) G. M. Coppinger and E. R. Bell, *J. Phys. Chem.,* **70,** 3479 (1966).

(8) D. J. Trecker, R. S. Foote, and C. L. Osborn, *Chem. Commun.,* 1034 (1968).

(9) D. Bellus and K. Schaffner, *Helv. Chim. Acta,* **51,** 221 (1968).

(10) (a) H. C. Beachell and I. L. Chang, *J. Polym. Sci.,* **10,** 503 (1972). (b) The photoproducts **2**, **3**, and **4** react with oxygen during photolysis.

(11) K. Schwetlick, R. Noack, and G. Schmieder *Z. Chem.,* **12,** 107 (1972).

(12) H. J. Hageman, *Recl. Trav. Chim. Pays-Bas.,* **91,** 362 (1972).

(13) R. Noack and K. Schwetlick, *Z. Chem.,* **12,** 108 (1972); **12,** 140 (1972); **12,** 143 (1972); **14,** 99 (1973).

(14) K. Schwetlick and R. Noack, *Z. Chem.,* **12,** 109 (1972).

(15) (a) M. V. Alfimov and I-G. Batekha, *Khim. Vys. Energ.,* **2,** 123 (1968); (b) M. V. Alfimov, V. A. Smirnov, *ibid.,* **2,** 186, (1968); (c) M. V. Alfimov, V. A. Smirnov, N. V. Seregin and V. Ya, *Agroskin, Dokl. Nauk SSSR,* **191,** 103 (1970).

(16) D. M. Findlay and M. F. Tchir, *J. Chem. Soc., Chem. Commun.,* 514 (1974).

(17) W. G. Dauben, L. Salem, and N. J. Turro, *Acc. Chem. Res.,* **8,** 41 (1975).

(18) F. Kraus, E. Gregorek, and H. Von Weyssenhoff, *Z. Phys. Chem.,* **82,** 139 (1972).

(19) R. W. Yip, R. O. Loutfy, Y. L. Chow, and L. K. Magdzinski, *Can. J. Chem.,* **50,** 3426 (1972).

(20) Y. Shigemitsu, T. Tominaga, T. Shimodair, Y. Odaira, and S. Tsutsumi, *Bull. Chem. Soc. Jpn.,* **39,** 2463 (1966).

(21) V. V. Zharkov and N. K. Rudnevskii, *Tr. Khim. Khim. Tekhnol.,* 175 (1965).

(22) A. D. McLaren and D. Shugar, "Photochemistry of Protein and Nucleic Acids", MacMillan, New York, N.Y., 1964, p 378.

(23) A referee suggested that a larger photoyield is to be expected at lower concentrations of **1** since more quanta of light are available for each molecule. However photolysis of **1** at the higher concentrations for extended periods of time (1 week) did not increase the photoyields over those obtained in 3 days.

(24) Care was taken to avoid loss of photoproducts during concentration.

Methylation of Nucleic Acid–Bases with Trimethyl Phosphate

Kiyoshi Yamauchi,* Toshizumi Tanabe, and Masayoshi Kinoshita

Department of Applied Chemistry, Osaka City University, Sumiyoshi-ku, Osaka, Japan

Received April 30, 1976

The action of trimethyl phosphate (TMP) on cytosine, thymine, uracil, adenine, and guanine has been examined in a homogeneous aqueous phase at 25–60 °C, pH 9–12. All these nucleic acid–bases underwent methylation reactions, showing the following reactivity order on the methylating site in each base: cytosine, N-1 > N-3; thymine and uracil, N-1 $\sim$ N-3; adenine, N-9 $\sim$ N-3 > N-7, N-1; guanine, N-1 $\gtrsim$ N-7 > N-3 > N-9, O-6. These results and reactions of monomethylated bases with TMP suggested TMP as an useful modifying agent for nucleic acids. The use of TMP as additives for commercial products was also considered briefly.

The direct N-alkylation of basic moieties of nucleic acids has been the subject of considerable chemical and biological interest in recent years. Such reactions may be not only useful in a synthetic point of view but also relevant to the study of mutagenic and carcinogenic effects which occur in living systems caused by alkylating agent.

Various alkylating agents have been employed in such investigations such as nitrogen[1,2] and sulfur[3,4] mustards as well as diazoalkanes,[5,6] alkyl esters of sulfurous oxy acids,[7–13] alkyl halides,[14–16] and others.[17–20]

However, there have been no alkylation studies with trimethyl phosphate (TMP), although TMP has been shown recently to cause mutagenic effects in male mice[21] as well as in Neurospora.[22] In vivo, TMP has been reported to function as alkylating agent, degrading in the rat to dimethyl hydrogen phosphate with formation of *S*-methylcysteine as an urinary metabolite.[23] It would, therefore, be interesting to study the reactivity of TMP toward nucleic acids, their components, and other natural products.

With these aspects in mind, we have studied the reactivity of TMP, showing previously N-methylation of imidazoles, purines, and pyrimidines upon fusing these bases in TMP at 160–220 °C.[24,25] Aside from its synthetic utility, however, this procedure would be too vigorous for the study of the action