Effects of Distant Substituents on Photoinduced Aromatic Substitution Reactions[1,2]

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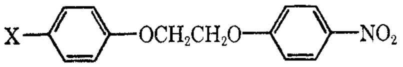
Electron-donating substituents (X) markedly retard photoinduced nucleophilic attack on compounds in the series $XC_6H_4OC_6H_4NO_2$. The methoxyl group ($X = OCH_3$) similarly retards photoinduced nucleophilic attack at the nitroaromatic ring in $XC_6H_4OCH_2CH_2OC_6H_4NO_2$. Emission-spectral data and experiments with model compounds suggest that the deactivation results from interaction of the photoexcited nitroaromatic ring with the dialkoxybenzene ring to yield a transient species which is inactive or of very low reactivity in nucleophilic substitution.

The photoinduced reactions of nitroaromatics with nucleophiles such as pyridine, hydroxide, and cyanide are markedly dependent on substituent groups in the aromatic compound.[2,4,5] For example, pyridine in dilute aqueous solution reacts readily with photoexcited 4-nitroanisole but fails to react with excited nitrobenzene or 4-nitrophenol.

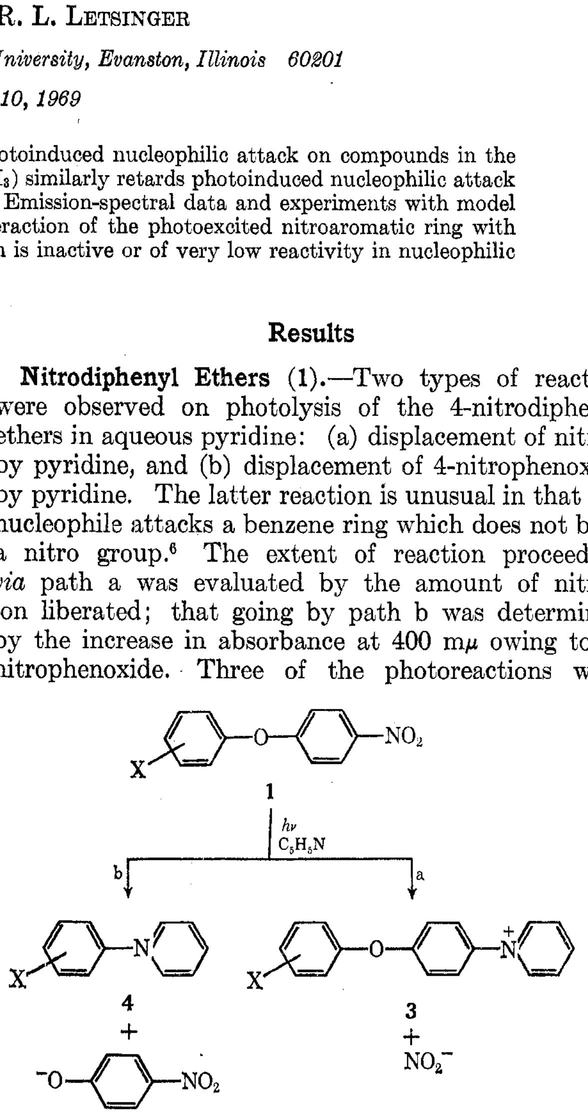
As part of a program aimed at learning more about the effects of substituent groups in such systems, we have examined photoreactions of a series of substituted 4-nitrodiphenyl ethers (**1**) and several 2-aryloxy-1-(4-nitrophenoxy)ethanes (**2**). Several features common to the two series led to this choice. All compounds have an oxygen atom *para* to the nitro group; therefore, the structures are favorable for some type of photoinduced substitution. Since the nitrophenoxy group is the dominant chromophore, the light-absorbing step should be essentially independent of the substituent. These series therefore provide a measure of effects of substituents exerted subsequent to the absorption of light. In addition, steric effects should be negligible, since the substituents are remote from the reactive nitroaromatic function. There are also characteristics unique to each system. Thus the oxygen bridge in **1** permits electronic effects to be transmitted from one ring to the other, whereas the two methylene groups in **2** would severely limit transmission of inductive and resonance effects. An aqueous solution containing a high concentration of pyridine (20% by volume) was selected as the reaction medium for the survey. Subsequently, the major effects were checked with key substrates reacting with ionic nucleophiles at low concentration.

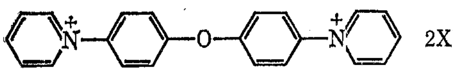


2a, X = H
b, X = CN
c, X = OCH_3

Results

Nitrodiphenyl Ethers (1).—Two types of reaction were observed on photolysis of the 4-nitrodiphenyl ethers in aqueous pyridine: (a) displacement of nitrite by pyridine, and (b) displacement of 4-nitrophenoxide by pyridine. The latter reaction is unusual in that the nucleophile attacks a benzene ring which does not bear a nitro group.[6] The extent of reaction proceeding *via* path a was evaluated by the amount of nitrite ion liberated; that going by path b was determined by the increase in absorbance at 400 mμ owing to 4-nitrophenoxide. Three of the photoreactions were carried out on a preparative scale and the pyridinium salts were isolated and characterized as picrates. N-[4-(4-Cyanophenoxy)phenyl]pyridinium picrate (cation **3**, X = 4-CN), N-4-(3-cyanophenoxy)phenyl pyridinium picrate (cation **3**, X = 3-CN), and the bis-N-pyridinium picrate **5** were obtained from reactions of the corresponding ethers (**1**, X = 4-CN, 3-CN, and 4-NO_2) in yields of 49, 94, and 56%, respectively.





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Rate and product data for photoreactions of the 4-nitrodiphenyl ethers in an aqueous solution 20% in pyridine and 22% in *t*-butyl alcohol at 25° are assembled in Tables I and II. It may be noted that the absorption spectra of the nitro compounds in the reaction solvent are indeed very similar. Accordingly,

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[1] This research was supported in part by a research grant from the National Science Foundation (GP 5715).

[2] Part VIII in the series on photoinduced substitution. For part VII, see R. L. Letsinger and J. H. McCain, *J. Amer. Chem. Soc.*, **91**, 6425 (1969).

[3] Public Health Service Predoctoral Fellow.

[4] R. L. Letsinger and O. B. Ramsay, *J. Amer. Chem. Soc.*, **86**, 1447 (1964); R. L. Letsinger, O. B. Ramsay, and J. H. McCain, *ibid.*, **87**, 2945 (1965).

[5] E. Havinga, R. O. de Jongh, and M. E. Kronenberg, *Helv. Chim. Acta.*, **50**, 2550 (1967), and references cited therein.

[6] This reaction was discovered by Dr. O. B. Ramsay, who characterized the nitrophenol and N-phenylpyridinium salt produced from the photoreaction of 4-nitrodiphenyl ether with pyridine: O. B. Ramsay and R. L. Letsinger, Abstracts, 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1964.

TABLE I
PHOTOREACTION OF $XC_6H_4OC_6H_4NO_2$ WITH PYRIDINE

Substituent	Registry no.	λ_{max},[a] mμ	$k_{obsd}/k_{obsd}^{parent}$ [b]
Parent		311	1.0
4′-Br	21969-04-0	309	1.6
4′-Cl	1836-74-4	308	2.9
3′-Cl	2303-23-3	307	1.4
4′-CN	17076-68-5	300[c]	1.7
3′-CN	17076-74-3	298[d]	1.7
4′-NO_2	101-63-3	310[e]	1.2
3′-OCH_3	22479-76-1	310	0.07
4′-OCH_3	6337-24-2	313	~0.003
4′-OH	22479-78-3	313	~0
3′-OH	22483-31-4	312	~0
4′-NH_2	6149-33-3	309	~0
3′-NH_2	22528-34-3	312	~0
4′-$NHCOCH_3$	2687-40-3	312	~0
3′-$NHCOCH_3$	22483-34-7	311	~0

[a] Determined in aqueous *t*-butyl alcohol (22%), log ε 4.06 ± 0.02 unless otherwise noted. [b] Reactions in 20% aqueous pyridine under N_2 atmosphere at 25°. [c] Log ε 4.10. [d] Log ε 4.09. [e] Log ε 4.24.

TABLE II
PRODUCTS FROM REACTIONS OF NITRODIPHENYL ETHERS WITH PYRIDINE

			Relative electrophoretic mobility at pH 10.8[a]		
Substituent	4-Nitrophenol, %	NO_2^-, phenol, %	Y	W	P
Parent	56	34	−1.0	+0.81	+1.1
4′-Br	55	43	−1.0	+0.97	+1.2
4′-Cl	60	35	−1.0	+0.98	+1.3
3′-Cl	10	80	−1.0	+0.74	
4′-CN	8	87	−1.0	+0.74	
3′-CN	4	91		+0.78	
4′-NO_2	6	90[b]		+2.0	
3′-OCH_3	10	(28)[c]			

[a] Relative to 4-nitrophenoxide. Y, W, and P refer to products which appear as yellow spots (4-nitrophenoxide) and white (N-pyridinium salt with *p*-oxygen) and purple spots (N-pyridinium salts without *p*-oxygen) on paper under uv light. [b] Based on reaction of both nitro groups; a total of 1.8 mol of NO_2^- was obtained/mol of compound. [c] Low because of long reaction time.

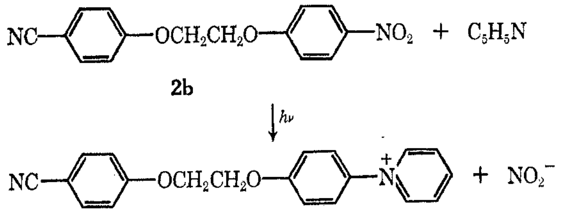
the relative rate constants approximately equal the relative quantum yields.

Three conclusions may be drawn from these results. First, electron-withdrawing groups in the 3′ and 4′ positions have little effect on the overall rate of the photochemical reaction in this system. The parent compound (4-nitrodiphenyl ether) and derivatives with chlorine, bromine, cyano, and nitro substituents at the 3′ or 4′ positions all react at rates within a factor of three of each other. Second, the strong electron-withdrawing substituents, nitro and cyano, and to a lesser extent 3′-chloro, favor reaction by path a (nitrite displacement) relative to path b (nitrophenoxide displacement). The reason for this behavior is not apparent at this time. Third, electron-donating groups such as hydroxyl, methoxyl, amino, and acetamino have a major effect on the photochemical reaction. Hydroxyl, amino, and acetamino substituents at the 3′ or 4′ positions quench the reaction completely. Methoxyl in the 3′ position inhibits the reaction somewhat (k_{obsd} = $^1/_{14}$ that of 4-nitrodiphenyl ether) and methoxyl in the 4′ position inhibits the reaction very strongly ($k_{obsd} < {}^1/_{300}$ that of 4-nitrodiphenyl ether).

Since interpretation of the effect of substituents possessing O–H and N–H bonds is complicated by possible ionization of the group in the photoexcited molecule,[7] further studies of the deactivating effect of electron-donating groups utilized methoxyl derivatives, for which deactivation by ionization is not possible.

The relative rates of reaction of 4-nitrodiphenyl ether (1×10^{-4} *M*) and 4′-methoxy-4-nitrodiphenyl ether (1×10^{-4} *M*) with sodium hydroxide (0.04 *M*), potassium cyanide (0.008 *M*), and ethylamine (0.1 *M*) in aqueous 22% *t*-butyl alcohol at 25° were determined to see whether the effect of the 4′-methoxyl group was general for nucleophilic substitution reactions. 4-Nitrodiphenyl ether was found to react readily with hydroxide to give 4-nitrophenoxide (91% by uv) and nitrite (5%). Under the same conditions, the reaction of 4′-methoxy-4-nitrodiphenyl ether was extremely slow, about $^1/_{150}$ of the rate for 4-nitrodiphenyl ether. Similar results were obtained with the other nucleophiles. In these cases the reactions were carried out in absorption cells and were followed by scanning the spectrum at appropriate time intervals of irradiation. With ethylamine the relative reactivity of the 4-methoxyphenyl and the phenyl derivatives was *ca.* $^1/_{120}$; with potassium cyanide the corresponding ratio was *ca.* $^1/_{300}$. It is therefore clear that 4′-methoxyl deactivates the excited state of the 4-nitrodiphenyl ether system responsible for nucleophilic substitution. The effect is observed in reactions of both charged and uncharged nucleophiles and at low (0.008 *M*) and very high (20% pyridine) nucleophile concentration.

2-(Aryloxy)ethyl 4-Nitrophenyl Ethers (2).—A preparative-scale reaction was carried out with 2-(4-cyanophenoxy)-1-(4-nitrophenoxy)ethane (**2b**) in aqueous pyridine in the same manner used for the 4-nitrodiphenyl ethers. An N-pyridinium product, **6**, was isolated as the picrate in 92% yield, showing that the reaction is completely analogous in type with that of 4-nitroanisole. Other reactions were carried out with dilute solutions of the ethers (1×10^{-4} *M*). That these also followed the same pathway was shown by analysis of the nitrite liberated and by electrophoresis of the organic products. In each case a single organic product was observed. It migrated as a +1 species and appeared as a white, fluorescent spot when viewed on paper under ultraviolet light.



2b

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Information on the rates of reaction of compounds **2a–c** and two related substances with pyridine are presented in Table III. 2-Phenoxy-1-(4-nitrophenoxy)ethane (**2a**) was found to react at about the same rate as 4-nitroanisole. 2-(4-Cyanophenoxy)-1-(4-nitrophenoxy)ethane (**2b**) reacted a little faster. The big

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[7] E. J. Baum, J. K. S. Wan, and J. N. Pitts, Jr., *J. Amer. Chem. Soc.*, **88**, 2652 (1966); G. Porter and P. Suppan, *Trans. Faraday Soc.*, **62**, 3375 (1966); D. Schulte-Frohlinde and C. V. Sonntag, *Z. Phys. Chem.* (Frankfurt am Main), **44**, 314 (1965).

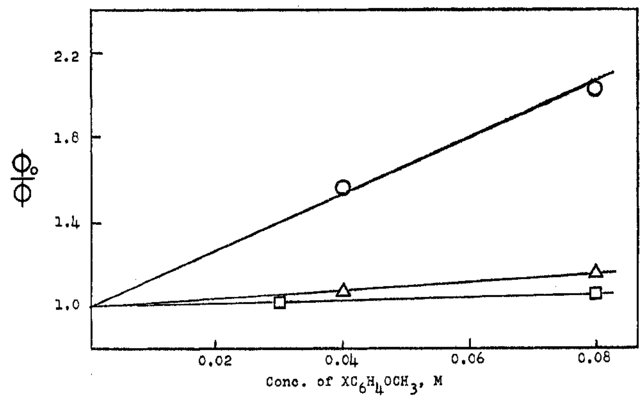

Figure 1.—Stern–Volmer plot for formation of 4-nitrophenoxide (measured by absorbance increase at 400 mμ) on irradiation of 4-nitroanisole and sodium hydroxide (0.008 *M*) in 22% *t*-BuOH at 25° in the presence of substituted anisoles, $XC_6H_4OCH_3$ (○, X = 4-OCH_3; △, X = H; □, X = 4-CN).

effect, as in the nitrodiphenyl ether series, was observed with the methoxy analog (**2c**), for which the rate was only $^1/_{23}$ that of 4-nitroanisole. Reactions of partial models for **2c**—2-methoxyethyl 4-nitrophenyl ether (**7**) and 3-(4-methoxyphenyl)propyl 4-nitrophenyl ether (**8**)—indicate that the low reactivity of **2c** is related to the dialkoxybenzene moiety. Neither the monoalkoxyphenyl substituent in **2a** nor that in **8** had an appreciable effect on the reaction. Also it does not appear reasonable to attribute the relatively low reactivity of **2c** to greater basicity of the oxygen at the 2 position of the ethane, since compound **7**, in which this oxygen should be even more basic than that in **2c**, exhibited no anomalous behavior.

TABLE III

PHOTOREACTIONS OF $XCH_3CH_2OC_6H_4NO_2$ WITH AQUEOUS PYRIDINE AT 25°

Compd	X	$k_{obsd}^{X}/k_{obsd}^{nitroanisole}$ [a]	NO_2,[b] %
2a	$C_6H_5O^-$	0.9	73
2b	p-$NCC_6H_4O^-$	1.8	83
2c	p-$CH_3OC_6H_4O^-$	0.043	(6)
7	CH_3O^-	1.4	85
8	p-$CH_3OC_6H_4CH_2^-$	1.5	

[a] Ratio of k_{obsd} for reaction of substituted ether to k_{obsd} for reaction of 4-nitroanisole under the same conditions. [b] Measured at end of the reaction. From control reactions it was found that the pyridinium salts are stable but nitrite slowly decomposes under the reaction conditions. These values are low as a consequence.

Deactivation by methoxyl was also observed for reactions of compounds **2** with other nucleophiles. As shown in Table IV, compound **2c** reacted considerably more slowly than **2a** and **2b** with hydroxide in aqueous *t*-butyl alcohol and with cyanide in aqueous dimethylacetamide.

TABLE IV

PHOTOREACTIONS OF $XC_6H_4OCH_2CH_2OC_6H_4NO_2$ WITH OH^- AND CN^-

Nucleophile (concn, *M*)	X	k_{obsd} relative to k_{obsd} for 4-nitroanisole
NaOH (0.04)[a]	H	0.2
	CN	0.7
	OCH_3	0.03
KCN (0.004)[b]	H	0.54
	CN	1.7
	OCH_3	0.014

[a] 50% v/v water-*t*-butyl alcohol. [b] 30% v/v dimethylformamide in water.

Intermolecular Quenching of Nucleophilic Substitution.—The experiments with compounds **1** and **2** indicate that a dialkylbenzene moiety interferes with the photoinduced reaction of a neighboring nitrophenoxy group with nucleophiles. To see whether a similar effect would obtain in an intermolecular system, we examined the reaction of 4-nitroanisole with hydroxide in the presence of anisole, 4-cyanoanisole, and 1,4-dimethoxybenzene. Solutions containing the reactants in absorption cells were irradiated with the 366-mμ band isolated by a Bausch & Lomb monochromator. At this wavelength only 4-nitroanisole in the mixture absorbs. Initial rates were determined by the increase in absorbance at 400 mμ (owing to formation of 4-nitrophenoxide). It is seen from the data in Figure 1 that 1,4-dimethoxybenzene does inhibit the reaction of photoexcited 4-nitroanisole with hydroxide. At a concentration of 0.08 *M* it reduces the initial rate of formation of 4-nitrophenoxide by a factor of 2. Anisole has only a slight effect and 4-cyanoanisole has no measurable effect on the reaction of 4-nitroanisole with hydroxide.

Emission Spectra.—One possible explanation for the slow reaction of **2c** is that excitation energy is transferred from the 4-nitrophenoxy group, the site of chemical attack, to the dialkoxybenzene moiety. Intramolecular energy transfer is a well-established phenomenon in other systems.[8] This possibility was examined by observing emission spectra of compound **2c** and models containing the same chromophores, *i.e.*, dimethoxybenzene, 4-nitroanisole, and a mixture of 1,4-dimethoxybenzene and 4-nitroanisole (Table V).

TABLE V

EMISSION FOR METHOXYBENZENE DERIVATIVES UNDER EXCITING LIGHT AT λ 300 mμ

Compd[a]	Fluorescence[b] intensity[d]	Phosphorescence[c] intensity[d]
p-$CH_3OC_6H_4OCH_3$	52	56
p-$CH_3OC_6H_4NO_2$	0	0
p-$CH_3OC_6H_4OCH_3$ + p-$CH_3OC_6H_4NO_2$	41	29
p-$CH_3OC_6H_4OCH_2$-$CH_2OC_6H_4NO_2$-p	0	0

[a] Concentration of 1.0×10^{-5} *M* each for fluorescence measurement; 3.6×10^{-4} *M* each for phosphorescence measurements. [b] Solvent, 50% aqueous *t*-BuOH; temperature, 25°; λ_{max} observed, 336 mμ. [c] Solvent, EPA; temperature, liquid N_2; λ_{max} observed, 416 mμ. The intensity units for phosphorescence differ from those for fluorescence. [d] In arbitrary units.

On excitation at 300 mμ, 1,4-dimethoxybenzene both fluoresces in 50% aqueous *t*-butyl alcohol at room temperature (λ_{max} 336 mμ) and phosphoresces in EPA (ether–pentane–alcohol) at liquid nitrogen temperature (λ_{max} 416 mμ). Under the same conditions

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[8] O. Schnapp and M. Levy, *J. Amer. Chem. Soc.*, **84**, 172 (1962); P. A. Leermakers, G. W. Byers, A. A. Lamola, and G. S. Hammond, *ibid.*, **85**, 2670 (1963); **87**, 2322 (1965); S. Shifrin, *Biochem. Biophys. Acta*, **81**, 205 (1964); S. A. Latt, H. T. Cheung, and E. R. Blout, *J. Amer. Chem. Soc.*, **87**, 995 (1965); R. A. Keller, *ibid.*, **90**, 1140 (1968); R. D. Rauh, T. R. Evans, and P. A. Leermakers, *ibid.*, **90**, 6897 (1968); J. R. DeMember and N. Filipescu, *ibid.*, **90**, 6425 (1968).

no emission was observed from 4-nitroanisole or compound **2c**. Fluorescence and phosphorescence from 1,4-dimethoxybenzene in solution with an equivalent amount of 4-nitroanisole was observed, but the intensity was considerably reduced.

Fluorescence from the mixture of 1,4-dimethoxybenzene and 4-nitroanisole shows that 1,4-dimethoxybenzene is excited in the presence of the 4-nitrophenoxy chromophore. Absence of fluorescence from compound **2c** therefore indicates that, if singlet excitation energy transfer is involved, the transfer is from the dialkoxybenzene ring to the 4-nitrophenoxy group rather than in the reverse sense. Intramolecular energy transfer therefore cannot account for the low reactivity of compound **2c** if the reaction is one in which the nucleophile attacks a singlet excited state.

If the triplet state of **2c** is the intermediate in the substitution reaction, the energy-transfer explanation requires that triplet excitation energy be transferred from the nitrophenoxy group to the dialkoxybenzene ring. In this case, phosphorescence from **2c** similar to that from 1,4-dimethoxybenzene should be observed. Since no phosphorescence from **2c** was detectable, although phosphorescence from a mixture of 1,4-dimethoxybenzene and 4-nitroanisole at the same concentration was easily measured, the energy-transfer mechanism can also be ruled out as an explanation for the low reactivity of **2c** if the intermediate is a triplet state.

Since transfer of electronic excitation energy can be ruled out for both singlet and triplet intermediates, the most plausible explanation for the deactivating effect of $CH_3OC_6H_4OR$, either intramolecularly or intermolecularly, is that this moiety forms a complex with electronically excited $R'OC_6H_4NO_2$ and that the complex is itself inactive toward nucleophiles and on dissociation affords $R'OC_6H_4NO_2$ which is likewise inactive (probably ground-state nitroaromatic). Considerable evidence from other systems supports the view that excited aromatic species indeed form complexes (*e.g.*, an "exciplex") with substances in the ground state.[9]

Experimental Section

Ultraviolet spectra were recorded on a Cary Model 11 spectrophotometer and nmr spectra were obtained with a Varian Model A-60 spectrometer. Chemical shifts are reported as parts per million downfield from tetramethylsilane. Emission spectra were measured with an Aminco-Bowman spectrophotofluorometer (SPF 4-8106), equipped with an Amino-Keirs phosphoroscope (C27-62140) attachment for phosphorescence measurements. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.

A Savant flat plate apparatus was used for separation of ions by electrophoresis. Separations were carried out on 55 × 15 cm Whatman 3-mm paper strips saturated with buffer solution. An applied potential of 2000 V was employed. Fluorescent products were detected by illumination of the dried paper with a Mineral Lamp.

Solvents for fluorometry were Fisher Spectroanalyzed Reagent methanol, Spectroquality Reagent hexane (Matheson Coleman and Bell), and 50% v/v *t*-butyl alcohol–water, prepared from freshly distilled samples.

Preparation of Substituted 4′-Nitrodiphenyl Ethers.—3′-Methoxy-4-nitrodiphenyl ether, mp 86–87° (lit.[10] mp 86.5–87°), 4′-methoxy-4-nitrodiphenyl ether, mp 109° (lit.[11] mp 110–111°), 3′-acetamino-4-nitrodiphenyl ether, mp 135–135.5° (lit.[10] mp 138–139°), and 4′-acetamino-4-diphenyl ether, mp 154–155° (lit.[10,12] mp 153°), were prepared by condensation of 4-bromonitrobenzene with the appropriate potassium phenoxide over copper–bronze by the general procedure of Stohr.[11] 3′-Hydroxy-4-nitrodiphenyl ether, mp 98–99° (lit.[10] mp 101–101°), and 4′-hydroxy-4-nitrodiphenyl ether were obtained by cleaving the methyl ethers with aluminum chloride in nitrobenzene at 0° as reported by Ito.[13] 3′-Amino-4-nitrodiphenyl ether, mp 79° (lit.[10] mp 80–81°), and 4′-amino-4-nitrodiphenyl ether, mp 134–135° (lit.[11] mp 134–135°), were made by hydrolyzing the corresponding acetamino derivatives with hydrochloric acid in refluxing ethanol.[12] 4-Amino-4-nitrodiphenyl ether was also synthesized by partial reduction of 4,4′-dinitrodiphenyl ether with hydrogen sulfide and ammonium hydroxide.[14] The compound prepared in this manner was identical with that prepared by hydrolysis of the 4′-acetamido derivative. 4′-Bromo-4-nitrodiphenyl ether, mp 60° (lit.[15] mp 61°), was made by bromination[16] of 4-nitrodiphenyl ether, and 3′-chloro-4-nitrodiphenyl ether, mp 57° (lit.[17] mp 59.5–60.4°), 3′-cyano-4-nitrodiphenyl ether, and 4′-cyano-4-nitrodiphenyl ether were synthesized by Sandmeyer reactions. Further details are provided for the cyano derivatives, since thay are new compounds.

A cold, aqueous solution of sodium nitrite (0.28 g, 0.004 mol) was added to an aqueous solution containing concentrated hydrochloric acid (4 ml) and 4′-amino-4-nitrodiphenyl ether (0.92 g, 0.004 mol) cooled in an ice bath. The mixture was stirred for 10 min, neutralized with sodium carbonate, and filtered. It was then added slowly to a cold, well-stirred mixture of cuprous cyanide solution (50 ml, 0.027 mol)[18] and benzene (50 ml). The mixture was stirred vigorously, allowed to warm to room temperature, and filtered. The yellow, flocculant precipitate was isolated by filtration and heated in water to decompose the complex. Extraction with benzene, evaporation of the solvent, and recrystallization of the residue from benzene and from ethanol gave **4′-cyano-4-nitrodiphenyl ether**, yield 0.27 g (28%), mp 162–163°, ir 4.45 μ (CN).

Anal. Calcd for $C_{13}H_8N_2O_3$: C, 65.00; H, 3.36; N, 11.64. Found: C, 65.49; H, 3.61; N, 11.40.

By the same procedure, **3′-cyano-4-nitrodiphenyl ether**, yield 0.35 g (38%), mp 106–106.5°, ir 4.45 μ (CN), was obtained from 3′-amino-4-nitrodiphenyl ether.

Anal. Calcd for $C_{13}H_8N_2O_3$: C, 65.00; H, 3.36; N, 11.64. Found: C, 64.81; H, 3.48; N, 11.69.

Since 4′-methoxy-4′-nitrodiphenyl ether plays a key role in the photochemical experiments, it was further characterized by the nmr spectrum and by elemental analysis, even though it has been previously described.[11]

Anal. Calcd for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.69; H, 4.45; N, 5.88.

2-(4-Nitrophenoxy)ethyl Tosylate.—Sodium 4-nitrophenoxide (39.6 g, 0.20 mol) was added to a solution of 2-bromoethanol (24.8 g, 0.20 mol) in anhydrous dimethylformamide (100 ml). The solution was refluxed overnight and poured onto ice. Recrystallization of the solid from benzene gave 2-(4-nitrophenoxy)ethanol, yield 35.2 g (95%), mp 85–86°.

A solution of this alcohol (14.65 g, 0.08 mol) in a minimal amount of anhydrous pyridine was cooled and added to a cold solution of *p*-toluenesulfonyl chloride (15.3 g, 0.08 mol) in pyridine (20 ml). The solution was refrigerated overnight and then poured onto ice. Recrystallization of the solid from benzene–hexane afforded 25.2 g (93%) of the title compound, mp 122–123°.

Anal. Calcd for $C_{15}H_{15}NO_6S$: C, 53.49; H, 4.49; N, 4.15. Found: C, 53.83; H, 4.66; N, 4.17.

Substituted 1-(Phenoxy)-2-(4-nitrophenoxy)ethanes.—The three compounds were prepared in the same manner, typified by the synthesis of the methoxy derivative.

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(9) See, *e.g.*, S. L. Murov, R. S. Cole, and G. S. Hammond, *J. Amer. Chem. Soc.*, **90**, 2957 (1968); R. S. Cook and G. S. Hammond, *ibid.*, **90**, 2958 (1968); J. B. Birks and L. G. Christophorou, *Nature*, **196**, 33 (1962).

(10) G. Modena, *Boll. Sci. Fac. Chim. Ind. Bologna*, **17**, 45 (1959).

(11) R. Stohr, *Z. Physiol. Chem.*, **201**, 142 (1931).

(12) F. F. Ray and L. Soffer, *J. Org. Chem.*, **14**, 1037 (1950).

(13) G. Ito, *Pharm. Bull.* (Tokyo), **5**, 397 (1957); *Chem. Abstr.*, **52**, 9006 (1958).

(14) Reduction procedure of A. Cerniani, R. Passerini, and G. Righi, *Boll. Sci. Fac. Chim. Ind. Bologna*, **12**, 114 (1954).

(15) H. A. Scarborough, *J. Chem. Soc.*, 2361 (1929).

(16) C. M. Suter, *J. Amer. Chem. Soc.*, **51**, 2581 (1929).

(17) M. Rolla and M. Sanesi, *Ric. Sci.*, A[2], **1**, 289 (1961).

(18) H. T. Clarke and R. R. Read, "Organic Syntheses," Coll. Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1946, p 514.

To a solution of the sodium salt of 4-methoxyphenol (1.46 g, 0.01 mol) in anhydrous dimethylformamide (10 ml) was added 2-(4-nitrophenoxy)ethyl tosylate (1.62 g, 0.0048 mol). The solution was heated at 75° with stirring for 6 hr and at 40–50° for 2 days; then it was poured into ice–water. The solid was collected and recrystallized from benzene-hexane to yield **1-(4-methoxyphenoxy)-2-(4-nitrophenoxy)ethane**: yield 1.31 g (94%); mp 115–116°; nmr ($CDCl_3$) 3.84 (3, methyl H), 4.45 (4, methylene H), 7.01–7.10, 7.23, and 7.42 (6, aromatic H), and 8.31 and 8.47 ppm (2, aromatic H). The ultraviolet spectrum was determined in aqueous solution 20% in pyridine and 22% in *t*-butyl alcohol, since this was the solution used in the photochemical reactions, uv λ_{max} 315 mμ (ϵ 1.22 × 10^4).

Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.22; H, 5.27; N, 4.98.

1-Phenoxy-2-(4-nitrophenoxy)ethane was similarly prepared from sodium phenoxide (3.84 g) and 2-(4-nitrophenoxy)ethyl tosylate (3.38 g) by reaction for 24 hr at 65° and pouring the product into water: yield 2.35 g (91%); mp 86–87°; λ_{max} (aqueous 20% pyridine–22% *t*-butyl alcohol) 315 mμ (ϵ 1.09 × 10^4); nmr ($CDCl_3$) 4.47 (4, methylene H), 7.01–7.26 and 7.37–7.53 (7, aromatic H), and 8.31 and 8.47 ppm (2, aromatic H).

Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.94; H, 5.00; N, 5.39.

1-(4-Cyanophenoxy)-2-(4-nitrophenoxy)ethane was synthesized by heating sodium 4-cyanophenoxide, which was prepared from 3.57 g of 4-cyanophenol, with the tosylate in DMF for 20 hr at 120°: yield 2.61 g (92%); mp 139°; λ_{max} (aqueous 20% pyridine–22% *t*-butyl alcohol) 313 mμ (ϵ 1.09 × 10^4); nmr ($CDCl_3$) 4.53 (4, methylene H), 7.09, 7.24, and 7.43 (4, aromatic H), and 7.69 and 7.85 ppm (2, aromatic H).

Anal. Calcd for $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.25; N, 9.85. Found: C, 63.50; H, 4.32; N, 9.90.

3-(4-Methoxyphenyl)-1-(4-nitrophenoxy)propane.—3-(4-Methoxyphenyl)propionic acid (Aldrich reagent grade, 9.0 g, 0.05 mol) in ether (50 ml) was added during 1 hr to lithium aluminum hydride (4.0 g, 0.1 mol) in dry ether (50 ml). The mixture was refluxed for 3 hr, 3% aqueous sodium hydroxide solution was added with stirring, and the precipitated salts were removed by filtration. The ether layer was separated, dried, and evaporated to give 8.12 g of 3-(4-methoxyphenyl)propanol. To a portion of this material (6.0 g) in carbon tetrachloride at 60° was added phosphorus tribromide (4.88 g) in carbon tetrachloride (5 ml). After 20 min at reflux the mixture was hydrolyzed and the organic layer was collected, dried, and evaporated to yield 1-bromo-3-(4-methoxyphenyl)propane (6.60 g). A portion of this product (5.80 g) was stirred with excess sodium 4-nitrophenoxide (12.1 g) in anhydrous dimethylformamide (25 ml) for 13 hr at 115°, and the mixture was poured onto ice. Recrystallization of the product from aqueous ethanol gave 3-(4-methoxyphenyl)-1-(4-nitrophenoxy)propane: yield 5.91 g (66% from the propionic acid); mp 87.5–88.5°; λ_{max} (aqueous 20% pyridine–22% *t*-butyl alcohol) 316 mμ (ϵ 1.18 × 10^4); nmr (CCl_4) 1.95–2.85 (4, methylene H), 3.87–4.07 (2, methylene H), 3.71 (3, methyl H), 6.61–7.07 (6, aromatic H), and 7.98 and 8.13 (2, aromatic H *ortho* to nitro).

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.89. Found: C, 67.11; H, 5.98; N, 4.91.

Kinetic Studies.—Monochromatic light for the series of reactions with 4-nitroanisole irradiated at 366 ± 6 mμ was obtained from a Bausch & Lomb high-intensity monochromator utilizing an L-33-86-35-01 super-pressure 200-W mercury source. Standard silica absorption cells (10.0-mm path) fitted with ground-glass stoppers served as the reaction vessels. The cell containing reactant solution was placed in a thermostated metal holder 2 cm from the monochromator exit slit. Efficient stirring was provided by a micro Teflon-coated magnetic stirring bar.

In other kinetic studies a GE 1200-W photochemical lamp (UA-11) cooled by a Vycor water condenser was employed.[3] A typical reaction with pyridine was carried out by pipeting a solution (1.0 ml) of the nitrophenyl ether (5.00 × 10^{-1} M) in *t*-butyl alcohol, pyridine (10.0 ml), and *t*-butyl alcohol (10.0 ml) into a volumetric flask and diluting to 50 ml with water. The solution was added to the reaction vessel (a low cylindrical vessel with an outside jacket for circulation of ethylene glycol at constant temperature) and covered with a large, flat Pyrex top equipped with a standard taper joint for joining to the reaction vessel and ports for admitting nitrogen and removing aliquots of solution. Prepurified nitrogen was bubbled through the solution for 30 min, then the exit port was closed, and a positive pressure of nitrogen was maintained within the vessel. The solution was placed under the photochemical lamp at zero time and the progress of reaction was followed by periodically removing samples for measuring the absorbance at the λ_{max} value of the compound being studied. After *ca.* 10 half-lives, a final reading was taken. Plots of log $(A - A_\infty)/(A_0 - A_\infty)$ were linear through 60–70% conversion of the nitroaromatic compound. Data are therefore presented in the form of relative pseudo-first-order rate constants.

Reactions with aqueous sodium hydroxide were followed by the decrease in absorbance at the λ_{max} of the aromatic and by the increase in absorbance at 400 mμ owing to 4-nitrophenoxide. Solutions in these cases were prepared by mixing a 5.00 × 10^{-3} M solution (0.5 ml) of the aromatic compound in *t*-butyl alcohol, 0.50 M aqueous sodium hydroxide (2.0 ml), and *t*-butyl alcohol (5.0 ml) and diluting the mixture to 25 ml. Reactions of the 2-aryloxy-1-(4-nitrophenoxy)ethanes with sodium hydroxide were followed by periodically determining the amount of nitrite ion liberated. Reactions with cyanide ion and with ethylamine were carried out in glass-stoppered absorbing cells (10.0-mm light path), irradiated by the GE lamp. The progress was followed by scanning the spectrum from 240 to 400 mμ at appropriate intervals. The concentration of nitrite liberated in the photochemical reactions was determined by the method of Rider and Mellon.[19]

General Procedure for Preparative-Scale Reactions.—Unless otherwise specified, the reaction mixtures were placed in a cylindrical, jacketed vessel (12.5-cm i.d.) maintained at 25° by flowing water. The top was covered by a Pyrex cover and the solution was irradiated with light from the GE lamp. After irradiation, the solution was evaporated *in vacuo* and the residue was taken up in a minimum amount of ethanol. On cooling and mixing with a saturated solution of picric acid in ethanol, the product precipitated as a picrate salt. It was collected by filtration and recrystallized from aqueous ethanol.

The **4,4′-bis-N-pyridinium picrate derivative** of diphenyl ether **5** was prepared by irradiating bis(4-nitrophenyl) ether (0.26 g) in pyridine (200 ml) and water (400 ml) for 6 hr and treating the product with picric acid. After two recrystallizations from aqueous ethanol, the product was obtained: yield 0.44 g (56%), mp 143–145°.

Anal. Calcd for $C_{34}H_{22}N_8O_{15}\cdot{}^1/_2H_2O$: C, 51.59; H, 2.92; N, 14.16. Found: C, 51.53; H, 2.87; N, 14.16.

N-[4-(4-Cyanophenoxy)phenyl]pyridinium picrate (3, X = 4-CN), yield 0.031 g (49%), mp 193–194°, was obtained from photolysis for 3 hr of 4′-cyano-4-nitrodiphenyl ether (0.030 g) in a solution prepared by diluting a mixture of *t*-butyl alcohol (66 ml) and pyridine (6 ml) to 300 ml with water.

Anal. Calcd for $C_{24}H_{15}N_5O_8\cdot H_2O$: C, 55.49; H, 3.29. Found: C, 55.32; H, 3.27.

The photoreaction of 2-(4-cyanophenoxy)-1-(4-nitrophenoxy)-ethane (0.142 g) was carried out by irradiating a solution in pyridine (200 ml) and water (400 ml) for 8 hr. After two recrystallizations from aqueous ethanol, the **N-4-[2-(4-cyanophenoxy)ethoxy]phenyl pyridinium** (**6**) **picrate** was obtained, yield 0.223 g (82%), mp 162–163°. The white fluorescent spot due to the cation had a mobility of +1.4 relative to the yellow spot due to picrate (−1.0) on electrophoresis at pH 7.9.

Anal. Calcd for $C_{16}H_{19}N_5O_9$: C, 57.25; H, 3.51; N, 12.83. Found: C, 57.36; H, 3.34; N, 12.77.

In the case of 3′-cyano-4-nitrodiphenyl ether, a solution containing the ether (0.046 g) in pyridine (23 ml) and *t*-butyl alcohol (46 ml) was diluted to 230 ml with water and irradiated in a narrow, cylindrical vessel with a Hanovia 450-W immersion lamp for 2 hr. The light was filtered by a Pyrex sleeve around the lamp. A stream of nitrogen was bubbled through the solution throughout the irradiation and the temperature was maintained below 25° by a stream of cold water around the immersion well. The optical density at 400 mμ showed that the 4-nitrophenol was formed in the reaction in no more than 3% yield. Precipitation with picric acid yielded 0.089 g (94%) of N-[4-(3-cyanophenoxy)phenyl]pyridinium picrate, mp 135–138°. The analytical sample, yield 0.064 g (67%), mp 137–138°, was obtained by three recrystallizations from aqueous ethanol.

Anal. Calcd for $C_{24}H_{15}N_5O_8$: C, 57.50; H, 3.07; N, 13.94. Found: C, 57.61; H, 3.20; N, 13.88.

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[19] B. F. Rider and M. G. Mellon, *Anal. Chem.*, **18**, 96 (1946).

Registry No.—**2a**, 22483-35-8; **2b**, 22483-36-9; **2c**, 22483-37-0; **3** (X = 4-CN), 22483-38-1; **5** (X = picrate), 22483-39-2; **6**, 22483-42-7; **7**, 22483-40-5; **8**, 22483-41-6; N-[4-(3-cyanophenoxy)phenyl]pyridinium picrate, 22483-43-8; 2-(4-nitrophenoxy)ethyl tosylate, 22483-44-9.

Stable Carbonium Ions. LXXXII.[1] Protonation and Cleavage of N-Alkoxycarbonyl-Substituted Amino Acids in Strong Acid Solution

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Protonation and cleavage of N-alkoxycarbonyl-substituted amino acids have been studied in SbF_5–FSO_3H–SO_2 solution. Complete alkyl–oxygen cleavage at −76° was observed for all the benzyloxycarbonyl and *t*-butyloxycarbonyl derivatives studied, to give dications having both protonated carboxylic and protonated carbamic functions. In the latter case, the trimethylcarbonium ion was observed. N-*n*-Butyloxycarbonyl DL-alanine did not cleave at −20°; N-*sec*-butyloxycarbonyl cleaved slowly at −50°; and N-vinyloxycarbonyl glycine and N-allyloxycarbonyl DL-alanine underwent complex change in the strong acid solution. The spectrum of di-O-protonated N-formylglycine was observed.

The benzyloxycarbonyl group is an important protecting group for the amino function in amino acids and peptides owing to its stability under amino acid coupling conditions, as well as the many methods available for its removal.[3] On removal, the free amino group is obtained, carbon dioxide is liberated, and a benzyl compound is formed. The *t*-butyloxycarbonyl group is

$$PhCH_2OCONHCHRCO_2H + 2HX \longrightarrow PhCH_2X + CO_2 + HXNH_2CHRCO_2H$$

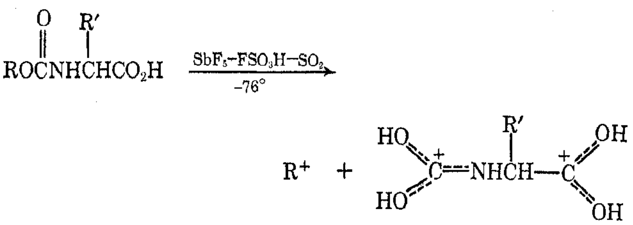
also widely used in peptide synthesis as an amino function protecting group. It is similarly removed under nonhydrolytic mild acid conditions to yield the free amino group, although, as is not the case for the benzyloxycarbonyl group, it is resistant to catalytic hydrogenation and treatment with sodium in liquid ammonia.

The following is the order of ease of removal of some amino-protecting groups for amino acids and peptides under nonhydrolytic acid conditions with evolution of carbon dioxide: *t*-butyloxycarbonyl > benzyloxycarbonyl > allyloxycarbonyl > *sec*-butyloxycarbonyl.[4,5]

Protonated carboxylic acids[6] and protonated alkyl carbamates and carbamic acids[7] have been investigated in our previous studies by nmr spectroscopy in the strong acid system SbF_5–FSO_3H–SO_2. It was of interest to extend these studies to the behavior of N-alkoxycarbonyl-substituted amino acids in SbF_5–FSO_3H–SO_2 solution and to investigate, over a range of temperature, their cleavage reactions.

Results and Discussion

N-Benzyloxycarbonyl and N-*t*-Butyloxycarbonyl Amino Acids.—When solutions of N-benzyloxycarbonyl and N-*t*-butyloxycarbonyl amino acids were prepared in SbF_5–FSO_3H–SO_2 solution at −70°, only at the products of alkyl–oxygen cleavage were observed. In the case of the N-*t*-butyloxycarbonyl amino acids, the cleaved trimethylcarbonium ion was observed as a singlet absorption at δ 4. In the case of the N-benzyloxycarbonyl amino acids, very broad, weak absorptions were observed at δ 7–10, probably corresponding to polymeric products of the cleaved benzyl cation.



I

R = *t*-butyl or benzyl (R′ was not observed for R = benzyl)

For the general species I, the protonated carboxylic function was observed as a singlet at *ca.* δ 13.1. The carboxylic protons are deshielded by *ca.* δ 0.9 compared with the carboxylic protons of protonated aliphatic carboxylic acids[6] owing to the protonated carbamic group on the α-carbon atom. Compared with the carboxylic protons of the simple diprotonated α-amino acids $RCH(NH_3^+)C^+(OH)_2$,[8] they are shielded by δ 0.9.

Only carbonyl oxygen protonation was observed for the carbamic group of I. The proton on nitrogen was observed as a broad absorption at *ca.* δ 7.7. Two resonances were seen for the two protons on the carbamic oxygen atoms. This is most likely a result of hindered rotation about the C_α–N bond and relatively free rotation about the C_α–O bonds. Both resonances appear in the region δ 10.5–11.0, and there is allylic coupling between the lower field resonance and the hydrogen atom on nitrogen. For the proton on the hydroxyl group *trans* to the proton on nitrogen with respect to the C–N bond, there is the possibility of a favorable planar W coupling path with the protons on nitrogen.[9] Consequently, the coupled lower field resonance is assigned to

[1] Part LXXXI: G. A. Olah and M. B. Comisarow, *J. Amer. Chem. Soc.*, **91**, 2955 (1969).

[2] National Institutes of Health Postdoctoral Research Investigator, 1967–1968.

[3] See, *e.g.*, M. Bodanszky and M. A. Ondetti, "Peptide Synthesis," Interscience Publishers, Inc., John Wiley & Sons, Inc., New York, N. Y., p 25.

[4] R. A. Boissonnas and G. Preitner, *Helv. Chim. Acta*, **36**, 875 (1953).

[5] J. P. Greenstein and M. Winitz, "Chemistry of Amino Acids," Vol. 2, John Wiley & Sons, Inc., New York, N. Y., 1961, pp 887–901 and 1187–1257.

[6] G. A. Olah and A. M. White, *J. Amer. Chem. Soc.*, **89**, 3591, 4752, 7072 (1967).

[7] G. A. Olah and M. Calin, *ibid.*, **90**, 401 (1968).

[8] G. A. Olah, D. L. Brydon, and R. D. Porter, *J. Org. Chem.*, **35**, 317 (1970)

[9] S. Sternhell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964).