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NITROPHENYL ETHERS AS POSSIBLE PHOTOAFFINITY LABELS.
THE NUCLEOPHILIC AROMATIC PHOTOSUBSTITUTION REVISITED.

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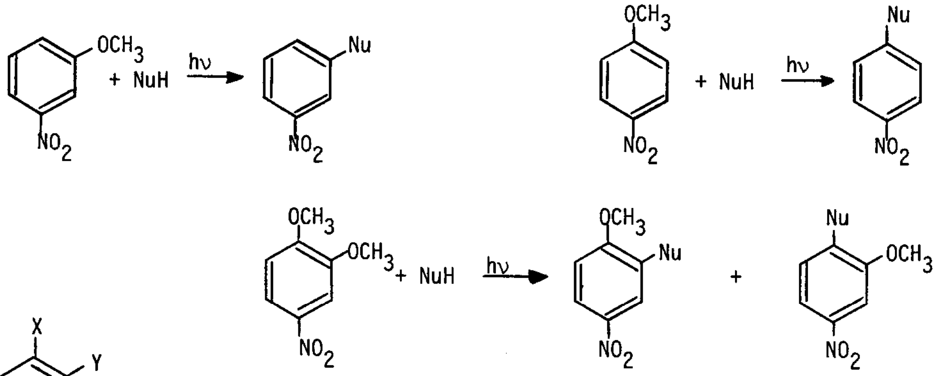
Summary: The photoreactions of nitrophenyl ethers with simple primary and secondary amines show a remarkable nucleophile influence on the reaction orientation. Calculations indicate a change from charge controlled to frontier orbital controlled reactions moving from smaller to larger amines.

Photoaffinity labelling has been extensively used in the study of biological receptor sites[1], aryl azides, diazocompounds and aromatic ketones being the classical reagents used as photolabile moieties. Cantor *et al.*[2] suggested the use of nitrophenyl ethers[3]. These compounds are inert in the dark at room temperature, but under UV light they react with nucleophiles (nucleophilic aromatic photosubstitution)[4]. We are interested in the use of nitrophenyl ethers as photoaffinity probes, but a survey of the related literature showed that the picture of the reactions between nitrophenyl ethers and amines was far from being complete, existing a considerable lack of information about reactions of secondary amines or even primary amines other than methylamine. Therefore, we have undertaken a study of these reactions, pointing out the importance of the nucleophile nature in the resulting reaction orientation. This factor had not been properly considered in earlier reports[4], overemphasizing the *meta*-orientating properties of the nitro group.

4-Nitroveratrole and 3- and 4-nitroanisole were the substrates selected for our study. In scheme 1 the reactions carried out are described. Some simple primary and secondary amines were used as nucleophiles. Reactions were carried out at room temperature using a large excess of nucleophile with a 400W Hg-medium pressure lamp and a pyrex filter. Water, water-methanol or water-acetonitrile were the solvents. In table 1 our results, along with some selected ones from the literature, are described. A clear tendency can be observed: in the 4-nitroveratrole photoreactions the reported *meta* orientation of the nitro group only holds for ammonia and methylamine. When the amine increases its volume and therefore its softness, Scheme 1



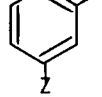
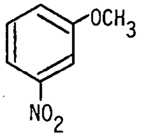
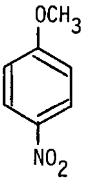
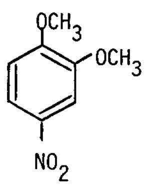


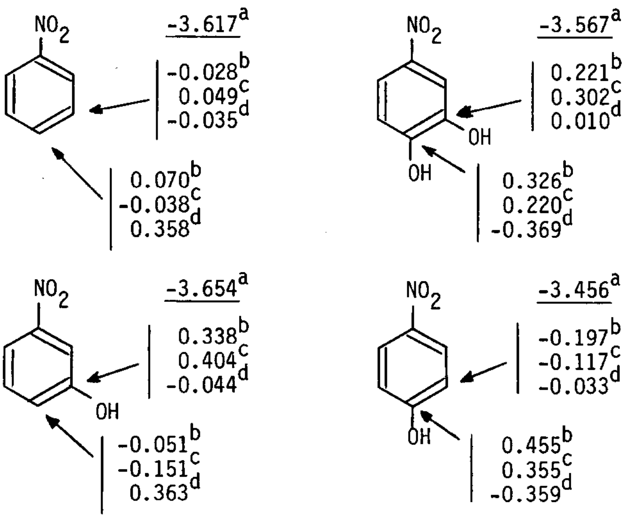
Table 1. Photoreactions of nitrophenyl ethers with amines

Substrate	Amine	Reaction conditions[a]	Reaction Products			Yield[b] (%)
			X	Y	Z	
	NH_3	c	H	NH_2	NO_2	90
	CH_3NH_2	c	H	$NHCH_3$	NO_2	d
	n-$BuNH_2$	H_2O/CH_3CN, 11h	H	OH	NO_2	44
	$(CH_3)_2NH$	H_2O/CH_3OH, 2h	------	------	------	e
	NH_3	c	OCH_3	H	NH_2	d
	$H_2NCH_2CO_2Et$	H_2O/CH_3CN, 22h	OCH_3	H	$NHCH_2CO_2Et$	14
	CH_3NH_2	c	$NHCH_3$	H	NO_2	54
	n-$BuNH_2$	H_2O/CH_3CN, 11h	NHBu-n	H	NO_2	14
	$(CH_3)_2NH$	H_2O, 2h	$N(CH_3)_2$	H	NO_2	31[f]
	Morpholine	H_2O/CH_3OH, 6.5 h	morpholino	H	NO_2	38
	Piperidine	H_2O/CH_3OH, 19h	piperidino	H	NO_2	87
	Aniline	H_2O/CH_3OH, 24h	------	------	------	e
	NH_3	c	OCH_3	NH_2	NO_2	d
	CH_3NH_2	H_2O/CH_3OH, 4h, phosphate buffer	OCH_3	$NHCH_3$	NO_2	81[g]
	n-$BuNH_2$	H_2O/CH_3OH, 4h	OCH_3	NHBu-n	NO_2	21
			NHBu-n	OCH_3	NO_2	15
	$(CH_3)_2NH$	H_2O/CH_3OH, 4h, phosphate buffer	$N(CH_3)_2$	OCH_3	NO_2	68
			OCH_3	OH	NO_2	14
	Morpholine	H_2O/CH_3OH, 4h	morpholino	OCH_3	NO_2	24

a) 400W Medium pressure Hg lamp with pyrex filter unless otherwise indicated. Room temp.
b) Isolated yields. The new products gave correct elementary analyses. Their full characterization will be reported elsewhere. c) Data from ref. 4a. d) No yield reported. e) No defined products could be isolated. f) A 65% yield is reported in ref. 4a. g) A 64% yield is reported in ref. 4a. h) A 150W medium pressure Hg lamp was used in this case.

there is a change in the orientating properties, and the prefered reactions are at the para position respect to the nitro group. Something similar happens for 3- and 4-nitroanisole. The yields of 3-nitroanilines in the photoreactions of 3-nitroanisole with n-butylamine and dimethylamine are zero, whilst the photoreactions between 4-nitroanisole and n-butylamine and secondary amines give reasonable yields of 4-nitroanilines, in agreement with the results for 4-nitroveratrole. Moreover, when meta-photosubstitution becomes slow, the photohydrolysis reaction can compete. This is what happens in the photoreactions between 3-nitroanisole and n-butylamine and between 4-nitroveratrole and dimethylamine, where 3-nitrophenol and 2-methoxy-5-nitrophenol are respectively obtained. The hard hydroxyl group behaves like ammonia and methylamine, the nitro group showing meta orientating properties in the photohydrolyses[4]. Such a competition is not observed for 4-nitroanisole. The meta orientating properties of the nitro group in the photohydrolysis of nitrophenyl ethers have been explained in the literature considering a charge controlled reaction[4b]. This has been confirmed in the present work. The net charges of the ground state and of the first excited state (S_1) in nitrobenzene, 3- and 4-nitrophenol and 4-nitrocatechol (used as models of 3- and 4-nitroanisole and 4-nitroveratrole) are shown in scheme 2. Calculations were carried out using the semiempirical MINDO/3 method[5] implemented in the MOPAC[6] program, that uses the half-electron model to calculate open-shell systems. In nitrobenzene and 4-nitrocatechol, a relative order inversion of the net charge between the meta and para positions (with respect to the nitro group) is produced going from the ground state to the excited state (S_1). In 3- and 4-nitrophenol the same tendency can be observed although no complete inversion is found. In this case the single OH group forces its attached carbon atom to be always the more positive. Nevertheless, the scheme 2 shows that there is a difference in positive charge absolute values between the meta position in 3-nitrophenol and the para position in 4-nitrophenol that can justify the different reactivity of ammonia (charge controlled reaction) versus the corresponding methyl ethers.

Scheme 2



a) Higher Half Occupied level energy (electronvolts)
b) Ground state net charge
c) Excited state (S_1) net charge
d) Higher Half Occupied level coefficients

These results predict the observed meta orientating properties of the nitro group in nucleophilic aromatic photosubstitutions using ammonia and methylamine as nucleophiles. However, the observed para orientation with larger and therefore softer amines may indicate that the reaction can be as well controlled by frontier orbitals.

The energetically closer frontier orbital pairs in these photoreactions would be HOMO (amine)-Lower Half Occupied level (excited nitrocompound) and LUMO(amine)-Higher Half Occupied level (excited nitrocompound). Considering that the Lower Half Occupied level (excited nitrocompound) is a σ orbital, the first interaction is negligible since it implies a very small overlap with the HOMO of the amine. To explain the cases in which the substitution is produced in para position respect to the nitro group, only the second previously mentioned interaction must be considered. In scheme 2 the energies and coefficients of the Higher Half Occupied level of our model nitrocompounds are also reported. In table 2 our calculated HOMO and LUMO energies of several amines are indicated. The main feature is the fact that the LUMO energy decreases from ammonia to secondary amines, thus making the reactants significant frontier orbitals energetically closer. This would explain the reaction orientation observed for amines larger than methylamine since as it is shown in scheme 2, the larger coefficient in the Higher Half Occupied level of the excited nitrocompound is always located at the para position respect to the nitro group.

Table 2

Amines frontier orbital energies in electronvolts

	NH_3	CH_3NH_2	n-$BuNH_2$	$(CH_3)_2NH$	Piperidine	Morpholine
LUMO	3.593	2.320	2.082	1.583	1.554	1.231
HOMO	-10.071	-9.206	-9.190	-8.578	-8.649	-8.777

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References

1.- "Photoaffinity Labelling", by H. Bayley and J.R. Knowles, in Methods in Enzymology, 46, 69, (1977). W.B. Jakoby and M. Wilchek, Eds. Academic Press. New York.

2.- P.C. Jelenc, C.R. Cantor, S.R. Simon, Proc. Natl. Acad. Sci. USA, 75, 3564, (1978).

3.- H. Gozlan, V. Homburger, M. Lucas, J. Bockaert, Biochem. Pharmacol., 31, 2879, (1982).

4.- a) J. Cornelisse, E. Havinga, Chem. Rev., 75, 353, (1975) and references cited therein.
b) J. Cornelisse, G.P. de Gunst, E. Havinga, Adv. Phys. Org. Chem., 11, 225, (1975) and references cited therein.

5.- R.C. Bingham, M.J.S. Dewar, D.H. Lo, J. Am. Chem. Soc., 97, 1285, (1975).

6.- J.P. Stewart, QCPE, 15, 455, (1983).

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