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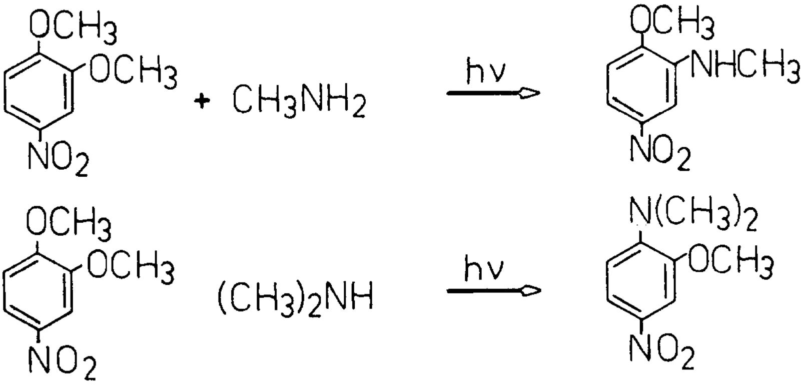
ON THE REGIOSELECTIVITY OF THE NUCLEOPHILIC AROMATIC PHOTOSUBSTITUTION. THE PHOTOREACTION OF 4-NITROVERATROLE WITH n-HEXYLAMINE.

Albert Cantos, Jorge Marquet,* and Marcial Moreno-Mañas
Departamento de Química. Universidad Autónoma de Barcelona.
Bellaterra 08193. Barcelona. Spain

Summary: 4-Nitroveratrole is photosubstituted with n-hexylamine giving rise to two isomeric anilines, N-hexyl-2-methoxy-5-nitroaniline and N-hexyl-2-methoxy-4-nitroaniline. Mechanistic evidence indicates that the first is produced in an S_N2Ar^* reaction through singlet and triplet excited states, whereas the second arises from a radical ion pair via electron transfer from the amine to a triplet excited state.

The Nucleophilic Aromatic Photosubstitution[1] has been suggested[2,3] as a potentially useful tool in the photoaffinity labelling technique[4]. Nitrophenyl ethers are inert in the dark at room temperature but under UV light they react with nucleophiles. This reaction has been extensively studied by Havinga[1], from the preparative and partially from the mechanistic viewpoint. Recently, Varma[5] has applied the Laser Flash Photolysis technique to the study of the photohydrolysis of several nitrophenyl ethers proposing a general mechanistic scheme that involves fast reaction between the nucleophile (OH^-) and the nitrophenyl ethers triplet excited states which give rise to a series of σ-complexes in their ground state.

Photohydrolysis of nitroanisoles show a meta regioselectivity (inverse to the thermal reaction) with respect to the nitro group[1]. In a previous report[6] we demonstrated that this fact only clearly holds for OH^- as a nucleophile since when amines are used, the regioselectivity depends on the features of the nucleophile. The meta regioselectivity is preferred for amines of high ionization potential, but it changes into para when amines of lower ionization potential are used (Scheme 1).

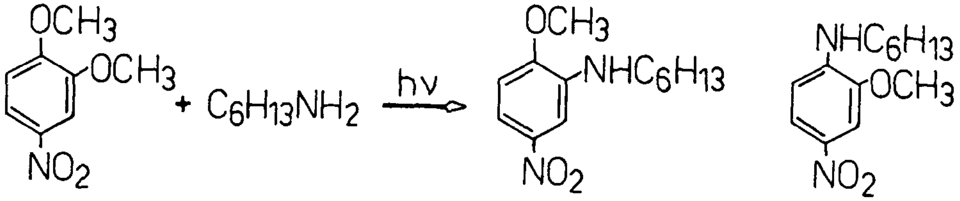


Scheme 1

We wish to describe here a series of mechanistic studies that have led us to modify our original explanation[6], introducing a previously not considered electron transfer step in the pathway to the *para* substitution products.

In the Table the relative yields (ϕ_{meta}/ϕ_{para}) of production of the *meta* *vs*. the *para* isomer in several photoreactions of 4-nitroveratrole with n-hexylamine are reported. We chosed this nucleophile for our studies due to the fact that both photoproducts (*meta* and *para*) were produced (in the standard conditions) in appropriate relative amounts for the ratio to be measured by G.C..

Table.- Effect of triplet quenchers, radical scavengers and solvents on the photoreactions of 4-nitroveratrole with n-hexylamine[a].



Meta **Para**

Reaction	Solution saturated with	Solvent	Additive	$(\phi_{meta}/\phi_{para})^{b}$
1	Air	MeOH/H_2O(20:80)	-----------	5.9
2	Air	MeOH/H_2O(20:80)	Potassium Sorbate[c]	16.3
3	Air	MeOH/H_2O(20:80)	1,3-Cyclohexadiene[c]	>30
4	Argon	MeOH/H_2O(20:80)	-----------	4.2
5	Air	MeOH/H_2O(20:80)	*m*-Dinitrobenzene[d]	>30
6	Argon	MeOH/H_2O(20:80)	MV^{2+} $2Cl^-$ [f]	>30
7	Air	Isopropanol	-----------	22
8	Air	Hexane	-----------	*g*

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a) 4-Nitroveratrole (2.5×10^{-3}M), n-hexylamine (2.5×10^{-1}M), 125W Hg high pressure lamp, pyrex filter, 1h of irradiation. b) Ratio by G.C. analysis. The value results from five measurements, eliminating the higher and lower ones and averaging the remaining three values. The products vere identified by comparison with authentical samples. c) 5.1×10^{-2}M. d) 3.7×10^{-3}M. e) A filter prepared with 0.005 g of *p*-nitroanisole in 1 ml of MeOH and 100 ml of water was used in addition to the pyrex filter to eliminate light under 320 nm and ensure MV^{2+} was not absorbing. f) 1.8×10^{-2}M. g) Very complex mixture of products.

The selected standard conditions, in order to perform comparisons were: MeOH/H_2O (20:80), (125W, Hg high pressure lamp), pyrex filter, 1h irradiation, 100 times excess of nucleophile with respect to substrate. The ϕ_{meta}/ϕ_{para} ratio in these conditions was 5.9 (Table, exp. 1). No precautions were taken to avoid oxygen, except in the reactions in which it is indicated.

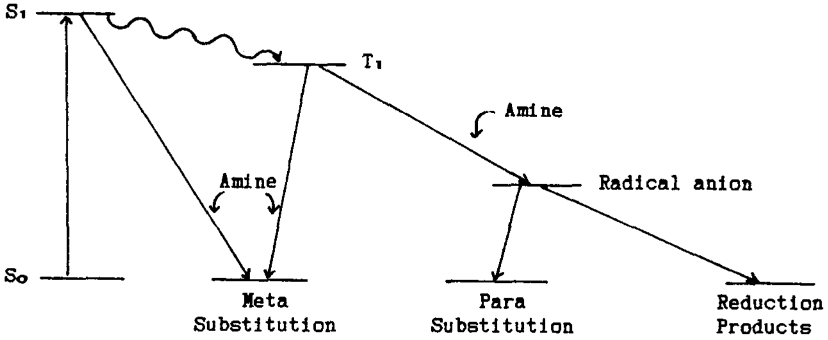
The influence of triplet quenchers on the ϕ_{meta}/ϕ_{para} ratio is shown in the Table. Parallel reactions in the standard conditions with and without the addition of triplet quenchers demonstrated that the ratio increased in all cases when quenchers were present (Table, exp.2 and 3). Even oxygen, that in other nitrophenyl ethers photosubstitutions reported cases[7] has a negligible influence, showed a small effect in the same direction (Table, exp.4). These results pointed out that the meta and the para photoproducts were coming out through different mechanistic pathways. In two quantitative parallel experiments, in the standard conditions, both in the absence and in the presence of potassium sorbate as triplet quencher, with measuring of the chromatographic peak areas in front of an added standard, the production of the meta photoproduct was 30% reduced whereas the production of the para one was 80% reduced. Assuming that the para product comes through the lowest triplet excited state (it is the more depending product on the presence of triplet quenchers), the obvious first conclusion states that the production of the meta photoproduct has a component through the lowest singlet excited state (mixed origin).

Parallel reactions carried out in the presence and in the absence of m-dinitrobenzene (radical scavenger and electron transfer quencher) showed clearly that its effect on the production of the para photoproduct was much more important than the corresponding effect (if any) on the production of the meta isomer (Table, exp.5). The same experiment carried out (under argon) with methyl viologen (MV^{2+}, strong electron acceptor) led to a similar result (Table, exp.6), and in addition the solution developed an intense blue colour attributed to the methyl viologen radical monocation ($MV^{\cdot+}$, λ_{max} 602 nm)[8]. This colour was not apparent in control experiments, when any of the reaction components was missing. Considering that both m-dinitrobenzene and MV^{2+} do not interact with the 4-nitroveratrole lowest triplet excited state[9], the best explanation for the observed effect would be the interaction with a later radical anion intermediate, formed by electron transfer from the amine to the lowest triplet excited state of the 4-nitroveratrole, and present only in the para photoproduct reaction path.

The results obtained when the solvent was changed to isopropanol and hexane are also described in the Table. The ϕ_{meta}/ϕ_{para} ratio increases on going from $MeOH/H_2O$ to isopropanol. In this last solvent the complexity of the reaction mixture also increases as shown by GC/MS analysis, the proportion of photoreduction products being important. This is even more evident in hexane where only a very complex reaction mixture, non amenable to analysis could be obtained. It is known that the triplet excited state lifetime of nitroanisoles depends strongly on the solvent properties[10], being longer in solvents with good hydrogen bond formation ability. Photoreductions of nitroaromatics have been shown to proceed by electron transfer[11,12] (in the presence of good electron donors) or by hydrogen atom transfer[13] to the substrate triplet excited state. The reported facts suggest again the involvement of a path through a triplet excited state and a radical ion pair in the production of the para isomer. It can be disrupted by the excited state lifetime reduction and by evolution of the radical ion pair intermediate to reduction products, fact that is easier in solvents with hydrogen atoms donating ability.

A mechanistic scheme that agrees with the reported facts is presented in Scheme 2. The meta isomer arises from singlet and triplet excited states in an S_N2Ar^* type photoreaction[1c]. The para photoproduct arises by electron transfer to the lowest triplet excited state giving a radical ion pair that on collapsing, would produce the substitution product or on diffusing would give rise to reduction products. This Scheme can also explain the reported[6] change in regioselectivity on going from amines of high ionization potential (meta) to amines of low ionization potential (para) as nucleophiles in photoreactions with 4-nitroveratrole (Scheme 1). It agrees as well with the explanation given in the literature[14] for the observed change in the regioselectivity of photo-Smiles reactions upon change of the amine type, with the important and interesting difference that in our case the electron transfer is to the triplet excited state. This is probably due to the fact we are dealing with an intermolecular photoreaction.

A full mechanistic account on the photoreactions of 4-nitroveratrole with different nucleophiles will be published in the near future.



Scheme 2

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