

ON THE REGIOSELECTIVITY OF THE NUCLEOPHILIC AROMATIC PHOTOSUBSTITUTION OF 4-NITROANISOLE.
A DUAL MECHANISTIC PATHWAY

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Summary: 4-Nitroanisole photoreacts with *n*-hexylamine and ethyl glycinate giving rise to regioselective methoxy and nitro group photosubstitutions respectively. Mechanistic evidences indicate the last is produced through a $S_N2^3Ar^*$ reaction whereas the first arises from a radical ion pair via electron transfer from the amine to a 4-nitroanisole triplet excited state.

Nucleophilic aromatic photosubstitutions have been the object of intense research since their discovery in 1956¹. In spite of the important effort done, mechanistic studies have been for years restricted almost to photohydrolysis reactions^{2,3}. Many reported experimental facts remain unexplained specially in cases when nucleophiles others than OH^- are used.

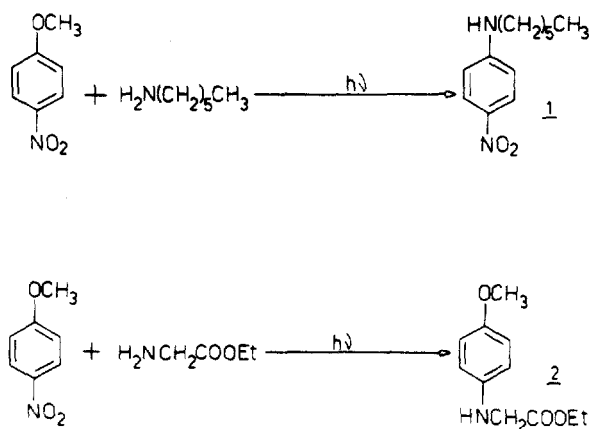
In the course of our investigation on the photosubstitution of 4-nitroveratrole with amines we found⁴ that the regioselectivity of this reaction depends on the ionization potential of the nucleophile. A mechanistic borderline between S_N2Ar^* ⁵ reactions (for high ionization potential amines) and electron transfer from the amine to the substrate triplet excited state (for low ionization potential amines) was proposed⁶. Some other related regioselectivity changes have been reported for photo-Smiles reactions⁷ and for the photosubstitution of 1-methoxy-4-nitronaphthalene with amine nucleophiles⁸.

The nitroanisoles, particularly *meta*- and *para*-nitroanisoles, are probably the most thoroughly investigated compounds in nucleophilic aromatic photosubstitution reactions¹. 4-Nitroanisole photoreacts⁸ readily with amines in aqueous solution giving rise to methoxy group photosubstitution. Nevertheless, van Vliet¹⁰ found that 4-nitroanisole photoreacts with ammonia giving rise to *p*-anisidine in low yield. At that time it was not clear whether this reaction was a photosubstitution or a photoreduction of the nitro group. Letsinger¹¹ reported the formation of 1-(*p*-methoxyphenyl)pyridinium nitrite in the photoreaction between *p*-nitroanisole and pyridine. The photosubstitution of the nitro group was clear in this case. An empirical rule termed "merging (resonance) stabilization" was invoked^{1a,2} to rationalize the effect of the nucleophile on the orientation of the photosubstitution. Thus electron donating groups would substitute the methoxy group in 4-nitroanisole whereas eventually electron attracting groups (tertiary amines that become ammonium cations, cyanide etc.) would photosubstitute the nitro group.

We wish to describe here a series of preliminary preparative and mechanistic studies that have led us to the conclusion that the nitro group photosubstitution in 4-nitroanisole

happens through a $S_N2^3Ar^*$ mechanism whereas the methoxy group photosubstitution is the consequence of a mechanistic path that includes electron transfer from the amine to a triplet excited state of the substrate, being the outcome of the reaction determined by the ionization potential of the used nucleophile.

In a previous report⁴ we showed that ethyl glycinate gives rise to nitro group photosubstitution in 4-nitroanisole, in spite of being a primary amine. We have now compared this photoreaction with the methoxy group photosubstitution that is produced when *n*-hexylamine is the nucleophile. Thus *N*-hexyl-4-nitroaniline 1, and *N*-ethoxycarbonylmethyl-4-methoxyaniline 2, were obtained in 16% and 15% preparative yields as the only isolated photosubstitution products after 2 and 12h of irradiation respectively in MeOH/H₂O (400 W Hg medium pressure lamp, pyrex filter). (Scheme 1).



The effects of triplet quenchers, radical scavengers and solvent polarity on the reactions of Scheme 1 are described in the Table. Parallel reactions in the presence and in the absence of potassium sorbate as triplet quencher showed a 83% and 52% decrease in photosubstitution production (exp. 1 and 2). This result suggested the involvement of triplet excited states in the reaction paths. Further mechanistic studies confirmed this conclusion. Thus the representation of $1/\phi$ versus $1/[Nu]$ gave good straight lines in both cases indicating that the photosubstitution product was of single origin and good linear Stern-Volmer plots were also obtained representing ϕ_0/ϕ versus potassium sorbate concentration¹².

Parallel reactions carried out in the presence and in the absence of *m*-dinitrobenzene showed a 95% decrease of photosubstitution for *n*-hexylamine when the radical scavenger was present. The corresponding value for the ethyl glycinate reaction was only 18%. The obvious conclusion is that the first reaction is much more affected than the second but the 18% value casts some doubts on the interpretation. Experiments 5 and 6 in the presence and in

the absence of methyl viologen (strong electron acceptor) gave clearer results. A 99% decrease in photosubstitution was observed for n-hexylamine in the presence of this additive whereas no difference with the blank was observed for ethyl glycinate. In addition only exp. 5 showed the strong blue colour attributed to the methyl viologen cation ($\lambda_{\text{max}}=600\text{nm}$)¹³. We interpret these results considering the methoxy group photosubstitution produced by n-hexylamine as the result of a single electron transfer step from the amine to the 4-nitroanisole excited triplet state. On the other hand the N-ethoxycarbonylmethyl-4-methoxyaniline, 2, must be produced in an $S_N2^3Ar^*$ reaction (Scheme 2). We attribute the observed mechanistic change to the different ionization potential of the nucleophiles. Interestingly enough, a relatively sharp threshold for the mechanistic change is deduced from our experiments since our calculations¹⁴ indicate that the ionization potential difference between n-hexylamine and ethyl glycinate is about 0.4 ev.

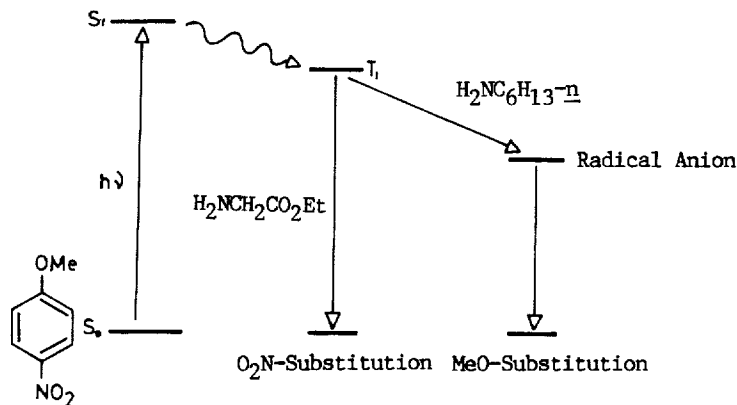
Table.- Effect of triplet quenchers, radical scavengers and solvents on the photoreactions of 4-nitroanisole with n-hexylamine and ethyl glycinate^a.

Exp.	Amine	Blank ^b	Solvent and irradiation time	Additives	Product	$(1 - (\Phi/\Phi_{\text{blank}})) \times 100^c$
1	<u>n</u> -C ₆ H ₁₃ NH ₂	<u>d</u>	MeOH/H ₂ O(20:80),15m.	Potassium Sorbate ^e	<u>1</u>	83
2	H ₂ NCH ₂ CO ₂ Et	<u>d</u>	MeOH/H ₂ O(20:80),15m.	Potassium Sorbate ^e	<u>2</u>	52
3	<u>n</u> -C ₆ H ₁₃ NH ₂	<u>d</u>	MeOH/H ₂ O(20:80),15m.	<u>m</u> -Dinitrobenzene ^f	<u>1</u>	95
4	H ₂ NCH ₂ CO ₂ Et	<u>d</u>	MeOH/H ₂ O(20:80),15m.	<u>m</u> -Dinitrobenzene ^f	<u>2</u>	18
5	<u>n</u> -C ₆ H ₁₃ NH ₂	<u>g</u>	MeOH/H ₂ O(20:80),3m.	MV ²⁺ 2Cl ^{-h}	<u>1</u>	99
6	H ₂ NCH ₂ CO ₂ Et	<u>g</u>	MeOH/H ₂ O(20:80),3m.	MV ²⁺ 2Cl ^{-h}	<u>2</u>	0
7	<u>n</u> -C ₆ H ₁₃ NH ₂	<u>i</u>	MeOH, 30m.	-----	<u>1</u>	100
8	H ₂ NCH ₂ CO ₂ Et	<u>i</u>	MeOH, 30m.	-----	<u>2</u>	98

a) General conditions: 125 W Hg high pressure lamp. To ensure the different additives were not absorbing, a filter prepared with triacetic acid lactone (0.1M) in t-butanol ($\lambda > 340\text{nm}$) was used. b) Each reaction was carried out in parallel to a blank (using a standard solvent mixture, MeOH/H₂O:20/80, and in the absence of additives). No precautions were taken to avoid oxygen, except for exp. 5 and 6. c) Photosubstitution production percentage of decrease referred to the blank reaction. The Φ/Φ_{blank} value corresponds to the normalized integration ratio of the substitution product gas chromatographic peaks in the compared photoreactions, using the integration of a fixed amount of internal reference. The values result from five measurements, eliminating the higher and lower ones and averaging the remaining three values. The products were identified by comparison with authentic samples. d) 4-nitroanisole ($1.9 \times 10^{-2}\text{M}$), amine (0.47M). e) 0.1M. f) 0.07M. g) 4-nitroanisole ($5.6 \times 10^{-3}\text{M}$), amine ($1.7 \times 10^{-2}\text{M}$). h) Methylviologen ($6.55 \times 10^{-4}\text{M}$). i) 4-nitroanisole ($6.5 \times 10^{-3}\text{M}$), amine ($4.6 \times 10^{-3}\text{M}$).

The effect of solvent change (exp. 7 and 8) can be rationalized considering the decreasing of excited state stabilization through hydrogen bond¹⁵ on going from water to methanol. This would reduce the triplet excited state lifetime decreasing the photoreaction efficiency.

A full mechanistic account on the photoreactions of nitrophenyl ethers with amine nucleophiles will be published in the near future.



Scheme 2

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