Topologically Controlled Coulombic Interactions, a New Tool in the Developing of Novel Reactivity. Photochemical and Electrochemical Cleavage of Phenyl Alkyl Ethers[1]

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The hypothesis that a specific placement of a positive charge would dramatically alter the behavior of a charged intermediate has been tested. Phenyl ethers substituted by electron-attracting groups do not undergo reductive fragmentation. However, related α-piperidino-ω-(4-substituted-phenoxy)-alkanes give alkyl ether photocleavage when the linker between the redox centers is short, or the usual substitution–reduction photochemistry when it is long. Mechanistic experiments suggest that the photofragmentation process operates through space intramolecular electron transfer to the triplet aromatic chromophore and that a coplanar relative orientation of the alkyl ether bond and the phenyl ring is compulsory for the photofragmentation to be observed. Configuration interaction AM1 calculations justify the described facts, indicating that the fragmentation process is only operative when a Coulombic stabilization of a σ^* intramolecular electron transfer excited state is produced. Electrochemical studies carried out with the corresponding quaternary salts (intermolecular generation of the phenyl ether radical anion) confirm the conclusions derived from the photochemical experiments.

Single electron transfer (SET) reactions have been the topic of recent widespread investigation[2] that has led to the development of novel reactions. In many cases the chemical activation achieved by single electron transfer is associated with enhancement of the reactivities of the individual radical ions with respect to the parent neutral molecules.[2a,3] Thus, strongly covalent C–C or C–heteroatom bonds in parent neutral molecules can be selectively labilized by SET processes.[4] In particular, reactions that involve the breaking of formal three-electron bonds have attracted increased attention from organic chemists in recent years.[5] This bond-breaking step is a critical component in such important processes as $S_{RN}1$ reactions[6] or the reductive cleavage of diaryl ethers and alkyl aryl ethers.[7] Symons,[8] Bunnett,[9] and Rossi[10] have proposed (on qualitative bases) that cleavage of C–X bonds in halogenoaromatic radical anions may be seen as the result of electron transfer from the π^* radical anion to the σ^* arylnucleofugal bond by an orbital crossing. This orbital crossing is made possible by lengthening or out of plane wagging motion of the C–X bond. In a first stage, a π^* radical anion, stable with respect to dissociation, would be formed. Then an intramolecular electron transfer would transform the π^* radical anion into a σ^* (fragmentative state) one. Efficient fragmentation in aryl and benzyl halides depends on a delicate balance. Thus, the same electron-attracting groups that can make the initial electron transfer step easier may keep the extra electron away from the σ bond that should be activated. When a cyano group replaces the nitro group either in *p*-nitroaryl or *p*-nitrobenzyl halides, the rate of dissociation of the radical anion measured by pulse radiolysis[11] increases by at least 5 orders of magnitude.

The reductive alkyl aryl ether cleavage has lately received important attention and the results through 1986 were reviewed by Maercker.[12] The first reaction step leads to radical anions $ROAr^{\bullet -}$, known since 1968 from ESR studies.[13] Dianions were also discussed in the past as intermediates,[14] although more recent literature[12,15] shows that in most cases this is a unnecessary hypothesis. Intermediates of the $ROAr^{\bullet -}$ type share many common features with the previously commented aryl and benzyl halide radical anions important in $S_{RN}1$

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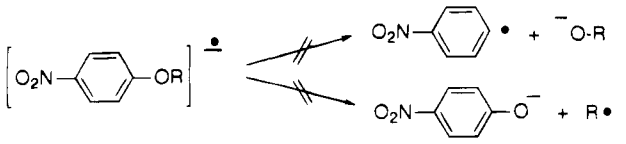
0022-3263/95/1960-3814$09.00/0

Scheme 1



reactions. In those cases and in addition to the previously indicated factors that can alter the fragmentation process, a new element must be taken into account, the "spin regioconservation principle".[16] Guthrie and Maslak proposed such a concept on the basis of fragmentation studies of aryl nitrobenzyl and benzyl nitroaryl ethers. These authors state that the fission of alkyl aryl ether radical anions only will take place unproblematically if the spin density remains on the radical which is split off. Therefore, in the case of alkyl aryl ether radical anions, the efficiency and selectivity of the fragmentation will depend on the probability of transition from the π^* state to the σ^* state, with this probability being a function of the coupling between these states and this coupling a direct function of the overlap between the σ^* orbital and the π system.

We have been involved lately in the study of nitroaryl ether nucleophilic photosubstitution,[17] and in spite of a well-demonstrated radical ion pair collapse mechanism,[18] no photocleavage of the ether linkages was observed in any case (Scheme 1). Similar results have been reported in the literature for photo-Smiles reactions[19] and for the photoreaction of 1-methoxy-4-nitronaphthalene with nucleophiles.[20] These results have been rationalized by considering the effect of the NO_2 group on the π^* state energy and on the spin density distribution in the radical anion (predictably concentrated in the NO_2 group), both effects acting in the same direction hindering the necessary $\pi^*-\sigma^*$ coupling and therefore preventing any fragmentation process.[21] Predictably, a similar situation is found when other electron-attracting groups (as CN) substitute on the phenyl ring in place of the NO_2.

All this considered, we proposed that by altering (through Coulombic interactions)[15c] the electronic density of the intermediate aryl ether radical anions, forcing the electronic excess to be located in the ether linkage, a previously unknown fragmentation could be obtained. Preliminary[1] calculations (Figure 1) suggested that a specific placement of the counterion, close to the alkyl ether bond of the intermediate radical anion, would give rise to a dramatic migration of the electronic excess, thus significantly weakening this bond. In order to test the theoretical predictions, we have explored the photochemistry of some 4-substituted phenyl ethers linked through a methylene chain to a tertiary amine and the reductive

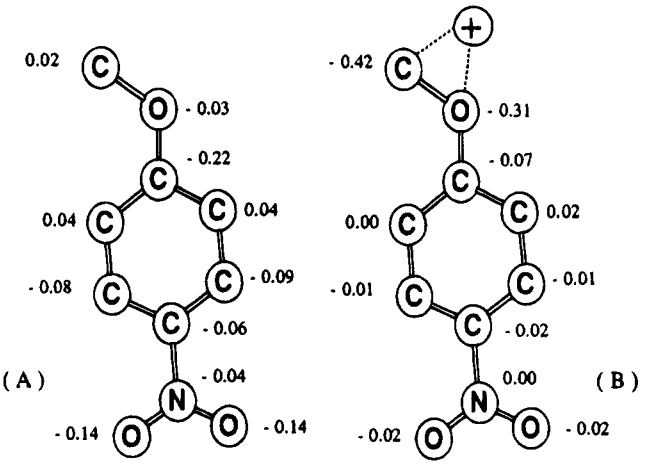
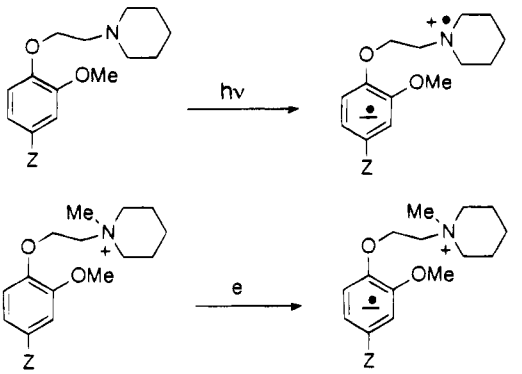


Figure 1. Excess net charge distribution for 4-nitroanisole radical anion (A) and the formally generated ion pair (B) (only values for heavy atoms shown).

Scheme 2



behavior of the corresponding quaternary ammonium salts (Scheme 2). In the first case, we expected that a topologically controlled Coulombic interaction (TCCI) would be created after a photoinduced intramolecular electron transfer process. In the second case, the TCCI could be achieved after an intermolecular electron transfer process from a suitable donor or from the electrode.

Experimental Results and Discussion

Photochemistry of 4-Substituted-Phenyl Piperidinoalkyl Ethers. In Table 1 the photoreactions of several 4-nitrophenyl piperidinoalkyl ethers are summarized and compared with the corresponding photoreactions of 4-nitroveratrole (**1**) and 4-nitroanisole (**2**) in the presence, or in the absence, of triethylamine as reducing agent. H_2O/MeOH or H_2O/CH_3CN at pH 12 was used as the medium.

The photohydrolysis of 4-nitroveratrole (expt 1, Table 1) is a well-known reaction[18a,b,22] that leads to photosubstitution of the methoxy group placed in the *meta* position with respect to the nitro group. The same result is obtained (expt 2, Table 1) when the photoreaction is carried out in the presence of triethylamine in H_2O/CH_3CN. The change of the medium to H_2O/MeOH induces the appearance of photoreduction products **4** and **5** (expt 3, Table 1). These experiments describe the "normal" photoreactivity of nitrophenyl ethers in basic aqueous solutions. This "normal" photoreactivity can also be found when product **6** (five methylene units in the linker)

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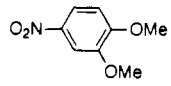
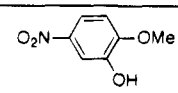
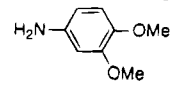
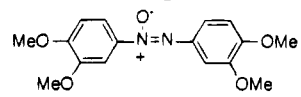
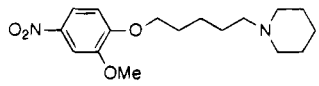
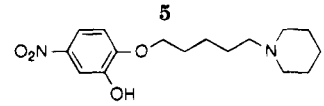
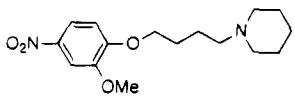
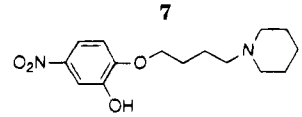
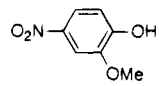
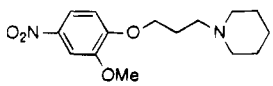
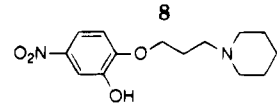
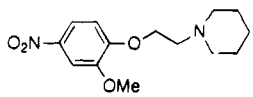
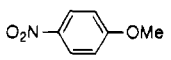
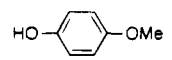
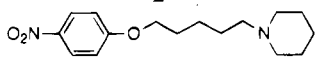
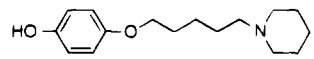
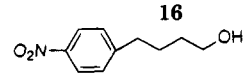
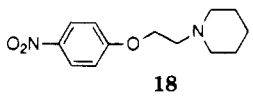
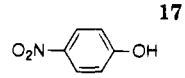
Table 1. Photoreactions of 4-Nitrophenyl Piperidinoalkyl Ethers

expt	substrate	conditions[a]	photoproducts	yield (%)[b]
1	 **1**	H_2O/CH_3CN[c]	 **3**	90
2	**1**	Et_3N, 8 min, H_2O/CH_3CN	**3**	90
3	**1**	Et_3N, 2 h, H_2O/MeOH	**3**	12
			 **4**	43
			 **5**	7
4	 **6**	H_2O/CH_3CN, 2 h	 **7**	88
5	 **9**	H_2O/CH_3CN, 8 min	 **10**	40
			 **8**	34
6	 **11**	H_2O/CH_3CN, 8 min	 **12**	10
			8	50
7	 **13**	H_2O/CH_3CN, 8 min	**8**	95
8	**13**	anhydrous MeOH, 8 min	**8**	95
			1	5
9	 **2**	H_2O/CH_3CN[d]	 **14**	80
10	 **15**	H_2O/CH_3CN, 8 min	 **16**	32
			 **17**	25
11	 **18**	H_2O/CH_3CN, 8 min	 **19**	90

[a] 400 W medium-pressure Hg lamp. Room temperature. H_2O/cosolvent (70:30), pH 12 in all the experiments except in expt 8 where MeONa was used as a base. Pyrex filter ($\lambda > 290$ nm). [b] Absolute preparative yields based on non recovered starting material. Conversion was more than 80% in all the cases. [c] Reference 18a. [d] Reference 22.

is irradiated in H_2O/CH_3CN (expt 4, Table 1). Photosubstitution of the *meta* methoxy group was the main observed process. 2-Methoxy-4-nitrophenol (**8**) was obtained in trace amounts. When the length of the linker is reduced (expts 5, 6, and 7, Table 1) to four, three, and two methylene units, a continuous change in photoreactivity is observed. Thus, when products **9** and **11** were irradiated using the standard conditions, major production of phenol **8** is observed, with the "normal" photosubstitution process (formation of photohydrolysis products **10** and **12**) becoming the minor one. This change in photoreactivity was complete when 1-piperidino-2-(2-methoxy-4-nitrophenoxy)ethane (**13**) was used as substrate. In this case 2-methoxy-4-nitrophenol (**8**) was obtained in practically quantitative amounts.

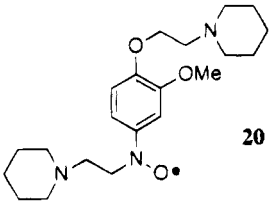
Comparison of the photoreactions where the "anomalous" reactivity was evident (expts 5, 6, and 7, Table 1) with the nitrophenyl ethers general photochemical behavior in front of high ionization potential nucleophiles (OH^-, expt 1, Table 1),[18a,b,22] even in the presence of reducing agents such as triethylamine (expts 2 and 3, Table 1), suggested that 2-methoxy-4-nitrophenol (**8**) in experiments 5, 6, and 7 was produced through a photofragmentation process. The result of experiment 8 (Table 1) strongly supports such an interpretation. Thus, when product **13** (two methylene unit linker) was irradiated

in anhydrous methanol, in the presence of sodium methoxide, the same "anomalous" behavior was observed, with the phenol **8** being obtained in almost quantitative amounts.

Experiments 9, 10, and 11 in Table 1 show that the same photoreactivity change is observed when 4-nitrophenyl derivatives are irradiated using the standard conditions. In experiment 10, in addition to the normal photohydrolysis product (that in the present system corresponds to the substitution of the nitro group),[23] 4-(4-nitrophenyl)butanol (**17**) was obtained.

An interesting common feature to all the studied (Table 1) 4-nitrophenyl piperidinoalkyl ethers is the appearance of a new band as a shoulder ($\lambda_{max} \approx 400-430$ nm) in the UV/vis spectrum. This band (probably a charge transfer band) is not present in the corresponding spectra of the isolated chromofores ($\lambda_{max} \approx 350$ nm for 4-nitroveratrole, **1**).

The basic fraction of the reaction crudes showed polymerization and decomposition in all the cases, precluding any further investigation on the fate of the piperidinoalkyl moiety after fragmentation. However, in some of the cases where the "anomalous" reactivity was present, and when the photoreactions were carried out in very diluted conditions, a new product, tentatively identified as 3-methoxy-4-(2-piperidinoethoxy)phenyl (2-piperidino)ethyl nitroxide (**20**) on the basis of its spectroscopic (UV, EPR, MS) behavior, could be isolated in trace amounts. The appearance of product **20** strongly suggests the presence of piperidinoalkyl radicals in solution.



20

The described results support the original hypothesis (TCCI) of the present work. Thus, in the "normal" situation (4-nitroveratrole, 4-nitroanisole), the nitrophenyl ether radical anion would present the charge density excess concentrated mainly in the nitro group. If a positive charge is placed at a short distance, in such a way that its range is limited to the part of the aromatic ring opposite to the nitro group, a charge density displacement in this direction would occur, with a concomitant weakening of the ether bonds. This is what it seems to happen, particularly when the methylene chain has two units. However, when the polymethylene linkage is five units long, this "anomalous" reactivity disappears. Inspection of the molecular models lead us to the preliminary conclusion that in this case the polymethylene chain is long enough to stabilize the excess negative charge in the nitro group and its surroundings. An alternative mechanistic hypothesis could be a 1,4-diradical fragment produced after hydrogen atom migration (common process in the chemistry of the amine radical cations)[24] or the operativity of some sort of cyclic transition state. The observed continuous change in photoreactivity on going from a short linker to a longer one does not fit the alternative explanations.

An important detail in these photoreactions is that they only work in basic media. Considering that the hydroxide ion does not seem to operate as a nucleophile, its effect can be assigned to the hindering of the excited state protonation (that would probably lead to photoreduction processes), which would cancel the negative charge in the nitrophenyl moiety, stopping the fragmentation reaction.

In Table 2, the photoreactivity of other alkyl phenyl ethers is summarized. From these results, it can be stated that the photofragmentative reactivity described for 4-nitrophenyl ethers with TCCI structure (Table 1) is quite general. Thus, 4-methoxybenzonitrile (**21**) is inert (expt 1, Table 2) when irradiated under the standard conditions. Almost the same result is found (expt 3, Table 2) with 4-(5-piperidinopentoxy)benzonitrile (**24**) being 4-buthoxybenzonitrile (**25**) the only isolated product in 5% yield. On the other hand, when 4-(2-piperidinoethoxy)benzonitrile (**22**) was irradiated (expt 2, Table 2), 4-cyanophenol (**23**) was obtained in practically quantitative amounts. In the case of chlorophenyl ethers (expts 4, 5, and 7, Table 2), the interpretation of the results is somewhat more complicated due to the fact that the C–Cl bond photochemical weakness makes the final products unstable (see, i.e., expt 6, Table 2). Nevertheless, our results show photofragmentation for short linker substrates (phenol, **28**, expt 5, Table 2) and chlorine substitution when longer linker substrates were used (product **16**, expt 7, Table 2). Experiments 8 and 9 in Table 2 indicate that the TCCI approach works even with nonsubstituted phenyl ethers.

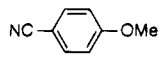
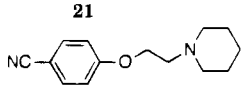
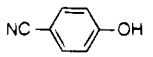
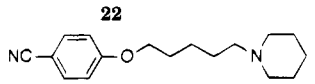
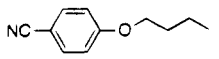
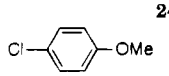
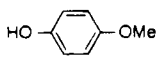
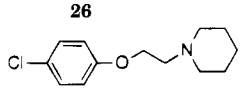
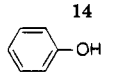
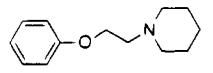
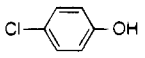
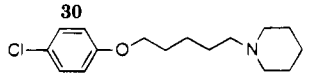
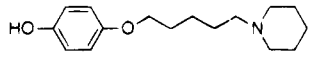
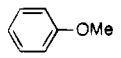
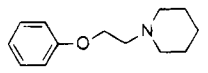
In Tables 1 and 2 there are two results that merit further comment. We refer to the appearance of 4-(4-nitrophenyl)butanol (**17**) in experiment 10, Table 1, and (4-cyanophenoxy)butane (**25**) in experiment 3, Table 2. In both cases (substrates **15** and **24**), the photofragmentation is not activated. In addition, there are no leaving groups in the *meta* position with respect to the nitro group, and therefore the alternative photosubstitution reactions that are present in other substrates are more difficult. Both photoproducts can be justified from an intramolecular electron transfer excited state (Scheme 3). The fragmentation of the C–C bond would lead to an internal radical pair. At this point, if the ring has a strong electron-withdrawing group (nitro), a radical collapse would occur giving rise to a σ-complex, direct precursor of 4-(4-nitrophenyl)butanol (**17**). If a weaker electron-withdrawing group (CN) is present, the collapse process would be slower, with hydrogen abstraction being the observed process, leading to (4-cyanophenoxy)butane (**25**).

The photofragmentation reactions can be "photosensitized". This was investigated using compounds **22**, **27**, and **29**, substrates transparent at $\lambda > 290$ nm, in such a way that under irradiation through a Pyrex filter only the sensitizer would be excited. Blank photoreactions led to the recovery of the starting materials. However, when the photoreactions were carried out in the presence of benzophenone, photofragmentation was observed in all the cases studied (Scheme 4). Benzophenone has a lower

(23) (a) Letsinger, R. L.; Ramsay, O. B.; McCain, J. H. *J. Am. Chem. Soc.* **1965**, *87*, 2945. (b) de Vries, S.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 601.

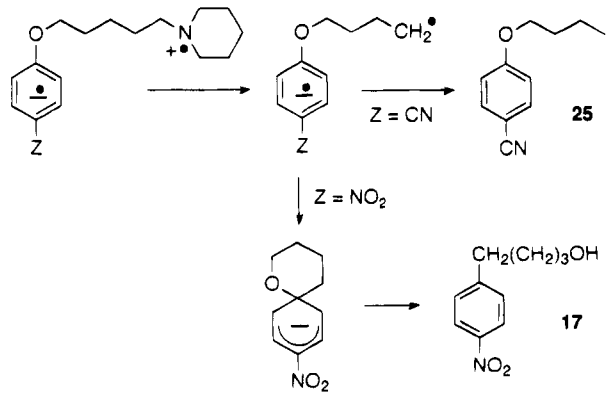
(24) (a) Padwa, A. *J. Am. Chem. Soc.* **1971**, *93*, 1400. (b) Padwa, A. *Acc. Chem. Res.* **1971**, *4*, 48. (c) Wagner, P. J.; Ersfeld, D. A. *J. Am. Chem. Soc.* **1976**, *98*, 4515.

Table 2. Photoreactions of Differently 4-Substituted-Phenyl Piperidinoalkyl Ethers

expt	substrate	conditions[a]	photoproducts	yield (%)[b]
1		H_2O/CH_3CN, 6.5 h		
2	**21** 	H_2O/CH_3CN, 6.5 h	 **23**	95
3	**22** 	H_2O/CH_3CN, 6.5 h	 **25**	5
4	**24** 	H_2O/CH_3CN, 10 min		78
5	**26**  **27**	H_2O/CH_3CN, 10 min	 **14** **28**  **29**	33 65
6		H_2O/CH_3CN, 10 min	**28**	83
7	**30**  **31**	H_2O/CH_3CN, 10 min	 **16**	20
8		H_2O/CH_3CN, 5.5 h	**28**	3
9	**32**  **29**	H_2O/CH_3CN, 5.5 h	**28**	27

[a] 400 W medium-pressure Hg lamp. Room temperature. H_2O/cosolvent (70:30), pH 12 in all the experiments. Quartz vessel. [b] Absolute preparative yields based on nonrecovered starting material. Conversion was more than 80% in all the cases.

Scheme 3



triplet energy (E_T = 287 kJ mol^{-1})[25] than the aromatic chromophore triplet state for those aromatic ethers (i.e., $E_{Tanisole}$ = 338 kJ mol^{-1}).[25] Therefore, energy transfer photosensitization to those aromatic chromophore triplet states has a rather low probability of occurring. Considering that our substrates show, in the apropriate conditions, charge transfer transitions, a possible explanation for the observed "photosensitization" would be the direct formation of a low energy triplet charge transfer excited state. Benzophenone is a good energy transfer sensitizer, and it could also act through an electron transfer and back electron transfer process that, if occurring faster than any intersystem crossing, would lead to the triplet charge transfer excited state probably responsible for the observed fragmentation. In addition, a rather inefficient photofragmentation (less than 20% after 1 h) was observed when 1-piperidino-2-(2-methoxy-4-nitrophenoxy)ethane (**13**) was irradiated with visible light (charge transfer band excitation, $\lambda \approx 420$ nm). It is well known that the photoefficiency of bond scission in triplet ion pairs is much higher than in singlet ones,[26] with back electron transfer being the main process in this last case.[27] The results suggest that this is also our case.

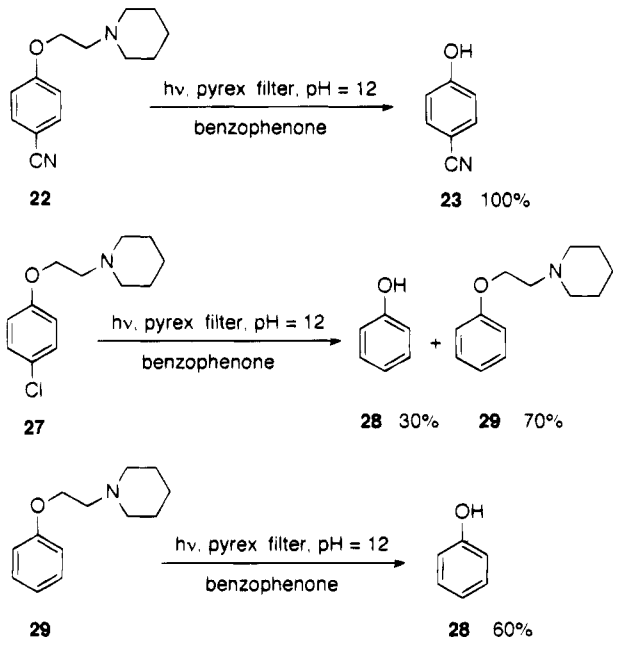
Those experiments agree with the operativity of a "triplet charge transfer excited state" as a key intermediate in the photofragmentation processes. This state can

(25) Carmichael, I.; Hug, G. L. In *Handbook of Organic Photochemistry*; Scaiano, J. C., Ed.; CRC Press: Boca Raton, FL, 1989; Vol. 1, p 369.

(26) Maslak, P.; Chapman, W. H. *J. Chem. Soc., Chem. Commun.* **1989**, 1809.

(27) Mauzerall, D. C. In *Photoinduced Electron Transfer*; Fox, M. A., Chanon, M., Eds.; Elsevier: Amsterdam, 1988; Part A, p 228.

Scheme 4

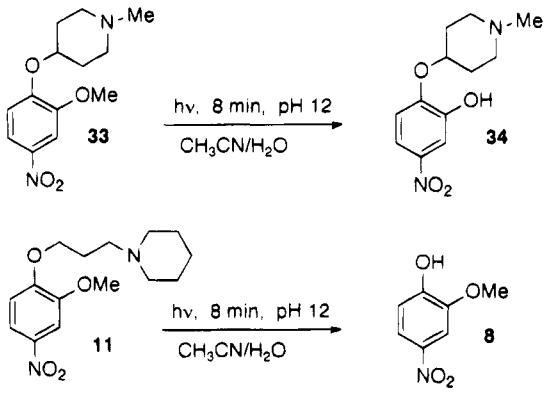


be efficiently reached by "photosensitization" with benzophenone or by excitation of the aromatic chromophore to its triplet excited state followed by intramolecular electron transfer. This last process is expected to be energetically favorable for all the considered cases, with the only exception being substrate **29**, where it is expected to be slightly endothermic.[28]

The conclusions were supported by the fact that UV irradiation of product **13** in the solid state led only to traces of 2-methoxy-4-nitrophenol (**8**) whereas when the solid was melt and irradiated, 27% of photofragmentation product **8** was obtained (blank experiments in the absence of irradiation led to the recovery of the starting material in both cases). Therefore, it seems that, for the photofragmentative process to be observed, the piperidinoalkyl chain must have some conformational freedom, probably to achieve the appropriate conformation for the through-space intramolecular electron transfer to occur.

The next point of interest was the influence of the alkyl ether bond relative orientation with respect to the benzene ring plane in the final outcome of the photofragmentation reaction. Recently, a relationship between the preferred conformation of methoxy-susbtituted aromatic compounds and the observed regioselectivity (alkyl ether vs aryl ether) in the reductive cleavage has been suggested. Thus, Herold and co-workers,[15c] on the basis of EPR studies and INDO calculations, state that a

Scheme 5



coplanar conformation of the methoxy group with respect to the benzene ring should favor the breaking of the Ar–O bond (demethoxylation), while an orthogonal conformation should favor the Me–O cleavage (demethylation). However, a decisive factor that can completely alter the final outcome of the reaction is the position of the countercation once the radical anion has been formed. The preferences advanced by Herold[15c] seem to be due to the fact that, when the radical anion is in an orthogonal conformation, the cation moves from a position close to the oxygen to a new position placed over the aromatic ring. Curiously enough, theoretical calculations (*vide infra*) predicted that, in the absence of any effect due to a different placement of the countercation, a coplanar relative orientation of the alkyl ether bond and the aromatic ring was needed for the photofragmentation of this bond to occur. ω-Aminoalkyl 4-nitrophenyl ethers give predominant breaking of the alkyl ether bond (dealkylation) when irradiated. In addition, this process happens through intramolecular electron transfer, and the final position of the countercation (before the fragmentation) is governed by the linker lenght which, in case the linker is short enough, would hinder any migration of the kind suggested by Herold (notice that in our cases the countercation role is played by the amino group radical cation). Therefore, those substrates can be interesting tools for establishing the conformational influence on the photofragmentative behavior of alkyl phenyl ethers. An example is described in Scheme 5 where the photoreactivity of 1-methyl-4-(2-methoxy-4-nitrophenoxy)piperidine (**33**) in the standard photofragmentative conditions is compared with the photoreactivity of 1-piperidino-3-(2-methoxy-4-nitrophenoxy)propane (**11**). Both products have a three-carbon linker, and their UV/vis spectroscopic properties are very similar. Thus, the product **33** also shows the charge transfer band in the UV/vis spectrum ($\lambda_{max} \approx 400$ nm), indicating it can achieve the "electron transfer" conformation. However, product **11** shows photofragmentation while substrate **33** presents only the "normal" photosubstitution reactivity. This "a priori" surprising result was understood after examination of the molecular models. Thus, this analysis indicated that product **11** was able to achieve an appropriate electron transfer conformation without taking the alkyl ether bond out of the plane of the benzene ring. However, for achieving the same type of conformation in the much more rigid **33** case, the alkyl ether bond had to be almost completely orthogonal to the benzene ring plane. This results strongly support our theoretical predictions (*vide infra*).

(28) The free energy change involved in electron transfer to give a radical ion pair can be obtained from the Weller equation, $\Delta G_{et} = F[(E_D)^{ox} - (E_A)^{red}] - \Delta E_{exc} + \Delta E_{coul}$ (Weller, A. *Z. Phys. Chem. (Munich)* **1982**, *93*, 130. Weller, A *Z. Phys. Chem. (Munich)* **1982**, *93*, 133. Mattay, J. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 825). Its application to our cases gives $\Delta G_{et} < 0$ for all of them, except for the substrate **29** where a rough estimation (due to the fact that the reduction potential of anisole is far beyond our measurement possibilities) taking $(E_A)^{red} \approx -3.2$V gives $\Delta G_{et} \approx +20$ kJ mol^{-1} in a solvent of $\epsilon \approx 70$. For a related example, see: Marquet, J.; Cantos, A.; Moreno-Mañas, M.; Cayón, E.; Gallardo, I. *Tetrahedron* **1992**, *48*, 1333.

(29) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

(30) Liotard, D. A.; Healy, E. F.; Ruiz, J. M.; Dewar, M. J. S. Ampac version 2.1. Quantum Chemistry Program Exchange, program 506, *QCPE Bull.* **1989**, *9*, 123.

(31) Roothaan, C. C. J. *Rev. Mod. Phys.* **1951**, *23*, 69.

(32) Bacaloglu, R.; Bunton, C. A.; Ortega, F. *J. Am. Chem. Soc.* **1989**, *111*, 1041.

Scheme 6

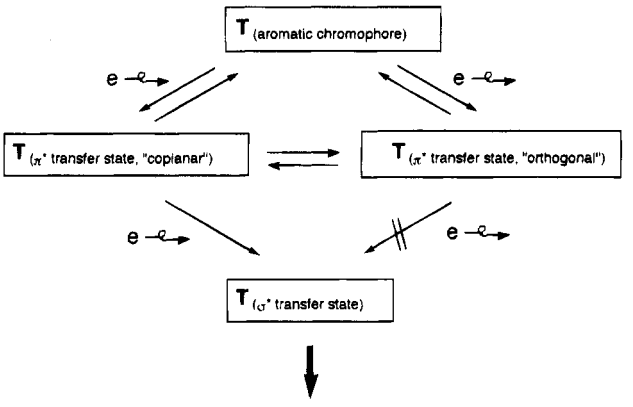
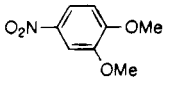
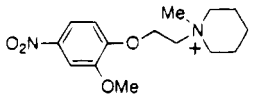
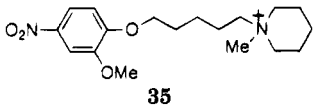


Table 3. First and Second Reduction Potentials of 4-Nitroveratrole (1) and Tetrafluoroborates 34 and 35 in DMF

substrate[a]	E°/(V)[b]	Ep2/V[c]
 1	−1.13	−2.21
 34	−1.08	−1.56
 35	−1.18	−1.95

[a] Potentials measured by cyclic voltametry in glassy carbon (13 °C). Solutions containing tetrabutylammonium tetrafluoroborate (0.1 M). [b] Standard potential vs SCE. [c] Peak potential vs SCE.

The experimental results described so far suggest the general mechanistic scheme described in Scheme 6 for the photofragmentation of piperidinoalkyl phenyl ethers. When the phenyl ring is substituted by an attracting group, this fragmentation is only possible if a TCCI effect is present and the alkyl ether bond is coplanar with the phenyl ring.

Reductive Electrochemistry of *N*-Methyl Quaternary Salts of 4-Nitrophenyl Piperidinoalkyl Ethers and Related Experiments. In order to support the electron transfer mechanism, and the TCCI effect on the outcome of our reactions, the electroreductive behavior of the tetrafluoroborates of *N*-methyl-*N*-(2-(2-methoxy-4-nitrophenoxy)ethyl)piperidinium (**34**) and *N*-methyl-*N*-(5-(2-methoxy-4-nitrophenoxy)pentyl)piperidinium (**35**) in DMF was investigated. In Table 3, the first and second reduction potentials of compounds **34**, **35**, and 4-nitroveratrole (**1**) in DMF are summarized. A small shift of the standard potential E° of the couple substrate/radical anion or substrate/zwitterionic radical is observed when comparing 4-nitroveratrole (**1**) (−1.13 V vs SCE) and the tetrafluoroborate **35** (−1.18 V vs SCE, long linker) with the tetrafluoroborate **34** (−1.08 V vs SCE short linker). Using a wider potential range, a second two-electron irreversible wave is obtained in all the cases. The appearance of an anodic peak at more positive potentials suggests the formation of the nitrosobenzene derivatives. Interestingly enough, the position of this second wave shows a wider variability in the studied compounds. Thus, for 4-nitroveratrole (**1**) (E_p = −2.21 V vs SCE) and

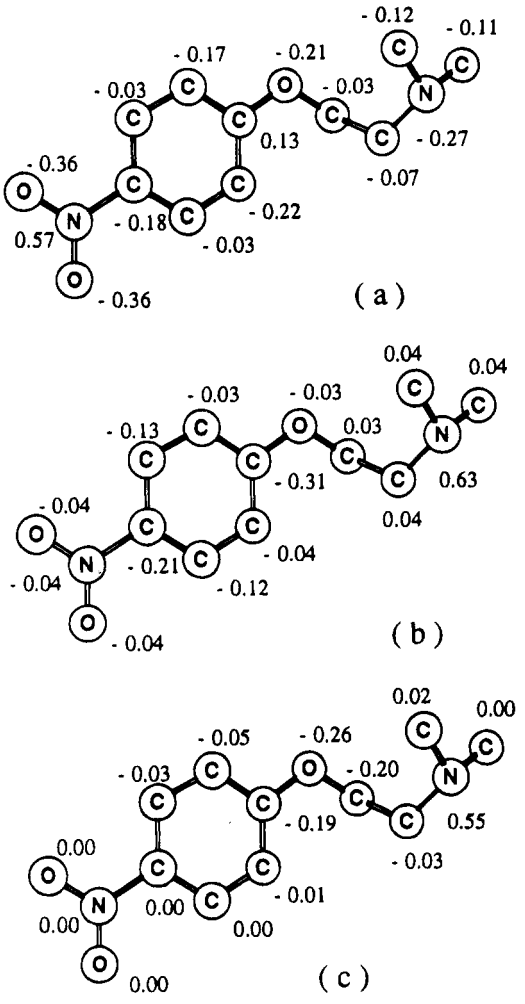


Figure 2. Net charges in the S_0 state (a) and net charge differences between T_1^{CT} (b) and T_2^{CT} (c), respectively, with S_0 for 1-(dimethylamino)-2-(4-nitrophenoxy)ethane (only values for heavy atoms shown).

the tetrafluoroborate **35** (E_p = −1.95 V vs SCE), this second wave appears at potentials clearly more negative than in the case of the tetrafluoroborate **34** (E_p = −1.56 V vs SCE). This behavior appears to be the electrochemical demonstration of the TCCI effect. After the first reduction of compounds **1** and **35**, the negative charge must be mainly concentrated in the nitro group, thus making any further reduction difficult. However, in the case of product **34**, the TCCI effect reduces the electronic density in the nitro group (see also Figure 1), with the second reduction being easier.

Preparative electrolyses of compounds **1**, **34**, and **35** were carried out in DMF (−1.2 V vs SCE, first reduction wave). Compounds **1** and **35** were found to be stable under the reaction conditions. However, compound **34** gave rise to reductive cleavage. Phenol **8** was obtained in 39% yield. The applied potential was selected in such a way as to allow only the first reduction to happen. Therefore, these results strongly support the operativity of a TCCI effect and perfectly agree with the results of the experiments performed by photochemical methods in very similar systems.

Theoretical Calculations

As has been shown above, the charge transfer triplet states seem to play a fundamental role in the photochem-

Table 4. More relevant Molecular Orbitals

m	orbital energy (eV)	type	m	orbital energy (eV)	type
2	−9.85	π'_0	4	−9.87	π'_0
	−9.62	n		−9.38	n
	−0.94	π_1		−0.95	π_1
	−0.27	π'_2		−0.29	π'_2
	0.64	π_3		0.62	π_3
	0.78	σ_1		0.75	σ_1
	1.56	σ_2		1.63	σ_2
3	−9.88	π'_0	5	−9.87	π'_0
	−9.48	n		−9.32	n
	−0.96	π_1		−0.95	π_1
	−0.31	π'_2		−0.30	π'_2
	0.61	π_3		0.61	π_3
	0.74	σ_1		0.75	σ_1
	1.62	σ_2		1.64	σ_2

ical cleavage of 4-nitrophenyl pyperidinoalkyl ethers (Scheme 6). In order to analyze the feasibility of this hypothetical mechanism, we have theoretically calculated the energies and the electronic wave functions corresponding to these excited states. For the sake of simplicity, we have replaced the pyperidino group by a dimethylamino group, $N(CH_3)_2$. All the molecular orbital (MO) calculations presented in this work were carried out using the semiempirical AM1 method[29] as implemented in the AMPAC[30] program.

First we fully optimized the ground states S_0 for the 4-nitrophenyl(dimethylamino)alkyl ethers (the analogous of compounds **13**, **11**, **9**, and **6**, in Table 1) which are obtained by successively enlarging the length of the alkyl ring $-(CH_2)_m-$ from $m = 2$ to $m = 5$. The restricted Hartree−Fock (RHF)[31] method has been used for these closed-shell calculations. In all the cases the nitro group, the phenyl ring, and the oxygen and carbon atoms that form the alkylic bond are in the same plane. The methylenic chain linker $-(CH_2)_m-$ is always unfolded.

Table 4 shows a classification of the more relevant molecular orbitals for every compound of the series. We have considered the most important contribution in order to label the orbital. The highest π occupied molecular orbital is indicated as the π_0. Virtual π molecular orbitals are labeled as π_1, π'_2, and so on. A prime is used as a superindex to denote that the π orbital is mainly located at the phenyl ring. σ_1 and σ_2 stand for the first two virtual σ orbitals. σ_1 is located in the nitro group and in the carbon atom to which is attached. On the other hand, σ_2 is an antibonding orbital located in the alkyl ether C−O bond. This orbital is the one to fill in order to favor the alkyl ether bond cleavage. Finally an n labels the highest occupied orbital which mainly corresponds to a lone pair of the amine nitrogen. In all the cases the order is maintained so that the HOMO is the n orbital whereas the LUMO is the π_1. Globally, the energy of any considered orbital is quite similar along the series.

In Table 5 we present for each compound the first five charge transfer triplet states obtained through configuration interaction (CI) calculations within the AM1 method. The CI configuration matrix has been obtained by considering all the mono- and bi-excitations coming from the HOMO n orbital and going to one of the first five unoccupied orbitals.

In the second column the vertical electronic transition energies coming from the ground state are given. The last column gives the major contributions to the electronic wave function for each CI state. Only those configurations that have a coefficient of significant weight in the CI expression are shown. These functions include the spin-adapted configurations obtained by taking appropriate linear combinations of the Slater determinants used in the CI.

Table 5. Charge Transfer Triplet States for the 4-Nitrophenyl (Dimethylamino)alkyl Ethers

m	energy (eV)	truncated CI wave function
2	6.416	$T_1^{CT} = 0.973\ (n \rightarrow \pi_1) + 0.214\ (n \rightarrow \pi_3)$
	6.427	$T_2^{CT} = 0.951\ (n \rightarrow \sigma_2)$
	7.064	$T_3^{CT} = 0.999\ (n \rightarrow \pi'_2)$
	8.427	$T_4^{CT} = 0.976\ (n \rightarrow \pi_3) - 0.214\ (n \rightarrow \pi_1)$
	8.663	$T_5^{CT} = 0.991\ (n \rightarrow \sigma_1)$
3	6.452	$T_1^{CT} = 0.981\ (n \rightarrow \pi_1) - 0.188\ (n \rightarrow \pi_3)$
	7.059	$T_2^{CT} = 0.999\ (n \rightarrow \pi'_2)$
	7.626	$T_3^{CT} = 0.979\ (n \rightarrow \sigma_2) - 0.202\ (n \rightarrow \sigma_1)$
	8.363	$T_4^{CT} = 0.981\ (n \rightarrow \pi_3) + 0.188\ (n \rightarrow \pi_1)$
	8.595	$T_5^{CT} = 0.979\ (n \rightarrow \sigma_1) + 0.202\ (n \rightarrow \sigma_2)$
4	6.685	$T_1^{CT} = 0.989\ (n \rightarrow \pi_1) + 0.144\ (n \rightarrow \pi_3)$
	7.274	$T_2^{CT} = 0.999\ (n \rightarrow \pi'_2)$
	8.279	$T_3^{CT} = 0.945\ (n \rightarrow \sigma_2) + 0.325\ (n \rightarrow \sigma_1)$
	8.481	$T_4^{CT} = 0.988\ (n \rightarrow \pi_3) - 0.144\ (n \rightarrow \pi_1)$
	8.708	$T_5^{CT} = 0.945\ (n \rightarrow \sigma_1) - 0.326\ (n \rightarrow \sigma_2)$
5	6.764	$T_1^{CT} = 0.993\ (n \rightarrow \pi_1)$
	7.348	$T_2^{CT} = 1.000\ (n \rightarrow \pi'_2)$
	8.505	$T_3^{CT} = 0.991\ (n \rightarrow \pi_3)$
	8.584	$T_4^{CT} = 0.712\ (n \rightarrow \sigma_1) + 0.700\ (n \rightarrow \sigma_2)$
	8.777	$T_5^{CT} = 0.712\ (n \rightarrow \sigma_2) - 0.702\ (n \rightarrow \sigma_1)$

It is noteworthy that, as one would expect, in all the cases the $n \rightarrow \sigma$ excitations do not mix with the $n \rightarrow \pi$ ones. It is also a general trend that an excitation to a π' orbital only combines with another π' excitation.

The main contribution to the lowest charge transfer triplet state always corresponds to the $n \rightarrow \pi_1$ electronic transition. That is, the negative charge is concentrated in the ring and the nitro group. The second charge transfer triplet state for the $m = 2$ case corresponds mainly to the excitation to the σ_2 orbital. We recall that this state leads to the alkyl C−O fragmentation. For larger m, the energy associated with this state increases. This state also has a progressively increasing contribution of the $n \rightarrow \sigma_1$ excitation. As a consequence, the state that leads to the C−O bond cleavage becomes the third charge transfer triplet T_3^{CT} for $m = 3$ and 4 whereas for $m = 5$ the $n \rightarrow \sigma_2$ excitation is almost equally distributed between the T_4^{CT} and T_5^{CT} states. Conversely, the energy of the first charge transfer triplet state T_1^{CT} does not appreciably vary along the series $m = 2$ to 5. Thus the energy gap between T_1^{CT} and the photofragmentative charge transfer triplet state monotonically increases as m increases.

A Mulliken analysis of the atomic charges for the different charge transfer triplet states has been used in order to clarify the nature of the states involved in the bond breaking. For instance, in Figure 2 the case $m = 2$ has been considered. In particular the net charges corresponding to the singlet ground state S_0 and the net charge differences between T_1^{CT} and T_2^{CT}, respectively, with S_0 are presented. It is clearly seen that, as both excited states are of the charge transfer type from the lone pair amine nitrogen orbital, the amine nitrogen atom suffers a considerable loss of negative charge in both cases. This negative charge is then distributed in quite a different manner for the two excited states. For T_1^{CT} the negative charge is distributed among the atoms of the benzene ring and the NO_2 fragment, whereas in T_2^{CT} the main negative increment is located in the oxygen atom of the ether and the alkylic carbon atom attached to it, thus favoring the bond breaking. An equivalent charge analysis for the rest of compounds of the series

Table 6. C–O Bond Orders

m	S_0	T_1^{CT} (n → π_1)	T^{CT} (n → σ_2)
2	0.94	0.94	0.70
3	0.94	0.94	0.67
4	0.94	0.94	0.68
5	0.94	0.94	0.76

(m = 3 to 5) reveals that the net charge characteristics of T_1^{CT} are not significantly modified, as expected from the fact that the wave functions of this state are very similar as shown in Table 5. Conversely, the state responsible of the bond breaking (which is T_2^{CT} for the m = 2 case and corresponds mainly to the n → σ_2 excitation, varying along the series and becoming T_3^{CT} from m = 3 and 4 and T_4^{CT} for m = 5) has a progressively increasing contribution from the n → σ_1 excitation. As a consequence the negative charge of the ether oxygen atom and its neighboring alkylic carbon atom for the state that should lead to the C–O cleavage diminishes along the series, whereas the negative charge in the nitro group and the phenylic carbon atom attached to it increases.

From this Mulliken analysis, it seems that, for the case of a short methylenic chain, a strong Coulombic interaction between the positive N amine center and the negative C–O alkyl region produces an important stabilitation of the n → σ_2 triplet state for the m = 2 case. As the methylenic chain becomes longer and longer, the increasing separation of charges destabilizes the n → σ_2 triplet state, the photofragmentation being progressively more and more difficult.

From the point of view of the bond order between the oxygen and the alkylic carbon atoms, clear differences can also be observed between the two kinds of triplet states considered, as can be seen in Table 6. The ground state S_0 has a constant value along the series. The T_1^{CT} state also has a constant value along the series and, what is more important, with virtually the same value of the ground state. On the contrary, the n → σ_2 triplet state has a clearly lower value so that the bond cleavage is favored in this state. Finally, it is noted that this value varies along the series, the m = 5 case being the upper bound.

Let us now consider the 1-methyl-4-(2-methoxy-4-nitrophenoxy)piperidine case (compound **33**) which, a priori, should be quite similar to the m = 3 compound of the series we have just analyzed. However, as stated in the previous section, product **33** exhibits a rather surprising behavior. For the sake of simplicity, we have suppressed the methoxy group in our calculations, in such a way that the 1-methyl-4-(4-nitrophenoxy)piperidine has been considered. In this case, for the ground state S_0 two geometrical minima have been obtained, one with the oxygen–alkylic carbon bond in the same plane of the benzene ring and another with this bond situated in an almost orthogonal plane.

Table 7 presents the results of the different charge transfer triplet states for both conformations following the same procedure outlined for the m = 2 to 5 series that gave the results presented in Table 5. The molecular orbitals are also qualitatively equivalent to the ones described previously in Table 4. The only significant difference is the σ_2 orbital of the orthogonal conformation which, in this case, mixes with the π system.

Results in Table 7 show that the coplanar configuration is indeed very similar to the m = 3 case, the energies of the different states being between 0.5 and 0.8 eV lower.

Table 7. Charge Transfer Triplet States for 1-Methyl-4-(4-nitrophenoxy)piperidine

m	energy (eV)	truncated CI wave function
coplanar	5.63	T_1^{CT} = 0.978 (n → π_1) + 0.204 (n → π_3)
	6.42	T_2^{CT} = 0.996 (n → π'_2)
	7.07	T_3^{CT} = 0.978 (n → σ_2) − 0.148 (n → σ_1)
	7.12	T_4^{CT} = 0.970 (n → π_3) − 0.200 (n → π_1)
	8.15	T_5^{CT} = 0.985 (n → σ_1) + 0.171 (n → σ_2)
orthogonal	5.80	T_1^{CT} = 0.965 (n → π_1) − 0.232 (n → π_3)
	6.64	T_2^{CT} = 0.999 (n → π'_2)
	7.56	T_3^{CT} = 0.853 (n → π_3) + 0.445 (n → σ_2) + 0.261 (n → σ_1)
	8.16	T_4^{CT} = 0.996 (n → σ_1)
	8.60	T_5^{CT} = 0.887 (n → σ_2) + 0.459 (n → π_3)

The relative position of the states, however, does not vary from the m = 3 case. The situation is quite different for the orthogonal conformation as, now, given the different simmetry of the σ_2 orbital, the n → σ_2 spin-adapted configuration does not mix with the n → σ_1 configuration but with the n → π_1 and n → π_2 ones. As a consequence of that, the n → σ_2 appears in the T_3^{CT} state but with only a minor contribution. This is also seen in the bond order between the ether oxygen and the alkylic carbon atom for this state that is 0.84, only slightly below the bond order of the singlet ground state (0.93). The state with the major contribution of the n → σ_2 excitation is now the fifth triplet T_5^{CT}. The energy of this state is, however, too high to be taken into account in the bond breaking process.

As a consequence of the above discussion, it could be expected that the coplanar but not the orthogonal conformation will lead to the photofragmentation of the alkylic ether. Taking in consideration that the coplanar conformation of the ground state for 1-methyl-4-(4-nitrophenyl)piperidine is somewhat lower in energy (1.0 kcal/mol), it seems rather surprising that the experimental results do not indicate photofragmentation for compound **33**. In order to explain the experimental facts, we should now remember that a previous step of the whole process involves an intramolecular electronic transition from the triplet state $T_{\pi\to\pi^*}$ to T_1^{CT}. It is known that the rate of these processes highly depends on the electron transfer matrix element between the initial and final states. It is generally assumed that the magnitude of this integral falls off exponentially with the distance between the electron donor and acceptor. For both the 1-(*N*,*N*-dimethylamino)-3-(4-nitrophenoxy)propane (case corresponding to m = 3) and the 1-methyl-4-(4-nitrophenoxy)piperidine at their minimum energy ground state conformations (coplanar), the donor (nitrogen) and acceptor (benzene ring) fragments are located quite far away. However, the m = 3 compound can adopt a folded conformation where the donor and acceptor units come close enough but the coplanarity of the alkylic C–O bond is preserved. Conversely, in the 1-methyl-4-(4-nitrophenoxy)piperidine, the piperidine ring prevents the nitrogen atom from coming to close to the benzene ring unless an almost orthogonal conformation is reached.

A calculation of the T_1^{CT} excited state for the 1-methyl-1-(4-nitrophenoxy)piperidine reveals that its minimum energy conformation is the orthogonal one, the coplanar conformation now being 12.41 kcal/mol above. Therefore, if the intramolecular electronic transfer $T_{\pi\to\pi^*}$ to T_1^{CT} takes place in the orthogonal conformation, where the photofragmentation is difficult, the back electron transfer would preferentially occur.

Finally, it has to be noted that, whereas calculations refer to gas phase compounds, experimental results come from solution media. However, as in similar precedent papers,[15c,32] we expect that the introduction of solvent effects would not qualitatively affect the main theoretical results of this paper, since we are comparing a series of compounds of similar electronic structure.

Experimental Section

General Considerations. All melting points are uncorrected. ^{1}H NMR were recorded at 80 or 400 MHz and the ^{13}C NMR at 20 or 100 MHz. 4-Nitroveratrole was prepared by nitration of veratrole.[33] Potassium 2-methoxy-4-nitrophenoxide was prepared according to the method of Pollecoff and Robinson.[34]

General Procedure for the Synthesis of α-Piperidino-ω-(2-methoxy-4-nitrophenoxy)alkanes, 6, 9, 11, and 13. Potassium 2-methoxy-4-nitrophenoxide dihydrate (0.049 mol), the α,ω-dibromoalkane (0.448 mol), and 300 mL of acetone were introduced in a 500 mL round-bottomed flask. The mixture was kept under reflux for 30 h, until disappearance of the red color. Then, the solvent was evaporated. The residue was dissolved in 50 mL of chloroform, and the organic solution was washed with sodium hydroxide (1 M) and water and dried and the solvent evaporated. The residue was chromatographed through silica gel using hexane/chloroform as eluent, thus obtaining the corresponding α-bromo-ω-(2-methoxy-4-nitrophenoxy)alkane.

A mixture of α-bromo-ω-(2-methoxy-4-nitrophenoxy)alkane (0.022 mol), piperidine (0.053 mol), potassium carbonate (0.18 mol), and acetone (300 mL) was placed in a 500 mL round-bottomed flask and refluxed under magnetic stirring for 24 h. After cooling, the solids were filtered, and the solvent and the excess of piperidine were evaporated. The crude α-piperidino-ω-(2-methoxy-4-nitrophenoxy)alkane was purified as indicated in each particular case.

1-Piperidino-5-(2-methoxy-4-nitrophenoxy)pentane (6). Product **6** (70% total yield) could not be crystallized and was purified by column chromatography through silica gel using chloroform/ethyl acetate as eluent: IR (KBr) 2935, 2856, 1588, 1514, 1467, 1452, 1340, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.60 (12H), 2.40 (m, 6H), 3.95 (s, 3H), 4.20 (t, J = 6.0 Hz, 2H), 6.91 (d, J = 8 Hz, 1H), 7.70 (d, J = 2.4 Hz, 1H), 7.85 (dd, J = 8 Hz, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 23.9, 24.4, 25.9, 26.5, 28.7, 54.5, 56.2, 59.1, 69.2, 106.8, 110.9, 117.3, 141.8, 149.5, 154.2; MS m/e (relative intensity) 154 (12), 98 (100), 55 (13). Anal. Calcd for $C_{17}H_{26}N_2O_4$: C, 63.27; H, 8.06; N, 8.69. Found: C, 62.83; H, 8.06; N, 8.59.

1-Piperidino-4-(2-methoxy-4-nitrophenoxy)butane (9). Product **9** (65% total yield) was purified by crystallization of the corresponding hydrochloride in ethyl acetate (mp 149–151 °C). The spectra correspond to the free base: IR (KBr) 2944, 1587, 1514, 1455, 1450, 1341, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40–1.95 (m, 10H), 2.41 (t, J = 5.7 Hz, 6H), 3.94 (s, 3H), 4.25 (t, J = 5.7 Hz, 2H), 6.95 (d, J = 8.6 Hz, 1H), 7.70 (d, J = 2.8 Hz, 1H), 7.85 (dd, J = 8.6 Hz, J = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.9, 24.1, 25.7, 26.7, 54.2, 55.9, 58.4, 69.1, 106.5, 110.8, 117.4, 140.9, 148.9, 154.1; MS m/e (relative intensity) 308 (M^+, 1), 167 (2), 140 (4), 127 (3) 88 (100), 55 (14), 42 (17). Anal. Calcd for $C_{16}H_{24}N_2O_4$: C, 55.73; H, 7.31; N, 8.12. Found: C, 55.59; H, 7.43; N, 7.69.

1-Piperidino-3-(2-methoxy-4-nitrophenoxy)propane (11). Product **11** (61% total yield) was purified by crystallization of the corresponding hydrochloride in acetone, mp 157–159 °C (lit.[35] mp 156.3–160.4 °C): IR (KBr) 2950, 2700, 2650, 1590, 1500, 1477, 1450, 1350, 1340 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.8–2.9 (m, 10H), 3.25 (m, 2H), 3.70 (m, 2H), 3.95 (s, 3H), 4.20 (t, J = 6.0 Hz, 2H), 6.91 (d, J = 8 Hz, 1H), , 7.70 (d, J = 2.4 Hz, 1H), 7.85 (dd, J = 8 Hz, J = 2.4 Hz, 1H), 11.80 (s, 1H).

1-Piperidino-2-(2-methoxy-4-nitrophenoxy)ethane (13). Product **13** was purified by recrystallization from benzene–pentane, mp 94–95 °C: IR (KBr) 2947, 2925, 1588, 1512, 1453, 1336 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.55 (m, 6H), 2.60 (m, 4H), 2.90 (t, J = 5.7 Hz, 2H), 3.95 (s, 3H), 4.25 (t, J = 5.7 Hz, 2H), 6.95 (d, J = 8.6 Hz, 1H), 7.70 (d, J = 2.8 Hz, 1H), 7.85 (dd, J = 8.6 Hz, J = 2.8 Hz, 1H); ^{13}C ($CDCl_3$) δ 23.9, 25.7, 54.8, 56.0, 57.2, 67.4, 106.7, 111.2, 117.3, 128.0, 141.2, 149.0, 153,9; MS m/e (relative intensity) 98 (100) 55 (10), 42 (17). Anal. Calcd for $C_{14}H_{20}N_2O_4$: C, 59.93; H, 7.13; N, 9.99. Found: C, 59.98; H, 7.14; N, 9.98.

General Procedure for the Synthesis of α-Piperidino-ω-(4-substituted-phenoxy)alkanes 15, 18, 22, 24, 27, 31, and 29. The appropriate phenol (0.042 mol), α,ω-dibromoalkane (0.175 mol), potassium carbonate (0.36 mol), and 300 mL of butanone were introduced in a 500 mL round-bottomed flask. The mixture was kept under reflux and vigorous stirring for 10 h. Then, the solids were filtered and the solvent and the excess of dibromoalkane evaporated. The residue was chromatographed through silica gel using hexane/chloroform as eluent, thus obtaining the corresponding α-bromo-ω-(4-substituted-phenoxy)alkane.

The α-bromo-ω-(4-substituted-phenoxy)alkane (0.022 mol), piperidine (0.053 mol), potassium carbonate (0.18 mol), and 300 mL of acetone were placed in a 500 mL round-bottomed flask, and the mixture was refluxed under magnetic stirring for 24 h. After cooling, the solids were filtered, and the solvent and the excess of piperidine were evaporated. The crude α-piperidino-ω-(2-methoxy-4-nitrophenoxy)alkane was purified as indicated in each particular case.

1-Piperidino-5-(4-nitrophenoxy)pentane (15). Product **15** (65% total yield) was purified by crystallization of the corresponding hydrochloride (prepared by bubbling HCl in a ethereal solution of the product) in acetic acid, mp 182–184 °C: IR (KBr) 2940, 2627, 2528, 1595, 1508, 1336 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.15–3.10 (m, 16H), 3.65 (m, 2H), 4.05 (t, J = 6.1 Hz, 2H), 6.95 (d, J = 10 Hz, 2H), 8.25 (d, J = 10 Hz, 2H), 12.00 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.2, 21.9, 22.5, 27.5, 52.3, 56.3, 67.6, 113.9, 125.0, 140.5, 163.4; MS m/e (relative intensity) 154 (20), 98 (100), 41 (15). Anal. Calcd for $C_{16}H_{24}N_2O_3$·HCl: C, 58.44; H, 7.66; N, 8.52. Found: C, 57.92; H, 7.98; N, 8.39.

1-Piperidino-2-(4-nitrophenoxy)ethane (18). Product **18** (70% total yield) was purified by recrystallization from benzene–pentane, mp 63–64 °C (lit.[36] mp 66 °C): IR (KBr) 2924, 1606, 1592, 1508, 1476, 1348 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.60 (m, 6H), 2.50 (m, 4H), 2.80 (t, J = 6 Hz, 2H), 4.25 (t, J = 6 Hz, 2H), 6.95 (d, J = 10 Hz, 2H), 8.25 (d, J = 10 Hz, 2H).

1-Piperidino-2-(4-cyanophenoxy)ethane [4-(2-piperidinoethoxy)benzonitrile] (22). Product **22** (50% total yield) was purified by distillation (165 °C oven temperature, 0.08 Torr), formation of the citrate, and recrystallization in methanol, mp 99–101 °C (lit.[37] mp 96–98 °C): ^{1}H NMR ($CDCl_3$), free base, δ 1.60 (m, 6H), 2.50 (m, 4H), 2.80 (t, J = 6.25 Hz, 2H), 4.20 (t, J = 6.25 Hz, 2H), 6.95 (d, J = 8.6 Hz, 2H), 7.65 (d, J = 8.6 Hz, 2H).

1-Piperidino-2-(4-cyanophenoxy)pentane [4-(5-Piperidinopentoxy)benzonitrile] (24). Product **24** (60% total yield) was purified by crystallization of the corresponding hydrochloride (prepared by bubbling HCl in a ethereal solution of the product) in ethyl acetate, mp 145–47 °C: IR (KBr) 2938, 2635, 2535, 2220, 1605, 1508, 1303 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10–3.05 (m, 16 H), 3.65 (m, 2H); 4.10 (t, J = 6.25 Hz, 2H), 6.95 (d, J = 8.6 Hz, 2H), 7.65 (d, J = 8.6 Hz, 2H), 12.2 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.66, 22.2, 22.9, 23.0, 28.0, 52.7, 56.7, 67.4, 103.4, 115.0, 118.8, 133.6, 161.9; MS m/e (relative intensity) 154 (15), 98 (100), 55 (10), 44 (16). Anal. Calcd. for $C_{17}H_{24}N_2O$·HCl: C, 66.11; H, 8.16; N, 9.07. Found: C, 66.01; H, 8.17; N, 9.04.

1-Piperidino-2-(4-chlorophenoxy)ethane (27). Product **27** (70% total yield) was purified by distillation (118 °C oven

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temperature, 0.05 Torr): IR (KBr) 2936, 1493, 1474, 1286, 824, 668 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (m, 6H), 2.50 (m, 4H), 2.85 (t, J = 6.4 Hz, 2H), 4.10 (t, J = 6.4 Hz, 2H), 6.90 (d, J = 8.5 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 23.9, 25.7, 54.7, 57.5, 66.2, 115.7, 125.2, 128.9, 157.3; MS m/e (relative intensity) 239 (M^+ 1), 98 (100), 70 (6), 55 (10), 42 (11). Anal. Calcd. for $C_{13}H_{18}ClNO$: C, 65.13; H, 7.57; N, 5.84; Cl, 14.78. Found: C, 65.00; H, 7.68; N, 5.83; Cl, 14.75.

1-Piperidino-5-(4-chlorophenoxy)pentane (31). Product **31** (65% total yield) was purified by crystallization of the corresponding hydrochloride (prepared by bubbling HCl in a ethereal solution of the product) in ethyl acetate, mp 178–180 °C: IR (KBr) 2942, 2642, 2538, 1492, 1474, 1246, 826; ^1H NMR ($CDCl_3$) δ 1.50–3.05 (m, 16H), 3.60 (m, 2H), 3.95 (t, J = 6.4 Hz, 2H), 6.90 (d, J = 8.5 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.8, 22.4, 23.1, 23.3, 28.3, 52.8, 57.8, 67.5, 115.7, 125.2, 129.0, 157.3; MS m/e (relative intensity) 244 (3), 98 (100), 70 (5), 55 (6), 42 (9). Anal. Calcd for $C_{16}H_{24}ClNO{\cdot}HCl$: C, 60.38; H, 7.92; N, 4.40. Found: C, 60.21; H, 7.97; N, 4.40.

1-Piperidino-2-phenoxyethane (29). Product **29** (75% total yield) was purified by distillation, bp 100 °C, 0.01 Torr, (lit.[34] bp 186–188 °C, 13 Torr): ^1H NMR (CDC_3) δ 1.65 (m, 6H), 2.6 (m, 4H), 2.90 (t, J = 6.25 Hz, 2H), 4.15 (t, J = 6.25 Hz, 2H), 6.98 (m, 3H), 7.25 (m, 2H).

Synthesis of 1-Methyl-4-(2-methoxy-4-nitrophenoxy)-piperidine (33). In a 50 mL round-bottomed flask, 25 mL of benzene, 1.69 g (0.010 mol) of 2-methoxy-4-nitrophenol, 3.93 g (0.015 mol) of triphenylphosphine, 1.72 g (0.015 mol) of 4-hydroxy-*N*-methylpiperidine, and 2.61 g (0.015 mol) of diethyl azodicarboxylate (DEAD) were introduced. The mixture was kept at room temperature for 2 weeks. Then, the solvent was evaporated and 9.56 g of residue was obtained. This residue was chromatographed through silica gel using chloroform as eluent. The fractions where the expected product was the major component (GC) were joined and washed with 0.1 N NaOH. The residue was chromatographed with the same conditions as before, but using as eluent mixtures chloroform/hexane first then pure chloroform, then mixtures chloroform/ethyl acetate, and finally pure ethyl acetate. In that way, 0.80 g (30% yield) of pure product **33** was obtained. In order to achieve the complete characterization, the corresponding hydrochloride was prepared by bubbling HCl gas through an ethereal solution of the product, mp 188–190 °C: IR (KBr) 2468, 1588, 1509, 1472, 1338, 797 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90–2.95 (m, 11H), 4.00 (s, 3H), 4.48 (m, 1H), 6.95 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 2.6 Hz, 1H), 7.97 (dd, J = 8.0 Hz, J = 2.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 30.4, 45.9, 52.4, 56.3, 107.5, 113.1, 117.5, 139.6, 141.4, 149.9, 152.6; MS m/e (relative intensity) 266 (M^+, 16), 98 (100), 70 (20), 55 (30), 44 (20), 42 (20). Anal. Calcd for $C_{13}H_{18}N_2O_4{\cdot}HCl$: C, 51.57; H, 6.32; N, 9.25. Found: C, 51.32; H, 6.37; N, 8.92.

Synthesis of *N*-Methyl-*N*-(2-(2-methoxy-4-nitrophenoxy)ethyl)piperidinium Tetrafluoroborate (34). 1-Piperidino-2-(2-methoxy-4-nitrophenoxy)ethane (**13**, 10 g, 0.036 mol) and 20 mL of methyl iodide were introduced in a 100 mL round-bottomed flask and kept under reflux for 20 min. Then, the methyl iodide was evaporated. The residue was dissolved in water and precipitated with tetrafluoroboric acid, mp 122–124 °C (acetone): IR (KBr) 3000, 1588, 1517, 1341, 1280, 1234, 1094, 869 cm^{-1}; ^1H NMR (deuterated methanol) δ 1.65 (m, 2H), 1.92 (m, 4H), 3.18 (s, 3H), 3.40 (m, 2H), 3.55 (m, 2H), 3.85 (m, 2H), 3.86 (s, 3H), 4.54 (m, 2H), 7.01 (d, J = 8 Hz, 1H), 7.75 (d, J = 2.4 Hz, 1H), 7.85 (dd, J = 8 Hz, J = 2.4 Hz, 1H); ^{13}C NMR (deuterated methanol) δ 20.8, 21.6, 57.0, 62.3, 63.5, 63.7, 107.8, 113.0, 118.9, 143.0, 150.0, 153.5; MS m/e (relative intensity) 294 (1), 262 (4), 183 (4), 169 (36), 139 (8), 112 (19), 98 (100), 79 (11). Anal. Calcd for $C_{15}H_{23}N_2O_4{\cdot}BF_4$: C, 47.14; H, 6.06; N, 7.33. Found: C, 47.19; H, 6.45; N, 7.32.

Synthesis of *N*-Methyl-*N*-(5-(2-methoxy-4-nitrophenoxy)pentyl)piperidinium Tetrafluoroborate (35). The same procedure was followed, mp 102–4 °C (acetone): IR (KBr) 2956, 2878, 1588, 1514, 1337, 1281, 1236, 1094 cm^{-1}; ^1H NMR (deuterated methanol) δ 1.60–2.01 (m, 12H), 3.10 (s, 3H), 3.37–3.44 (m, 6H), 3.91 (s, 3H), 4.19 (t, J = 6.0 Hz, 2H), 7.13 (d, J = 7.8 Hz, 1H), 7.82 (d, J = 2.4 Hz, 1H), 7.92 (dd, J = 7.8 Hz, J = 2.4 Hz, 1H); ^{13}C NMR δ 20.9, 22.0, 22.4, 24.2, 29.4, 56.7, 62.2, 64.8, 40.1, 107.6, 112.7, 118.7, 145.6, 150.5, 155.6. Anal. Calcd for $C_{18}H_{29}N_2O_4{\cdot}BF_4$: C, 50.96; H, 6.89; N, 6.60. Found: C, 50.59; H, 6.70; N, 6.67.

General Procedure for the Photochemical Reactions Described in Tables 1 and 2 and in Schemes 4 and 5. In a 600 mL photochemical reactor, 1 mmol of substrate dissolved in 600 mL of cosolvent/water at pH 12 (adjusted with NaOH) was introduced (in the experiments in the presence of benzophenone, Scheme 4, 0.1 mmol was introduced in the photochemical reactor). The solution was irradiated with a 400 W medium-pressure Hg lamp at room temperature for the time given. Then, the reaction mixture was extracted with chloroform, and the aqueous phase was acidified with HCl (1 M) and extracted again with chloroform. The aqueous phase was neutralized and extracted again with chloroform. The three organic layers were dried, and the solvent was evaporated. Phenols were obtained directly from the acid medium extraction. Aminophenols were obtained from the final neutral medium extraction. All other reaction products were obtained from the residue of the initial extraction after column chromatography through silica gel using mixtures of chloroform/hexane as eluent. In the different reactions described in Tables 1 and 2 and Schemes 4 and 5, the following products (commercial products not described, neither product **29** previously described) were obtained with the yields given in the tables and schemes.

2-Methoxy-5-nitrophenol (3): mp 104–106 °C (lit.[38] mp 105 °C).

3,4-Dimethoxyaniline (4): mp 86–88 °C (lit.[39] mp 87–88 °C).

3,3',4,4'-Tetramethoxyazoxybenzene (5): mp 153–155 °C (lit.[40] mp 172–182 °C); IR (KBr) 2950, 1597, 1570, 1450, 1415, 1332 cm^{-1}; ^1H NMR ($CDCl_3$) 3.95 (s, 12H), 6.91 (dd, J = 9.6 Hz, J = 2.4 Hz, 2H), 7.95 (dd, J = 9.6 Hz, J = 2.4 Hz, 4H); MS m/e (relative intensity) 319 (4), 318 (M^+, 25), 275 (12), 167 (13), 151 (62), 137 (100), 108 (74), 107 (50). Anal. Calcd for $C_{16}H_{18}N_2O_5$: C, 60.31; H, 5.65; N, 8.80. Found: C, 60.39; H, 5.71; N, 8.74.

1-Piperidino-5-(2-hydroxy-4-nitrophenoxy)pentane (7). Product **7** was purified by crystallization of the corresponding hydrochloride in chloroform/pentane, mp 194–196 °C: IR (KBr) 3010, 2950, 1590, 1522, 1430, 1340, cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (m, 6H), 1.95 (m, 4H), 2.30 (m, 2H), 2.70 (m, 2H), 3.00 (m, 2H), 3.60 (m, 2H), 4.20 (t, J = 7.5 Hz, 2H), 6.90 (d, J = 9 Hz, 1H), 7.90 (m, 2H); MS m/e (relative intensity) 308 (M^+, 2), 154 (10), 98 (100). Anal. Calcd for $C_{16}H_{24}N_2O_4{\cdot}HCl$: C, 55.72; H, 7.30; N, 8.12. Found: C, 55.75; H, 7.28; N, 7.81.

2-Methoxy-4-nitrophenol (8): mp 102–4 °C (lit.[39] mp 103–4 °C).

4-Piperidino-1-(2-hydroxy-4-nitrophenoxy)butane (10). Product **10** (oil) was identified by comparison of its spectrocopic constants with those of product **7**: IR (KBr) 3010, 2950, 1590, 1522, 1430, 1340, 1270 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05–2.20 (m, 10H), 2.85 (m, 6H), 4.20 (t, J = 7.5 Hz, 2H), 6.90 (d, J = 9 Hz, 1H), 7.80 (m, 2H).

3-Piperidino-1-(2-hydroxy-4-nitrophenoxy)propane (12). Product **12** (oil) was identified by comparison of its spectrocopic constants with those of product **7**: IR (KBr) 3010, 2950, 1590, 1522, 1430, 1340, 1270 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60–2.20 (m, 8H), 2.70 (m, 6H), 4.20 (t, J = 7.25 Hz, 2H), 5.05 (broad, 1H), 6.90 (d, J = 9 Hz, 1H), 7.90 (m, 2H).

1-Piperidino-5-(4-hydroxyphenoxy)pentane (16): colorless oil; IR (film) 3300, 2928, 1510, 1474, 1228, 828 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30–1.70 (m, 12H), 2.40–2.80 (m, 6H), 3.82 (t, J = 6.5 Hz, 2H), 6.75 (dd, J = 8.7 Hz, 4H); MS m/e (relative intensity) 262 (M^+ – 1, 1), 155 (3), 154 (25), 99 (7), 98 (100).

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4-(4-Nitrophenyl)butan-1-ol (17): colorless oil;[40] IR (film) 3350, 2900, 1300, 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40–1.73 (m, 4H), 2.77 (t, J = 7.7 Hz, 2H), 3.65 (t, J = 6.5 Hz, 2H) 7.33 (d, J = 8.7 Hz, 2H), 8.15 (d, J = 8.7 Hz, 2H); MS m/e (relative intensity) 195 (M^+, 5), 177 (14), 160 (10), 149 (100), 133 (16), 119 (14), 116 (11) 91 (17), 78 (10).

3-Methoxy-4-(2-piperidinoethoxy)phenyl 2-Piperidinoethyl Nitroxide (20). This product was obtained in trace amounts in experiment 7 of Table 1, and the structure was tentatively proposed on the basis of its spectroscopic behavior: IR (KBr) 3856, 3644, 2943, 2835, 1621, 1400, 1327, 1023; UV/vis (MeOH) λ_{max} = 564 nm; ESR ($CHCl_3$) triplet (relative intensity 1:1:1), a_N = 1.1 mT; MS m/e (relative intensity) 278 (4), 262 (25), 248 (55), 231 (23), 217 (85), 201 (35), 98 (31), 84 (19), 43 (100).

4-Butoxybenzonitrile (25): bp 118–120 °C, 0.5 Torr (lit.[41] bp 147–148 °C, 3 Torr); ^1H NMR ($CDCl_3$) δ 0.90–1.90 (m, 6H), 4.20 (t, J = 6.25 Hz, 2H), 6.95 (d, J = 8.6 Hz, 2H), 7.65 (d, J = 8.6 Hz, 2H).

Electrolysis of *N*-Methyl-*N*-(2-(2-methoxy-4-nitrophenoxy)ethyl)piperidinium Tetrafluoroborate (34). A solution of product **34** (0.243 g, 0.64 mmol) in 150 mL of DMF (0.1 M Et_4NBF_4 as supporting electrolite) was electrolyzed using −1.2 V as applied potential with glassy carbon as electrode and under inert (N_2) atmosphere. After 61 coulombs (1 equiv) were consumed, the reaction was quenched by addition of 30 mL of 1 M HCl. The reaction crude was extracted between ether/water and the organic layer washed several times with water. The organic layer was dried and evaporated. The solid residue, 0.042 g (39% yield), was identified as 2-methoxy-4-nitrophenol (**8**, mp 102–104 °C). Similar electrolysis attempted with 4-nitroveratrole (**1**) and *N*-methyl-*N*-(5-(2-methoxy-4-nitrophenoxy)pentyl)piperidinium tetrafluoroborate (**35**) led to the recovery of the starting materials.

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