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Thermal and Photochemical Racemization of Chiral Aromatic Sulfoxides via the Intermediacy of Sulfoxide Radical Cations

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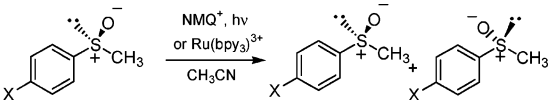
ABSTRACT



Efficient racemization of enantiomerically pure methyl aryl sulfoxides was obtained by *N*-methylquinolinium tetrafluoborate (NMQ$^+$) sensitized photolysis and by one-electron oxidation catalyzed by tris(2,2′-bipyridyl)ruthenium(III) hexafluorophosphate.

Enantiopure sulfoxides are attracting continuous attention for their importance as bioactive compounds, valuable intermediates in organic synthesis, and ligands for asymmetric transformations.[1] Recently, some chiral sulfoxides have also found important application as drugs.[2] Studies concerning the optical stability of sulfoxides and the experimental conditions which may lead to their stereomutation are therefore of interest.

The thermal racemization or epimerization of sulfoxides has been investigated in detail for many years,[3] and it has been established that the process can occur by pyramidal inversion at the sulfur, a process requiring 38−41 kcal/mol, or can involve C−S bond scission and recombination of the radical fragments, depending on the structure. Generally, quite drastic conditions (temperatures around 200 °C or highly acidic media) are required. Inversion of the sulfur center is also possible by direct irradiation of the sulfoxide.[4] However, in this case too, photoracemization through α-cleavage is also possible.[5] The possibility to assist photoracemization through sensitization has been investigated by Mislow and Hammond.[6] Naphthalene was used as the sensitizer, and it was concluded that in this case sulfur inversion occurs in an exciplex between naphthalene and sulfoxide. More recently, this conclusion has been supported by a study of the quenching rate by sulfoxides of the excited

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state of naphthalene and substituted naphthalenes,[7] and the formation of a complex with a significant charge-transfer character was suggested.

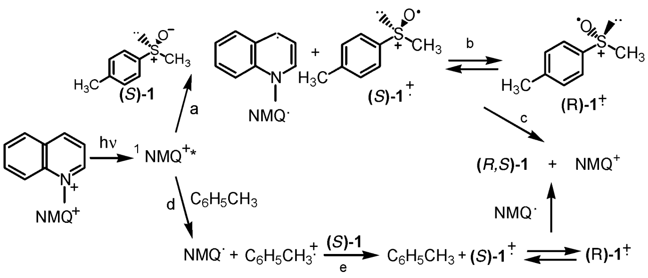
We now want to show that the racemization of chiral sulfoxides can also be performed by electron-transfer processes involving the reversible formation of sulfoxide radical cations. This possibility, which has been overlooked so far, is clearly suggested by DFT calculations on methyl phenyl sulfoxide radical cation, which showed that the pyramidal inversion of the SOMe group in the radical cation requires a much lower energy (ca. 10 kcal/mol) than in the neutral parent substrate.

Thus, a smooth and efficient photoracemization of enantiomerically pure methyl aryl sulfoxides is promoted by *N*-methylquinolinium tetrafluoborate (NMQ$^+$) sensitized photolysis, a process leading to the formation of a sulfoxide radical cation.[8] Moreover, racemization of sulfoxides can also be accomplished in a thermal reaction by catalysis with tris(2,2′-bipyridyl)ruthenium(III) hexafluorophosphate [Ru^{III}(bpy)$_3$], and in this case too, evidence was obtained that an electron-transfer process occurs.

DFT Calculations. The geometry of the methyl phenyl sulfoxide radical cation was optimized by DFT calculations performed with the Gaussian 98 program using the three-parameter hybrid functional B3LYP with the 6-311G* basis set. The sulfur atom exhibits a pyramidal geometry with a degree of pyramidalization of 28.4°.[9] The transition state geometry for the inversion was found by optimizing a planar structure (degree of pyramidalization 0°). The analysis of the vibrational frequencies found that the planar conformer was a first-order saddle point on the energy hypersurface. The barrier for the sulfur pyramidal inversion (10.9 kcal/mol) was calculated as the energy difference between the total energy of the planar and pyramidal conformation (details in the Supporting Information). When the same type of calculations were carried out for the neutral methyl phenyl sulfoxide, an inversion barrier of 42.7 kcal/mol was obtained.[10]

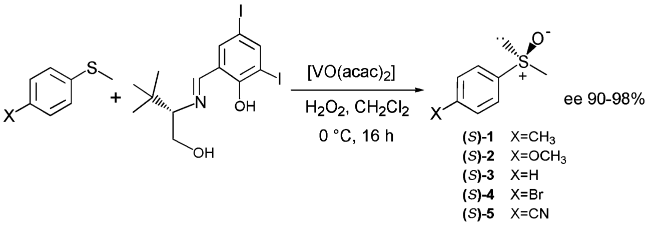
NMQ$^+$ Photosensitized Racemization. A solution of NMQ$^+$ (8×10^{-3} M) and (*S*)-methyl *p*-tolyl sulfoxide (*S*)-**1** (1.6×10^{-2} M) in N_2-saturated CH_3CN was irradiated in a photoreactor (360 nm) for 10 min at 25 °C. HPLC analysis on a Chiralcel OB column showed the presence of the two enantiomers (*S*)-**1** and (*R*)-**1**. The enantiomeric ratio [(*R*)-**1**/(*S*)-**1**], determined by the integration of the two peaks, was equal to 0.33. No photoproducts aside from stereoisomers of **1** were observed by HPLC and ^{1}HNMR analysis of the reaction mixtures. As already mentioned, our previous laser photolysis study has shown the formation of sulfoxide radical cations by excited NMQ$^+$;[8] moreover, it was found that the main fate of the radical cation is that of undergoing back electron transfer to regenerate the neutral sulfoxide and NMQ$^+$. It is therefore reasonable to suggest that sulfoxide radical cations are key intermediates in the racemization process and that the racemization mechanism can be that described in Scheme 1 (upper part). The reduced *N*-methylquinolinium radical (NMQ$^•$) is formed together with the (*S*)-sulfoxide radical cation (path a), which then can racemize (path b) before or in competition with back electron transfer (path c).[11] In line with this interpretation, when the photoreaction was carried out in the presence of toluene, used as co-sensitizer to increase the efficiency of the process (the yield of radical cations),[12] a substantial increase in the extent of racemization was observed, with the enantiomeric ratio (*R*)-**1**/(*S*)-**1** being 0.5 after only 5 min of irradiation. In this case, as shown in the lower part of Scheme 1, the actual electron acceptor is the toluene radical cation (path e), which shows that the racemization observed in the presence of NMQ$^+$ is not due, as in the naphthalene case, to the formation of an exciplex between excited NMQ$^+$ and the sulfoxide.

Scheme 1



Racemization Catalyzed by Ru^{III}(bpy)$_3$. Racemization of a series of chiral *p*-substituted methyl phenyl sulfoxides, synthesized as described in Scheme 2,[13] has been shown to occur in MeCN, at room temperature, in the presence of the bona fide outer sphere oxidant tris(2,2′-bipyridyl)ruthenium(III) hexafluorophosphate [Ru^{III}(bpy)$_3$], for brevity also indicated as Ru(III). This oxidant is characterized by a a

Scheme 2



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[9] Degree of pyramidalization equals 360 − $\sum$ bond angles to the S atom (Ganguly, B.; Freed, D. A.; Kozlowski, M. C. *J. Org. Chem.* **2001**, *66*, 1103).

[10] This value is comparable to the experimentally observed activation energy of 38.4 kcal/mol for methyl *p*-tolyl sulfoxide.[3]

[11] With a barrier of 10 kcal/mol, an inversion rate larger than 10^5 s^{-1} can be estimated, fast enough to be competitive with back electron transfer given the very low concentration of radical cations and NMQ$^•$ (ca. 10^{-5} M in the laser flash photolysis experiments[8]). Of course, this holds even more in the steady state experiments where the radical ion concentration is much lower.

reduction potential of 1.24 V vs SCE,[14] much lower than that of the aryl sulfoxides.

After the complete loss of optical activity (Figure 1), spectrophotometric analysis of the mixtures indicates that the oxidant that shows a strong absorption in the visible region of the spectrum (λ_{max} = 520 nm)[15] is not consumed during the racemization process. [$Ru^{III}(bpy)_3$], therefore, behaves as an actual catalyst. Moreover, after solvent evaporation, HPLC, and ^{1}HNMR analysis, no oxidation products aside from stereoisomers of **1** were observed, thus indicating that the loss of optical activity was not due to substrate decomposition.

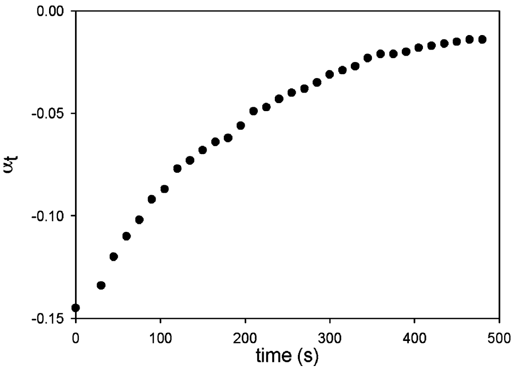

Figure 1. Loss of optical activity as a function of time for the reaction of (*S*)-**2** with $Ru^{III}(bpy)_3$.

Racemization rates were shown to follow first-order kinetics, and pseudo-first-order rate constants, k_{obs}[16] (Table 1), were determined from the slope of the straight line obtained when $-\ln(\alpha_t/\alpha_o)$ is plotted against time in accord with eq 1 (see Figure S5 in the Supporting Information).

$$-\ln(\alpha_t/\alpha_o) = k_{obs}t \qquad (1)$$

where α_t is the rotation at time t and α_o is the initial rotation. It also turned out that the racemization rate linearly increases with the initial and constant Ru(III) concentration, indicating a process first order in sulfoxide and first order in Ru(III) (Table S1 and Figure S2 in the Supporting Information), and the second-order rate constants, k_2, can be calculated as usual (eq 2).

$$k_{obs} = k_2[Ru^{III}(bpy)_3]_0 \qquad (2)$$

The values of k_{obs} and k_2 are reported in Table 1, together with the oxidation potentials of the investigated sulfoxides. Very small effects were observed when the reaction was carried out in the presence of salts (Table 1, entries 2 and 3), whereas a very slight decrease was noted in the presence of $Ru^{II}(bpy)_3$ (Table 1, entries 4 and 5).

Table 1. Sulfoxide Oxidation Potentials, k_{obs} and k_2 Values for the Racemization of Chiral Aromatic Sulfoxides (*S*)-**1**/(*S*)-**5** (0.013 M) with $Ru(bpy)_3(PF_6)_3$ (0.0013 M) at 20 °C in CH_3CN

sulfoxide	E_p (V vs SCE)[a]	k_{obs} (s^{-1})	k_2 ($M^{-1}\,s^{-1}$)
(*S*)-**1**	1.95	4.7×10^{-4}	0.36
		4.4×10^{-4b}	
		4.1×10^{-4c}	
		3.3×10^{-4d}	
		2.2×10^{-4e}	
(*S*)-**2**	1.90	5.2×10^{-3}	4.0
(*S*)-**3**	2.01	1.5×10^{-4}	0.12
(*S*)-**4**	2.05	2.6×10^{-5}	0.02
(*S*)-**5**	2.16	1.6×10^{-6}	1.3×10^{-3}

[a] From ref 8. [b] $[Bu_4NBF_4] = 1.3 \times 10^{-3}$ M. [c] $[Bu_4NBF_4] = 3.3 \times 10^{-3}$ M. [d] $[Ru(bpy)_3(PF_6)_2] = 6.0 \times 10^{-4}$ M. [e] $[Ru(bpy)_3(PF_6)_2] = 1.2 \times 10^{-3}$ M.

The reactivity data reported in Table 1 show that the reaction rate is very sensitive to the oxidation potential of the sulfoxide as well as the electron-donating power of the substituent, increasing as the former decreases and the latter increases. A good linear correlation is obtained by plotting log k_2 against the substituent σ^+ constants ($\rho^+ = -2.4$, $r^2 = 0.984$), as shown in Figure 2.

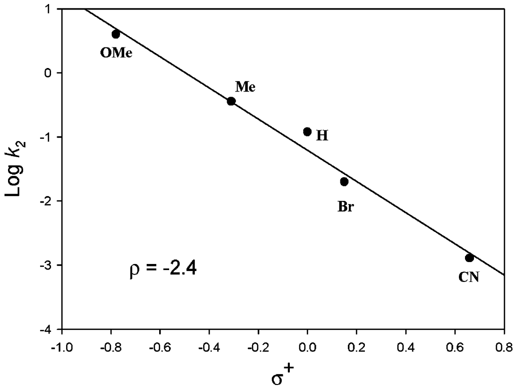

Figure 2. Dependence of the rate constants of electron transfer (k_2) in the oxidation of chiral aromatic sulfoxides (*S*)-**1**/(*S*)-**5** with $Ru(bpy)_3(PF_6)_3$ at 20 °C in CH_3CN upon the Hammett σ^+ constants.

This relative high and negative ρ value is consistent with an electron-transfer mechanism which may be that described

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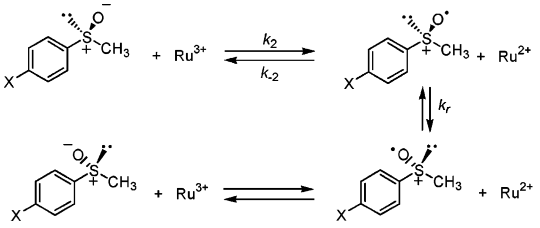
(16) The value of k_{obs} refers to the rate of formation of the racemized sulfoxide. It is twice the rate constant for the inversion process.

Scheme 3



in Scheme 3. We suggest that the racemization rate (k_r) of the radical cation is substantially faster than $k_{-2} \times [\mathrm{Ru^{II}}(\mathrm{bpy})_3]$ due to the extremely low concentration of Ru(II),[17] so that the rate is practically determined in the electron-transfer step. This is also indicated by the very small effect of Ru(II) concentration on the reaction rate, certainly not compatible with an electron-transfer process in which the rate is equilibrium controlled.[18]

In line with a rate-determining electron-transfer mechanism is also the satisfactory fit (Figure 3) obtained when the reactivity data are reported against $\Delta G^{\circ\prime}$ (the standard free energy for the electron-transfer step corrected for the electrostatic interaction arising from the charge variation in the reactants upon electron transfer) according to the Marcus equation (see Supporting Information).

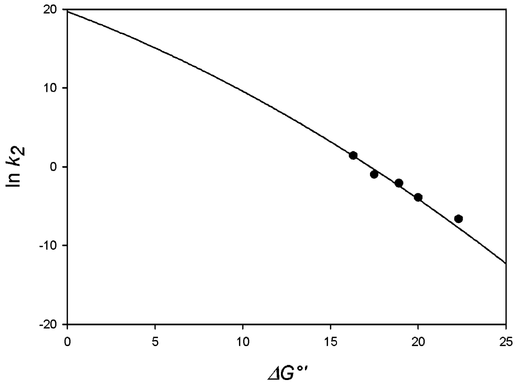


Figure 3. Diagram of ln k_2 versus $\Delta G^{\circ\prime}$ for the reactions of chiral aromatic sulfoxides (*S*)-**1**/(*S*)-**5** with $\mathrm{Ru^{III}(bpy)_3(PF_6)_3}$. The solid circles correspond to the experimental values; the curve is calculated by nonlinear least-squares fit to the Marcus equation with $Z = 6 \times 10^{12}$.

The best fit of the experimental data is obtained for a λ value of 23.3 kcal $\mathrm{mol^{-1}}$, which represents the overall (reactants and solvent) reorganization energy associated with the transfer of one electron from aromatic sulfoxides (*S*)-**1**/(*S*)-**5** to $\mathrm{Ru^{III}(bpy)_3}$.

Since the reorganization energy for the $\mathrm{Ru^{II}(bpy)_3/Ru^{III}(bpy)_3}$ self-exchange reaction is 32 kcal/mol in MeCN,[19] a reorganization energy as low as 14 kcal/mol can be calculated for the $\mathrm{ArSOCH_3/ArSOCH_3^{+\bullet}}$ self-exchange reaction.

Whereas there should be little doubt that a low reorganization energy is required for the $\mathrm{ArSOCH_3/ArSOCH_3^{+\bullet}}$ couple (slight variations in bond distances and bond angles have been estimated by DFT calculations on passing from the neutral aromatic sulfoxide to the radical cation[8]), the value given should be seen with some caution being based on $\Delta G^{\circ\prime}$ values calculated by the peak potentials of the sulfoxides.

In conclusion, this study has shown for the first time that a mild racemization of chiral aromatic sulfoxides can occur in the presence of electron-transfer reagents that leads to the reversible formation of sulfoxide radical cations.[20] This is due to the fact that the inversion barrier in the SOR group is much lower in the radical cation (ca. 10 kcal/mol) than in the neutral sulfoxide (38−41 kcal/mol) as well as to the low reorganization energy for the $\mathrm{ArSOCH_3/ArSOCH_3^{+\bullet}}$ couple. The racemization can take place both by photosensitized and thermal electron transfer. Interestingly, in the latter case, the racemization can be performed by outer sphere one-electron-transfer oxidants with a reduction potential significantly lower than the oxidation potential of the aromatic sulfoxide.[21] Apart from the theoretical interest, these results suggest that an optical activation of racemic sulfoxides might be obtained via an electron-transfer process induced by a chiral metal complex. Another implication is that our observations may raise some concern about the optical stability of chiral aromatic sulfoxide drugs in the presence of oxidizing metalloenzymes or metal ions.

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Supporting Information Available: Starting materials, $\mathrm{NMQ^+}$ photosensitized racemization, racemization catalyzed by $\mathrm{Ru^{III}(bpy)_3}$, DFT calculations, and determination of the reorganization energy. This material is available free of charge via the Internet at http://pubs.acs.org.

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[17] No Ru(III) is reduced in the process. Thus the maximum Ru(II) concentration is that at the equilibrium, i.e., ca 10^{-9} M.

[18] If the rate would be controlled by the electron-transfer equilibrium constant, a much higher effect of Ru(II) would be expected as [Ru(II)] passes from the equilibrium concentration (ca. 10^{-9} M, no Ru(II) added) to a concentration of 0.0012 M, entry 5 in Table 1.

[19] Chan, M.-S.; Wahl, A. C. *J. Phys. Chem.* **1978**, *82*, 2542−2549.

[20] Of course, the racemization process for chiral ArSOR compounds can occur only if no other competitive routes, in particular, the fragmentation to an alkyl carbocation ($\mathrm{R^+}$) and a sulfinyl radical ($\mathrm{ArSO^\bullet}$), are available for the radical cations. In that case, it is of paramount importance to know the fragmentation rate that may be higher or lower than the racemization rate. Laser and steady state photolysis studies underway in our laboratory are showing that the fragmentation rate is extremely low when R is a primary or secondary alkyl group.

[21] We have observed that the racemization also occurs with Ce(IV) ammonium nitrate. The rate is slower than with $\mathrm{Ru^{III}(bpy)_3}$, in line with the lower reduction potential of Ce(IV).