

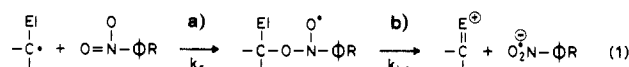
Reactivity of α -Heteroatom-Substituted Alkyl Radicals with Nitrobenzenes in Aqueous Solution: An Entropy-Controlled Electron-Transfer/Addition Mechanism

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Abstract: α -Hydroxy- and α -alkoxyalkyl radicals and 5-hydroxy-5,6-dihydropyrimidin-6-yl radicals react with para-substituted nitrobenzenes in aqueous solution with rate constants (at 20 °C) between 4×10^7 and $2 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$, i.e., below the diffusional level. The activation parameters for these reactions, which lead to addition or to electron-transfer products, have been determined. The less-than-diffusion-controlled rate constants are not due to large activation enthalpies but to very negative activation enthalpies [-10 to $-80 \text{ J (mol K)}^{-1}$]. In fact, the enthalpies are in most cases below those for diffusion in water. The results are explained in terms of formation of a charge-transfer complex between the reactants and an ionic type transition state that results from electron transfer between the reactants. Solvent immobilization, caused by the ionic transition-state structures, leads to the negative activation entropies. The two different types of final product, i.e., nitroxyl and radical anion, are derived from the ion-pair-type transition state by collapse (giving addition/nitroxyl) or by separation by solvent (yielding electron-transfer/radical anion).

Nitroaromatics have been used for a long time as probes for reducing radicals produced by photolysis, radiolysis, or chemical initiation.^{2–4} Interest in their radical chemistry has been stimulated by the hope that they may be useful as sensitizers in the radiotherapy of cancer.⁵ It was recognized early that the reactivity of the nitroaromatics with reducing radicals is determined by the reducing strength of the radical^{2–4,6} and by the oxidizing power of the nitroaromatic,⁷ suggestive of an electron-transfer mechanism. In apparent contrast to this is the fact that in many cases the interaction between radicals and nitroaromatics does not lead to (outer-sphere) electron transfer.^{3,4,5e} Addition via covalent bond formation between C_α of the radical and an oxygen of the nitro group to give nitroxyl-type tetrahedral intermediates I (eq 1a)



I

was found to be an important reaction channel in the case of α -alkoxy⁸ and α -hydroxyalkyl^{3,9} and of 5,6-dihydropyrimidin-6-yl radicals.^{10,11} However, some of the nitroxyl tetrahedral intermediates¹² were found to undergo a unimolecular heterolysis (rate

constant k_{ns}) to yield the radical anion of the nitroaromatic and the one-electron oxidation product of the radical^{8–11} (eq 1b), this reaction constituting the actual electron-transfer step. The addition/elimination sequence is an example for inner-sphere or “bonded”¹³ electron transfer.

The decomposition of the nitroxyl by heterolytic C–O bond cleavage (which provides a measure for the reducing properties of the carbon-centered radical) is to a large degree entropy controlled,^{9,11} and this raises the question of whether a similar situation exists with respect to the C–O bond formation leading to the nitroxyl (rate constant k_r , eq 1a). This could, in principle, explain the fact that rate constants for reaction of carbon-centered radicals with nitroaromatics are often clearly below the diffusion-controlled limit.¹⁴ The results presented below show that this is indeed the case and that this refers also to reactions that lead to electron-transfer products as well. The data provide an example for reactions whose rates are not controlled by enthalpy but by the entropy changes that occur along the way from reactants to products, the entropy changes being due to solvent immobilization in an ionic electron-transfer transition state.

Experimental Section

The compounds were all commercially available. The aqueous solutions (pH 5–7, water purified with a Millipore Milli-Q system) typically contained 0.1 M alcohol or 2 mM of a pyrimidine and 0.2–1 mM of a nitrobenzene, and they were saturated with N_2O in order to convert e_{aq}^- into OH. The solutions were irradiated with 0.1–0.4- μs pulses from a 3-MeV van de Graaff accelerator by using doses such that 0.5–3 μM radicals were produced.

The reactions of the alcohol or pyrimidine-6-yl radicals with the nitrobenzenes were monitored by the buildup of optical density (OD) at λ_{max} of the nitroxyl radicals (i.e., $\approx 20 \text{ nm}$ below λ_{max} of the nitrobenzene radical anions^{9,10}). The temperature of the solutions could be kept constant within $\pm 0.1 \text{ }^\circ\text{C}$ by using cells that are an integral part of a heat exchanger.⁹ It was varied between 0 and 70 °C. Arrhenius plots were constructed from measurements at five or more different temperatures. The correlation coefficients were usually ≥ 0.99 , in a few cases they were ≥ 0.98 . The error limits for the activation parameters given in the tables are from a statistical analysis of the experimental Arrhenius plots.

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Table I. Rate Constants k_r^d and Activation Parameters^{b,c} for Reaction of α -Oxyalkyl Radicals $-\dot{O}C<$ with 4-Substituted Nitrobenzenes

nitrobenzene R (obs λ , nm)	CH_2OH ($\dot{\text{C}}\text{H}_2\text{OCH}_3$)			$\text{CH}_3\dot{\text{C}}\text{HOH}$ ($\text{CH}_2\text{CH}_2\dot{\text{C}}\text{HOCH}_2$)			$(\text{CH}_3)_2\dot{\text{C}}\text{OH}$		
	$k_r^d/\text{M}^{-1}\text{s}^{-1}$	ΔH^\ddagger	ΔS^\ddagger	$k_r^d/\text{M}^{-1}\text{s}^{-1}$	ΔH^\ddagger	ΔS^\ddagger	$k_r^d/\text{M}^{-1}\text{s}^{-1}$	ΔH^\ddagger	ΔS^\ddagger
COCH ₃ (330)	8.6×10^7	6.9	-69.5	1.0×10^9	8.9	-42	1.5×10^9	14.8	-15
CN (315)	5.0×10^7 ^e	14.1 ^e	-49 ^e	1.0×10^9 ^f	11.1 ^f	-34 ^f			
	1.0×10^8	5.9	-70	1.2×10^9	7.3	-45	2.7×10^9	16.1	-10
CONH ₂ (310, 320)	1.0×10^8 ^g	7.1 ^g	-67 ^g	1.3×10^9 ^f	9.1 ^f	-39 ^f			
	7.3×10^7	7.6	-67	4.3×10^8	6.5	-54.5	2.2×10^9	14.5	-18
CF ₃ (285, 290, 295)	1.2×10^8	9.2	-60	4.3×10^8	9.1	-47	2.0×10^9	15.4	-15
SO ₃ ⁻ (300, 310)	6.2×10^7	4.4	-81	6.0×10^8	5.4	-60.5	1.7×10^9	13.8	-22

^aAt 20 °C. ^bTemperature range 0–60 °C, correlation coefficients of the Arrhenius plots ≥ 0.99 , ΔH^\ddagger (at 298 K) in kJ/mol, ΔS^\ddagger in J/(mol K). Error limits are estimated to be ± 2 kJ/mol for ΔH^\ddagger and ± 6 J/(mol K) for ΔS^\ddagger . ^c[Alcohol] = 1.0 M, [nitrobenzene] = 0.2–1 mM, pH 4.5–6. ^dFrom ref 9; for R = COCH₃ similar values are reported by ref 4. ^eValue refers to reaction of $\dot{\text{C}}\text{H}_2\text{OCH}_3$. ^fValue refers to reaction of $\text{CH}_2\text{CH}_2\dot{\text{C}}\text{HOCH}_2$. ^gSolvent is D₂O.

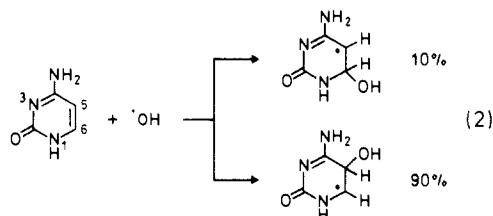
Table II. Rate Constants and Activation Parameters for Reaction of 5-Hydroxy-5,6-dihydropyrimidin-6-yl Radicals with 4-Substituted Nitrobenzenes^a

nitrobenzene R (obs λ , nm)	5-OH-U [*]			5-OH-6-MeU [*]			5-OH-C [*]			1-Me-5-OH-C [*]		
	$k_r/\text{M}^{-1}\text{s}^{-1}$	ΔH^\ddagger	ΔS^\ddagger	$k_r/\text{M}^{-1}\text{s}^{-1}$	ΔH^\ddagger	ΔS^\ddagger	$k_r/\text{M}^{-1}\text{s}^{-1}$	ΔH^\ddagger	ΔS^\ddagger	$k_r/\text{M}^{-1}\text{s}^{-1}$	ΔH^\ddagger	ΔS^\ddagger
COCH ₃ (330)	4.4×10^7 ^b	4.4	-83	3.2×10^8 ^b	3.9	-68	1.2×10^8 ^b	7.9	-61	2.1×10^8 ^b	8.3	-57
CN (315)	6.0×10^7	5.0	-78	4.4×10^8	2.2	-72	2.0×10^8	3.9	-73	3.0×10^8	4.6	-67
CONH ₂ (310, 320)	4.0×10^7	9.5	-66	2.5×10^8	3.0	-74	1.0×10^8	5.1	-74	1.7×10^8	8.0	-61
SO ₃ ⁻ (300, 310)	4.0×10^7	10.8	-63	2.0×10^8	2	-82	8.0×10^7	5.2	-76	1.2×10^8	11.2	-53

^a[Nitrobenzene] = 0.2–1 mM, [pyrimidine] = 2–4 mM. The other conditions and definitions are as described in Table I. ^bFrom ref 10.

Results and Discussion

Reaction of OH with alcohols or ethers proceeds by H abstraction predominantly from C _{α} to give α -hydroxy- or α -alkoxyalkyl radicals;^{8,15} in the case of pyrimidines OH adds to the C(5)/C(6) double bond;^{16,17} cf eq 2, which refers to the OH reaction with cytosine. This reaction is quite selective: $\geq 90\%$



of the OH radicals add at C(5) to give the reducing 6-yl radical. The remaining $\leq 10\%$ add to C(6), giving rise to the oxidizing 5-yl radical.¹⁷ The 6-yl-type radicals of pyrimidines^{10,11} and the α -hydroxy,^{3,4,9} and α -alkoxyalkyl^{6,18} radicals react with nitrobenzenes by addition (see eq 1a) and/or by one-electron reduction, depending on the substituents at C _{α} of the radicals and on the R at the nitrobenzene, whereas the 5-yl radicals of the pyrimidines are unreactive. In the present study the rate constants of these bimolecular reactions were determined as a function of temperature (using two different concentrations of the nitrobenzene) in the range 0–70 °C in order to obtain the activation parameters, and the results are presented in Tables I and II.

1. Reactions of α -Hydroxyalkyl Radicals (Table I). In the case of $\dot{\text{C}}\text{H}_2\text{OH}$, which reacts with nitrobenzenes *exclusively* by addition to the nitro group to give nitroxyl radicals⁹ (eq 1a), the rate constants increase weakly with increasing $\sigma(\text{R})$ from 6×10^7 for R = SO₃⁻ [$\sigma_p(\text{SO}_3^-) = 0.10$] to $\approx 1 \times 10^8$ M⁻¹ s⁻¹ for R = CF₃ and CN [$\sigma_p(\text{CF}_3) = 0.53$; $\sigma_p(\text{CN}) = 0.70$].

In Figure 1 this and additional rate data (from ref 9) are tested for a systematic dependence on the oxidizing power of the nitrobenzene. As can be seen, $\log k_r$ increases linearly with E_1^\ddagger , the one-electron reduction potential of the nitrobenzene at pH 7.¹⁹

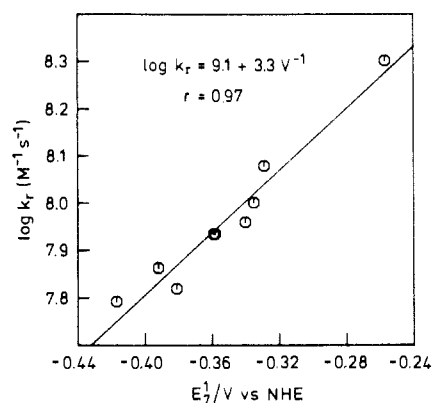


Figure 1. Dependence of $\log k_r$ ($\dot{\text{C}}\text{H}_2\text{OH} + \text{RC}_6\text{H}_4\text{NO}_2$) on E_1^\ddagger ($\text{RC}_6\text{H}_4\text{NO}_2$)¹⁹ (Marcus plot). The line through the experimental points is described ($r = 0.97$) by $\log k_r = 9.1 + 3.3 \text{ V}^{-1}$.

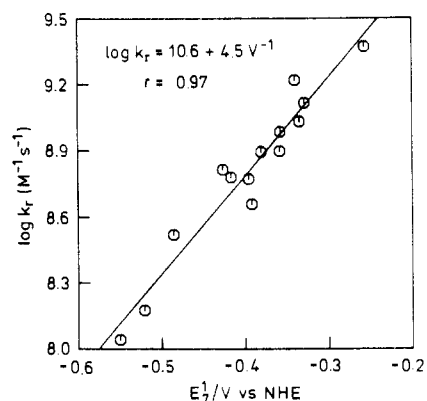


Figure 2. Marcus plot for the reaction of $\text{CH}_3\dot{\text{C}}\text{HOH}$ with $\text{RC}_6\text{H}_4\text{NO}_2$; $\log k_r = 10.6 + 4.5 \text{ V}^{-1}$ ($r = 0.97$).

The Marcus-type dependence is described by the relation $\log k_r(\dot{\text{C}}\text{H}_2\text{OH}) = 9.1 + 3.3 \text{ V}^{-1}$ ($r = 0.97$).

In Table I are given also the activation parameters for the formation of nitroxyl. It is interesting that the activation *enthalpies* are very small, in fact, smaller than the enthalpy of diffusion in

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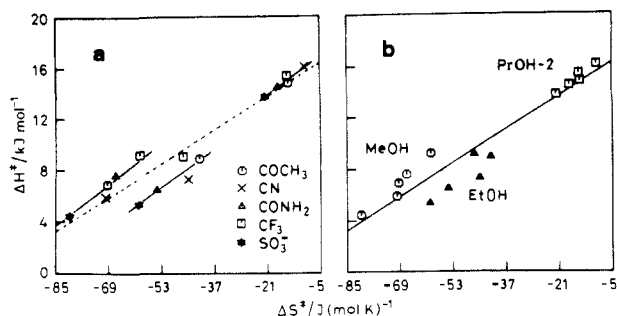


Figure 3. Dependence of ΔH^\ddagger on ΔS^\ddagger for the reactions of $\dot{\text{C}}\text{H}_2\text{OH}$, $\text{CH}_3\dot{\text{C}}\text{HOH}$, and $(\text{CH}_3)_2\dot{\text{C}}\text{OH}$ with $p\text{-RC}_6\text{H}_4\text{NO}_2$. (a) The symbols identify the nitrobenzenes, R: CH_3CO (O), CN (X), CONH_2 (Δ), CF_3 (\square), SO_3^- (*). (b) The symbols identify the α -hydroxyalkyl radicals: $\dot{\text{C}}\text{H}_2\text{OH}$ (O), $\text{CH}_3\dot{\text{C}}\text{HOH}$ (Δ), $(\text{CH}_3)_2\dot{\text{C}}\text{OH}$ (\square). The slope corresponds to an isokinetic temperature of 162 K.

H_2O (12–20 kJ mol^{-1}).²¹ The fact that the k_r values are definitely below the diffusion limit ($\approx 5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$) is thus caused by the very negative activation entropies of, on the average, $\approx -72 \text{ J (mol K)}^{-1}$, which corresponds to preexponential factors of $\approx 10^8 \text{ M}^{-1} \text{ s}^{-1}$.

Substitution in $\dot{\text{C}}\text{H}_2\text{OH}$ of one H atom at C_α by the electron-donating methyl group, i.e., going from $\dot{\text{C}}\text{H}_2\text{OH}$ to $\text{CH}_3\dot{\text{C}}\text{HOH}$, increases the rate constants k_r by approximately a factor of 8. As seen from the activation parameters, this rate increase is entirely due to the effect the structural change has on the activation entropies, which are clearly more positive than in the case of $\dot{\text{C}}\text{H}_2\text{OH}$. As with $\dot{\text{C}}\text{H}_2\text{OH}$, the dependence of k_r on E_1^\ddagger (nitrobenzene) follows a Marcus relation, i.e., $\log k_r(\text{CH}_3\dot{\text{C}}\text{HOH}) = 10.6 + 4.5 \text{ V}^{-1}$ ($r = 0.97$, see Figure 2).

Introducing one additional methyl group at C_α , i.e., going to $(\text{CH}_3)_2\dot{\text{C}}\text{OH}$, results in a further increase in k_r , which now approaches the diffusion-controlled range. This rate-enhancing effect is again entirely due to the increase in ΔS^\ddagger , which is now $\approx -16 \text{ J (mol K)}^{-1}$. In fact, the effect of the more positive entropies overcompensates the rate-decreasing effect of the larger activation enthalpies, which are now in the region typical for diffusion in water. The gradual increase in activation entropy and the (less conspicuous, but systematic) rise in activation enthalpy on replacing H at C_α by CH_3 is seen with all five nitrobenzenes investigated. A graphic representation of the situation is shown in Figure 3 in which the ΔH^\ddagger values are plotted as a function of the corresponding ΔS^\ddagger values for the various alcohol radical/nitrobenzene couples (isokinetic plot). If a straight line is drawn through the experimental points, a slope corresponding to an isokinetic temperature of 162 K is obtained. This value, being much below the experimental temperature range (273–343 K), demonstrates clearly that the reaction is entropy controlled.

In Figure 3, the data points are marked in two different ways: In (a), each nitrobenzene is identified by a symbol of its own. Thus, three sets each containing five members are formed. This representation emphasizes the effect of the nature of the nitrobenzene on the activation parameters. In (b), the symbols identify the alcohol radical, and thus, the consequences of varying its nature are being stressed. It is interesting that the lines that may be drawn through the data points to characterize the effects of changing the nitrobenzene have roughly the same slope as those that describe the effects of varying the structure of the α -hydroxyalkyl radical.

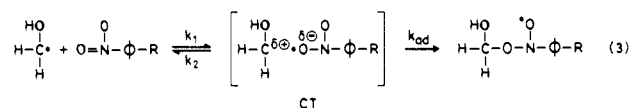
2. Reactions of 5-Hydroxy-5,6-dihydropyrimidin-6-yl Radicals (Table II). These radicals react with nitrobenzenes exclusively by addition to the nitro group to give nitroxyl radicals.¹⁰ However, with the corresponding 6-methyl-6-yl radicals the reaction leads to electron-transfer and addition products.¹¹

As seen in Table II, the less-than-diffusion-controlled rate constants for reaction at 20 °C (k_r) do not result from the ac-

tivation enthalpies being high but from the entropies being very low. As in the case of the alcohol radicals [except $(\text{CH}_3)_2\dot{\text{C}}\text{OH}$], the ΔH^\ddagger values for reaction tend to be even lower than those for diffusion in H_2O . The activation entropies are in the range $-(60\text{--}80) \text{ J (mol K)}^{-1}$, similar to the values for reaction of $\dot{\text{C}}\text{H}_2\text{OH}$ and $\text{CH}_3\dot{\text{C}}\text{HOH}$ (Table I). The activation parameters for reaction of the four different pyrimidin-6-yl radicals studied are all quite similar, and pronounced dependences on structure are not visible.

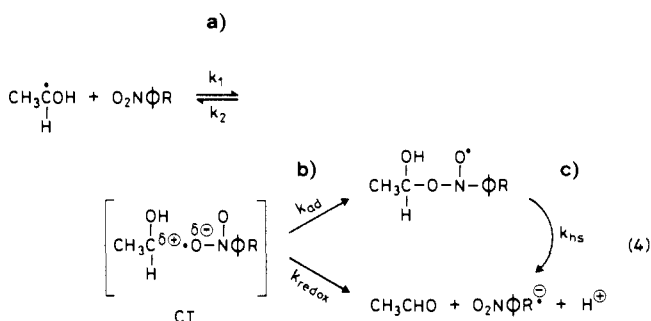
3. Mechanistic Conclusions. Basically, two phenomena have to be explained: (a) the activation enthalpies having values lower than that for diffusion in water, (b) the very negative activation entropies.

(a) Concerning the activation enthalpies, it is suggested that the experimentally measured rate constant k_r contains an equilibrium constant K that characterizes the formation of a charge-transfer (CT) complex between the radical and the nitrobenzene; cf. eq 3 for the case of hydroxymethyl whereby $K =$



k_1/k_2 . On this basis, the small activation energy for k_r results from an increase with temperature not only of k_1 and k_{ad} , but from an even stronger one for k_2 , the rate constant for back-reaction to the reactants.

A CT interaction between α -hydroxyalkyl radicals and nitrobenzenes is not unreasonable since, on the basis of their redox potentials,²⁰ α -hydroxyalkyl radicals are excellent electron donors while nitrobenzenes are strong electron acceptors. In fact, a CT complex has previously been proposed⁹ for the system $\text{CH}_3\dot{\text{C}}\text{HOH}$ /nitrobenzene to account for the formation with equal rates but different yields of two different products, i.e., the radical anion and the nitroxyl, cf. eq 4. In this system, k_{ad} and k_{redox}



were found to be $\geq 10^6 \text{ s}^{-1}$ for all nitrobenzenes with R's having Hammett σ_p values ≥ -0.20 . The nitroxyls give additional redox products via a heterolysis reaction (eq 4c) with rate constants k_{hs} between 10^2 and 10^4 s^{-1} .⁹

In the case of $(\text{CH}_3)_2\dot{\text{C}}\text{OH}$, addition to give nitroxyl radicals was also observed, however, with most nitrobenzenes $k_{\text{hs}} \geq 10^6 \text{ s}^{-1}$, so the reaction appears as if it proceeds exclusively by electron transfer.^{9,22} $(\text{CH}_3)_2\dot{\text{C}}\text{OH}$ is the only radical for which the activation enthalpy is not below the value for diffusion in the solvent water. This is explainable by assuming that k_2 has a temperature coefficient similar to that of k_{ad} and k_{redox} . In fact, with $(\text{CH}_3)_2\dot{\text{C}}\text{OH}$, k_2 cannot be large compared with $k_{\text{ad}} + k_{\text{redox}}$, since otherwise k_r could not be in the diffusion-controlled range (see Table I).

(b) The activation entropies are only slightly negative in the case of $(\text{CH}_3)_2\dot{\text{C}}\text{OH}$. The entropies decrease considerably on going to $\text{CH}_3\dot{\text{C}}\text{HOH}$ and $\dot{\text{C}}\text{H}_2\text{OH}$. This decrease is so strong that it overcompensates the effect of the activation enthalpies which, as pointed out in (a), become smaller in this direction. This is the reason for the decrease in the rate constants k_r . The compensatory effect on k_r of methyl substitution at C_α is quantitatively expressed by the isokinetic relation (Figure 3).

(21) An Arrhenius plot of fluidity data gives $E_A = 18 \text{ kJ mol}^{-1}$. Data from: Landolt-Börnstein *Transport Phenomena I*; Springer: Berlin, 1969; Vol. a, p 581.

(22) However, in isopropyl alcohol/water (95:5, v/v) $(\text{CH}_3)_2\dot{\text{C}}\text{OH}$ was shown to react exclusively by addition/elimination.⁹

The difficulty in understanding the activation entropies in terms of mechanism is due to the fact that the rate-determining step can be the formation of the CT complex (k_1) and/or its decomposition (k_{ad} or k_{redox}). It is likely that this depends on the nature of the alcohol radical. It is reasonable to assume that k_1 , the rate constant for formation of the CT complex, is essentially diffusion controlled for all the alcohol radicals. If this is so, then in the case of $\dot{C}H_2OH$ the ratio k_2/k_{ad} must be $\gg 1$ since k_1 is much less than diffusion controlled. This means that k_{ad} is rate determining. With the other extreme, $(CH_3)_2\dot{C}OH$, k_2 must be slow and k_{redox} ($+k_{ad}$) must be fast, so here it is k_1 that is rate determining. This conclusion is in agreement with the activation parameters for reaction of $(CH_3)_2\dot{C}OH$, which are typical for a diffusion-controlled reaction. The situation can be summarized as follows:

$$(k_2/k_{ad})_{\dot{C}H_2OH} > [k_2/(k_{ad} + k_{redox})]_{CH_3\dot{C}HOH} > [k_2/[k_{redox} (+k_{ad})]]_{(CH_3)_2\dot{C}OH} \approx 1$$

On this basis, the large entropy loss in the case of $\dot{C}H_2OH$ can be explained as follows: The transition state for decomposition of the CT complex to give the nitroxyl radical is strongly ionic, with the positive charge located on C_α and the negative one on the nitro group.²³ The ion pair so formed immobilizes adjacent water molecules,²³ and thus the entropy decreases as the result of the loss in the degrees of freedom of solvent molecules. Delocalization of charge leads to less freezing of water molecules and therefore to smaller losses of entropy. E.g., in the case of $R_1, R_2 = CH_3$, the positive charge can be delocalized to the methyl group(s), resulting in a considerably smaller charge density at C_α than in the case of $R_1 = R_2 = H$. This then is the reason for the decrease in the loss of entropy in going to $R_1, R_2 = CH_3$.

It is interesting that the activation parameters for reaction of the α -alkoxyalkyl radicals²⁴ $CH_3O\dot{C}H_2$ and $\dot{C}H_2CH_2\dot{C}HOCH_2$ are very similar to those of the related α -hydroxyalkyl radicals $HO\dot{C}H_2$ and $CH_3\dot{C}HOH$ (Table I). This means that in the transition state deprotonation from the OH group is not important, in spite of the high charge density at C_α . If it were important, the entropy loss should be larger by up to 30 J (mol K)⁻¹ for, e.g., $HO\dot{C}H_2$ compared with $CH_3O\dot{C}H_2$.²⁵ In agreement with this is the fact that the rate constants and activation parameters for reaction of $\dot{C}H_2OH(D)$ with 4-nitrobenzotrile are the same in H_2O and in D_2O (see Table I). A solvent kinetic isotope effect of 1 indicates that deprotonation in the transition state is essentially not taking place. Concerning the extent to which electron transfer occurs in the transition state, an impression may be gained from the slopes of Marcus plots (Figures 1 and 2). For $\dot{C}H_2OH$ the value is quite low, i.e., 3.3 V⁻¹, which may be compared with 7–11 V⁻¹ expected for outer-sphere electron transfer.²⁶

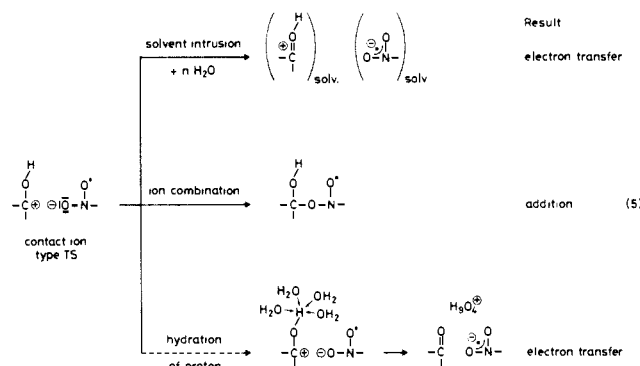
For $CH_3\dot{C}HOH$, the Marcus slope for reaction is 4.5 V⁻¹, indicating a larger degree of electron transfer in the transition state than for $\dot{C}H_2OH$. This is in agreement with the fact that $CH_3\dot{C}HOH$ reacts to give both addition and electron-transfer products.⁹ A larger extent of electron transfer that does not lead, by solvent immobilization, to a larger loss of entropy can only be explained in terms of a lower charge density, i.e., by charge delocalization to the methyl group.

With respect to deprotonation $CH_3\dot{C}HOH$ behaves like $\dot{C}H_2OH$: the only slightly larger loss of entropy for $CH_3\dot{C}HOH$ compared with the $\dot{C}H_2CH_2\dot{C}HOCH_2$ case indicates that proton

transfer to neighboring water molecules is not an important path of dissipation of positive charge in the transition state.

On the basis of these considerations a unified quasi outer-sphere \rightarrow inner-sphere^{27,28} mechanism can be formulated for the reactions of carbon-centered radicals substituted at C_α by a heteroatom. The mechanism takes account of the "nucleophilicity" of these radicals²⁹ and is modeled on Winstein's concept of "contact" and "solvent separated" ion pairs. It involves the idea that in the transition state a large degree of electron transfer occurs (from the CT complex or the reactants) to give a quasi ion pair. The ensuing chemistry is that of the "ion pairs". If the ion pair collapses, a bond is formed to give a nitroxyl as a product, i.e., ion-pair collapse leads to addition. If, on the other hand, the solvent gets a chance to separate the ions, the electron-transfer products (i.e., the ions) are trapped, and ion combination will be much less likely to occur. In support of this electron-transfer/addition mechanism is the fact that the reactivity of $\dot{C}H_2OH$ (which reacts exclusively by addition) and that of $CH_3\dot{C}HOH$ (which reacts significantly by addition) follow a Marcus relation (Figures 1 and 2).

A special case and a particularly important one involves the reactions of α -hydroxy- and α -aminoalkyl radicals. In the hypothetical case (eq 5, bottom) that electron transfer was taking



place followed by or concerted with proton transfer and (full) hydration of the proton, the electron would be trapped on the nitrobenzene for good, since hydration of the proton is irreversible due to the enormous exothermicity of this reaction.³⁰ In other words, proton transfer would "freeze", i.e., finalize electron transfer.

This electron-transfer/addition mechanism allows conclusions to be drawn on the effect of solvent (polarity) on the outcome of reaction 5: A polar solvent will favor the electron-transfer route (5a) in a twofold way (1) by stabilizing charge separation and (2) by enabling ion-pair separation, thereby finishing the job of electron transfer. In contrast, a nonpolar one will support the addition path (5b), if not by a change of mechanism to a nonionic direction, then certainly by providing little competition for ion-pair collapse.³¹ Thus, in this concept the solvent plays a crucial role in determining which way the reaction goes between a nucleophilic radical²⁹ and an electrophilic molecule. For those cases where the adducts undergo (spontaneous or catalyzed) heterolysis, the mechanism discussed above can be expanded to then become an

(23) The charge density at the anion is very low, due to the efficient delocalization over the aromatic system (see ref 9 for ESR data on the radical anions). Therefore, freezing of water molecules should predominantly be induced by the cation. In fact, hydration of carbocations has been shown to lead to ΔS^\ddagger losses of up to 84 J (mol K)⁻¹: Steenken, S.; Buschek, J.; McClelland, R. A. *J. Am. Chem. Soc.* **1986**, *108*, 2808. McClelland, R. A.; Steenken, S. *J. Am. Chem. Soc.*, in press.

(24) These radicals react exclusively by addition to give nitroxyl radicals.¹⁸ (25) Hydration of a proton by four water molecules leads to an entropy loss of 105 J (mol K)⁻¹. Cf.: (a) Frost, A. A.; Pearson, R. G. *Kinetics and Mechanism*; Wiley: New York, 1961. (b) Buschmann, H.-J.; Dutkiewicz, E.; Knoche, W. *Ber. Bunsen-Ges. Phys. Chem.* **1982**, *86*, 129.

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(27) For relevant discussions of the concept of organic inner-sphere mechanism, see: Ebersson, L. *Adv. Phys. Org. Chem.* **1982**, *18*, 79. *J. Mol. Catal.* **1983**, *20*, 27. Ebersson, L.; Radner, F. *Acc. Chem. Res.* **1987**, *20*, 53. See also: Julliard, M.; Chanon, M. *Chem. Rev.* **1983**, *83*, 425. Pross, A. *Acc. Chem. Res.* **1985**, *18*, 212. Todres, Z. V. *Tetrahedron* **1985**, *41*, 2771. Shaik, S. S. *Prog. Phys. Org. Chem.* **1985**, *15*, 197. For further examples, see: Steenken, S. In *Free Radicals: Chemistry, Pathology and Medicine*; Rice-Evans, C., Dormondy, T., Eds.; Richelieu: London, 1988; p 51.

(28) For a review on inner-sphere mechanism in oxidation reactions by the OH radical, see: Steenken, S. *J. Chem. Soc., Faraday Trans. 1* **1987**, *83*, 113.

(29) Minisci, F.; Citterio, A. *Adv. Free Radical Chem.* **1980**, *6*, 65.

(30) Hydration of a free proton yields 1135 kJ mol⁻¹; cf.: Reference 25a. Meot-Ner, M. *J. Phys. Chem.* **1987**, *91*, 417.

(31) In agreement with this is the fact that $(CH_3)_2\dot{C}OH$ reacts with 4-nitrobenzotrile exclusively by addition in the solvent mixture 95% isopropyl alcohol/5% water, while it gives 100% electron-transfer products in water (see ref 9).

electron-transfer (et)/addition (ad)/elimination (el) mechanism.

4. Further Conclusions. It is interesting to compare the activation parameters for reaction of $\text{CH}_3\dot{\text{C}}\text{HOH}$ (in which radical anion and nitroxyl are produced, see eq 3)⁹ with those⁹ for heterolytic decomposition of the nitroxyl (rate constant k_{hs} , eq 3). For the heterolysis the activation enthalpies (average 35 kJ mol⁻¹) are higher, whereas the activation entropies [average -53 J (mol K)⁻¹] are the same as those for the production of nitroxyl (-50 units). If it is taken into account that the formation reaction is bimolecular (with an intrinsic energy loss), whereas the heterolysis reaction is unimolecular (where one molecule is broken up to give three components, thereby leading to an intrinsic entropy gain), the same number for the overall entropy loss means that there is a lot more solvent immobilization in the transition state of the heterolysis than in the formation of the nitroxyl. This is probably the consequence of deprotonation (from the hemiacetal OH) in the transition state of the heterolysis, eq 4c (as shown by the solvent kinetic isotope effect⁹).

Another relevant aspect is the thermodynamics of the reaction of α -hydroxyalkyl radicals with nitrobenzenes. For instance, in the case of $\dot{\text{C}}\text{H}_2\text{OH}$, the weakest electron donor in its class, (outer-sphere) electron transfer is thermodynamically highly favorable [on the basis of the redox potentials,²⁰ the driving force (ΔG) for the reaction $\dot{\text{C}}\text{H}_2\text{OH} + 4\text{-NAP} \rightarrow \text{CH}_2\text{O} + 4\text{-NAP}^{\cdot-} + \text{H}^+$ is equal to 1 eV, which corresponds to 96 kJ mol⁻¹]. In spite of this, the reaction proceeds exclusively by addition.⁹ For an explanation it has to be considered that an important part of the driving force results from hydration of the proton,³⁰ and is therefore not available unless the proton is fully hydrated in the

transition state (which is not the case, see section 3b). However, even if it was taking place, this would lead to an even more drastic reorganization of the solvent shell than in the case of addition, with a correspondingly high loss²⁵ of entropy.

In this connection, it is interesting to compare nitroaromatics with molecular oxygen. Like nitroaromatics, oxygen reacts with α -hydroxyalkyl radicals exclusively by addition,^{15a,32} and this in spite of the fact that electron transfer (to give alkanone, $\text{O}_2^{\cdot-}$, and H^+) is thermodynamically even more favorable than in the case of the nitrocompounds, which are weaker oxidants than O_2 .²⁰ It has previously been pointed out^{5e,10} that this similarity in behavior may be related to the ability of nitroaromatics to replace oxygen as a radiation sensitizer.

Note Added in Proof. The electron-transfer/addition mechanism suggested shows strong parallels with that³³ proposed for collapse of ion and radical pairs produced by charge-transfer photochemistry of electron donor-acceptor complexes.

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Synthesis and Properties of Purinophanes: Relationship between the Magnitude of Hypochromism and Stacking Geometry of Purine Rings^{†1}

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Abstract: Twelve purinophanes 1-12, in which two purine rings are fixed with different modes of stacking by two or three polymethylene chains, have been prepared by either stepwise introduction of the linking chains or quasi-dimerization of disubstituted purine derivatives. The five kinds of stacking geometries of the two component rings in the purinophanes were determined by X-ray analysis and/or ¹H NMR. The interplanar distances vary from 3.2 to 6.6 Å. All of the purinophanes 1-12 show large hypochromism (decrease in integrated absorption intensity compared with two molar monomeric references or one molar dimeric linear compound), and the maximum value was 47.6% for 6. This is the largest value so far observed for dimeric nucleic acid bases. The hypochromism values of the purinophanes 1-8, 11, and 12 are almost identical in four different media (ethanol, water, 0.1 N HCl, 0.1 N NaOH). The bridge protons of these purinophanes show complex multiplets in their NMR spectra, in contrast to the first-order coupling patterns of acyclic reference compounds. These results indicate that the conformations of 1-8, 11, and 12 are almost frozen in the various media, at room temperature. On the basis of the structures determined by X-ray analysis, hypochromism values were calculated for three purinophanes by the Pariser-Parr-Pople method including configurational interactions. These, however, gave not always satisfactory agreement with observed values. By use of the simplified equation for hypochromism presented by Ts'o et al., the relationship between the hypochromism values and the geometrical parameters from the X-ray results was analyzed. Good correlations between them were found, and empirical formulas are postulated to estimate the values of hypochromism for a given geometry of two purine rings stacked in parallel.

It is well-known that nucleic acid bases are stacked with interplanar distances of about 3.4 Å in the helical structure of DNA

and this stacking brings about a significant decrease in the intensity of the longest wavelength absorption band. In fact, the double helix absorbs roughly 40% less than does a mixture of the component monomers. This phenomenon, i.e., hypochromism, has been widely used as the evidence of stacked structures of various π systems, including nucleic acid bases in solution. Theoretical explanations of hypochromism were carried out independently by

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