Thermal Stability of 2,2,6,6-Tetramethylpiperidine-1-oxyl (TEMPO) and Related *N*-Alkoxyamines

Maria Victoria Ciriano,[†] **Hans-Gert Korth,**[‡] **Wibo B. van Scheppingen,**[†] **and Peter Mulder*,**[†]

Contribution from the Leiden Institute of Chemistry, Leiden University, P.O. Box 9502, 2300 RA Leiden, The Netherlands, and Institut für Organische Chemie, Universität-GH Essen, D-45117 Essen, Germany

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Abstract: The carbon−oxygen bond dissociation enthalpies, BDE(C−O), in several *N*-alkoxyamine derivatives based on 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) have been determined in the liquid phase by photoacoustic calorimetry. The BDE(C−O) and the BDE(C−H) in the corresponding hydrocarbons follow a linear correlation: BDE(C−O) = 1.04BDE(C−H) − 62.1 kcal mol^{-1}. When an electronegative element adjacent to the C−O bond is present, as in tetrahydrofuryl, a substantial deviation from the correlation is noticed. Due to the anomeric interaction the (THF) *N*-alkoxyamine is stabilized by an additional 14 kcal mol^{-1}. The Arrhenius expression for the homolytic decomposition of methyl-TEMPO in the gas phase obeys $k/s^{-1} = 10^{15.3}$ exp($-45.3/RT$) to yield a BDE(C−O) of 47 ± 1 kcal mol^{-1} at 298 K. Furthermore, a high reactivity of TEMPO toward hydrogen donors, 1,4-cyclohexadiene or 9,10-dihydroanthracene, has been observed. Above 380 K, TEMPO is converted into the hydroxyamine 2,2,6,6-tetramethyl-1-piperidinol (TEMPOH) and the amine 2,2,6,6-tetramethylpiperidine (TEMPH). An acid-catalyzed mechanism for TEMPO deoxygenation is proposed.

Introduction

It is well documented that carbon-centered radicals can be effectively trapped by free radical species such as molecular oxygen[1] or nitric oxide,[2] with rate constants near the diffusion-controlled limit, i.e., beyond 10^9 M^{-1} s^{-1}. The reactions play an important role in various fields, for example lipid peroxidation in biological systems or degradation of organic compounds in the troposphere. By way of contrast, the recombination rates with persistent sterically hindered organic nitroxides are significantly slower. The kinetic behavior of carbon-centered radicals (R•) with 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) has been studied in quite some detail.[3] The variation in rate constants can be associated with the structure of R•, ranging from 10^9 (1-nonyl) to as low as 10^6 M^{-1} s^{-1} for sterically hindered species such as triphenylmethyl.

The use of persistent nitroxides in radical polymerization has been gaining in importance in recent years. It enables the preparation of polymers with a complex architecture and polydispersities well below the theoretical limit for conventional free radical polymerization processes.[4,5] The thermally labile bond in the *N*-alkoxyamine, formed between the growing polymer chain and the nitroxide, is used in what can be described as "living" free radical polymerization. Through reversible thermal bond homolysis the chain-propagating carbon-centered radical is released allowing the addition of the next monomer to the chain. At the same time, the radical concentration is kept low, preventing random termination. Hence, knowledge of the bond dissociation enthalpy (BDE) for the carbon−oxygen bond in *N*-alkoxyamines plays a pivotal role in understanding the polymerization dynamics. An insight into structural effects on the energetics is also beneficial in designing new nitroxide derivatives to provide bond cleavage within a specific temperature range. Despite their importance, experimental thermodynamic data regarding these bonds are scarce.

In this paper, we report on the C−O bond dissociation enthalpies for some prototype *N*-alkoxyamines derived from TEMPO as well as on the thermal stability of TEMPO, applying three different techniques: very low pressure pyrolysis (VLPP) in the gas phase, photoacoustic calorimetry (PAC), and thermolysis in sealed Pyrex tubes in the liquid phase.

Experimental Section

Chemicals were acquired from commercial sources and used as received, except 9,10-dihydroanthracene which was recrystallized twice from boiling methanol. For the PAC experiments the solvents (spectrograde) were thoroughly distilled, 2-hydroxybenzophenone was recrystallized from ethanol, di-*tert*-butyl peroxide was passed over activated alumina, and 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) was purified by sublimation. (2′,2′,6′,6′-Tetramethyl-1′-piperidinyl-oxy)−methane (methyl-TEMPO) was prepared by treating TEMPO (2.3 mmol) with methyllithium (4.6 mmol) at 195 K in 30 mL of anhydrous diethyl ether which was stirred under nitrogen. After being warmed to room temperature the solution was passed twice over activated alumina (yield: 78%). 1-(2′,2′,6′,6′-Tetramethyl-1′-piperidinyloxy)−tetrahy-

* Address correspondence to this author. Fax: (31)-71-5274492. E-mail: P.Mulder@Chem.LeidenUniv.NL.

† Leiden University.

‡ Universität-GH Essen.

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drofuran (THF−TEMPO) and (2′,2′,6′,6′-tetramethyl-1′-piperidinyl-oxy)−cyclohexane (cyclohexyl-TEMPO) were prepared by adding di-*tert*-butyl peroxide (3.3 mmol) and TEMPO (6.6 mmol) to tetrahydro-furan or cyclohexane (10 mL). The reaction mixture was deoxygenated, and the vessel was closed under argon and then heated at 390 K for 16 h. The solvent was removed by evaporation. The products were identified by GC/MS analysis and quantified by GC/FID (yields ca. 75%).

Photoacoustic Calorimetry. Photoacoustic calorimetry (PAC) has recently become an established tool for the determination of enthalpies for photoinitiated processes. Details have been described before.[6] The instrument is calibrated, under the same conditions as the experiment (i.e. solvent composition), using dilute solutions of *o*-hydroxyben-zophenone as a reference compound, which converts all the absorbed light into heat within a few nanoseconds.

The amount of TEMPO was varied from 0.01 to 0.06 M to ensure that the PAC signal was independent of the concentration. The dependence of the PAC signal on the light intensity was verified by applying neutral density filters. For that purpose a solution of di-*tert*-butyl peroxide (A ≈ 0.1), 0.5 M 1,4-cyclohexadiene, and 0.01 M TEMPO in isooctane was used. A linear relationship was obtained demonstrating that two-photon processes did not occur.

Very Low Pressure Pyrolysis. The VLPP instrument has been described before.[7] The vessel containing the substrate was placed in melting ice in the case of methyl-TEMPO and in a water bath at room temperature when TEMPO was under investigation. The spectra between m/z 15 and 180 were recorded with use of an ionization energy of 20 eV to avoid a large degree of fragmentation of the reagent and products. The retrieved intensities were corrected for the fragmentation of the starting compound. The initial substrate concentration (intensity of the molecular ion, I_0) was derived from blank runs at low temperatures. From the decrease of the molecular ion abundance (I) relative to I_0, the rate constants for unimolecular decay, k_{uni}, were calculated at each temperature according to $k_{uni} = k_e(I_0 - I)/I$, with k_e as the escape rate constant: $k_e = 1.47(T/M)^{1/2}$ (M = molar mass of the reactant, 1.47 is an instrument constant). The Arrhenius expression at infinite pressure was obtained by use of the RRKM algorithm.[7,8]

Liquid-Phase Product Studies. The experiments were carried out in sealed Pyrex tubes (ca. 1.5 mL), which were charged for about one-third with the reactants and an internal standard (naphthalene). Subsequently, the tubes were degassed three times by freeze−pump−helium−thaw cycles, sealed under vacuum (ca. 400 Pa) and placed in a thermostat-controlled oven. Final temperatures were reached within 5 min starting from room temperature, and the overall reaction time was 60 min unless stated otherwise. After rapidly cooling to room temperature, the tube was decapped and a mixture of toluene and an external standard (dodecane) was added.
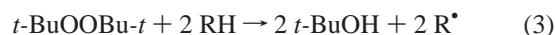
Samples were analyzed on an HP 5890A gas chromatograph (Hewlett-Packard GC) with hydrogen as the carrier gas and a flame ionization detector (FID). For the identification of unknown products, an HP 5890A GC with helium as the carrier gas and an HP 5972 mass selective detector (Hewlett-Packard) was used. Both GCs were equipped with apolar capillary columns (Chrompack CP-Sil-5 CB, 50 m, 0.32 mm i.d., 0.4 μm film thickness, and Hewlett-Packard HP-1MS, 30 m, 0.25 mm i.d., 0.25 μm film thickness, respectively). For quantification, molar response factors were derived from calibration mixtures or estimated based on the number of carbon and oxygen atoms.

Density Functional Theory Calculations. The calculations were performed with the Gaussian 94 rev. E.3 package on an IBM RS6000 computer and a Silicon Graphics Indy workstation. The B3LYP method with the 6-31G(d,p) basis set was employed for geometry optimization and the frequency routines. The basis set was chosen to obtain optimum results with respect to accuracy and calculation time. The calculated

vibrational frequencies were corrected by a factor of 0.9805 to compensate for anharmonicity.[9]

Results

C−O Bond Enthalpies in *N*-Alkoxyamines by Photoa-coustic Calorimetry. Typically, a PAC experiment involves the irradiation of a solution containing the substrate (RH) and di-*tert*-butyl peroxide. After laser pulsed photolysis, *tert*-butoxyl radicals are instantaneously produced (eq 1) and subsequently abstract hydrogen atoms from the substrate (eq 2). The overall process is given by eq 3.

$$t\text{-BuOOBu-}t \xrightarrow{h\nu} 2\ t\text{-BuO}^{\bullet} \qquad (1)$$

$$t\text{-BuO}^{\bullet} + RH \rightarrow t\text{-BuOH} + R^{\bullet} \qquad (2)$$

$$t\text{-BuOOBu-}t + 2\ RH \rightarrow 2\ t\text{-BuOH} + 2\ R^{\bullet} \qquad (3)$$

The observed reaction enthalpy ($\Delta_3 H_{obs}$) is retrieved according to eq 4, in which $E_{h\nu}$ is the laser energy (84.8 kcal mol^{-1}) and Φ is the photochemical quantum yield for photodissociation of the peroxide in a particular solvent. The apparent fraction of photon energy released as heat (f_{obs}) is determined experimen-tally.

$$\Delta_3 H_{obs} = \frac{E_{h\nu}}{\Phi}(1 - f_{obs}) \qquad (4)$$

The BDE(C−H) in RH can be calculated by using eq 5, where $\Delta\Delta H_{solv}$ is the change in heats of solvation for the process that converts one di-*tert*-butyl peroxide into two *tert*-butyl alcohols, ΔV_1 is the (positive) chemical volume change due to reaction 1, χ_s is the adiabatic expansion coefficient of the solvent, and the constant 86.0 contains the gas phase heats of formation (in kcal mol^{-1}) (0.5 $\Delta_f H°(t\text{-BuOOBu-}t) - \Delta_f H°(t\text{-BuOH}) + \Delta_f H°\text{-}(\text{H}^{\bullet})$).

$$\text{BDE(C−H)} = 0.5\ \Delta_3 H_{obs} - 0.5(\Delta\Delta H_{solv} - \Delta V_1/\chi_s) + 86.0$$
$$(5)$$

When TEMPO is added to the solution, R$^{\bullet}$ is scavenged according to eq 6. By using the overall reaction enthalpy (eq 7), the BDE(C−O) in R-TEMPO can be retrieved according to eq 8.

$$R^{\bullet} + TEMPO \rightarrow R\text{-TEMPO} \qquad (6)$$

$$t\text{-BuOOBu-}t + 2\ RH + 2\ TEMPO \rightarrow$$
$$2\ t\text{-BuOH} + 2\ R\text{-TEMPO} \quad (7)$$

$$\text{BDE(C−O)} = -0.5[(\Delta_7 H)_{obs} - (\Delta_3 H)_{obs}] - \Delta V_6/\chi_s \qquad (8)$$

The magnitude of the chemical volume change in eq 1 ($\Delta V_1/\chi_s$) has been determined to be 4 kcal mol^{-1} for various solvents.[6] Considering that the difference in number of species on going from reactants to products in eq 6 is equal but opposite in sign, one can assume that $\Delta V_1/\chi_s = -\Delta V_6/\chi_s$.

We have determined the BDE(C−H) for cyclohexane, 1,4-cyclohexadiene, tetrahydrofuran (α-C), and triethylamine (α-C), and the BDE(C−O) for the related *N*-alkoxyamines.

In the case of cyclohexane (CHEX), the hydrogen abstraction reaction is too slow for the PAC time window of less than 1 μs.[10] This time constraint is relieved by adding a second reactant

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Table 1. BDE(C—H) for R—H and BDE(C—O) for R-TEMPO As Determined by PAC[a]

R[b]	R—H		R-TEMPO	
	$\Delta_3 H_{obs}$	BDE(C—H)[c]	$\Delta_7 H_{obs}$	BDE(C—O)[d]
c-C$_6$H$_{11}$	14[e]	98	−59[e]	40
C$_6$H$_7$	−29	77	−56	18
C$_4$H$_7$O	−2[f]	92	−82[g]	48[h]
(C$_2$H$_5$)$_2$NCHCH$_3$	−4[i]	89	−71[i]	38

[a] In kcal mol^{-1}, reported BDEs based on at least two runs, error margins ±1.5 kcal mol^{-1}. Solvent: isooctane except for THF and cyclohexane for which the neat liquids were applied. [CHD] = 0.3 M, [(C$_2$H$_5$)$_3$N] = 0.5 M. Quantum yields: $\Phi_{isooctane}$ = 0.83, Φ_{CHEX} = 0.78, Φ_{THF} = 0.85, $\Phi_{ethyl\ acetate}$ = 0.86.[6a] $(\Delta\Delta H_{solv})_{app}$ = $\Delta\Delta H_{solv} - \Delta V_l/\chi_s$ (see eq 5): cyclohexane and isooctane, −10 kcal mol^{-1}; THF and ethyl acetate, −13 kcal mol^{-1}.[6a] [b] c-C$_6$H$_{11}$: cyclohexyl. C$_6$H$_7$: 1,4-cyclohexadienyl. C$_4$H$_7$O: α-tetrahydrofuryl. [c] See eq 5. [d] See eq 8. [e] Competition experiments with a mixture of 0.3 M 1,4-cyclohexadiene and 8.9 M cyclohexane resulted in $\Delta_3 H_{obs}$ = −14 kcal mol^{-1} and $\Delta_7 H_{obs}$ = −57 kcal mol^{-1}. With $k_{2,CHD}$ = 3.0 × 10^7 M^{-1} s^{-1},[6a] $k_{2,CHEX}$ = 5.5 × 10^5 M^{-1} s^{-1},[12] ξ becomes 0.65.[10,11] According to enthalpy data for CHD, $\Delta_3 H_{obs}$ = 14 kcal mol^{-1} and $\Delta_7 H_{obs}$ = −59 kcal mol^{-1} can be derived for CHEX. [f] Experimentally $\Delta_3 H_{obs}$ = −1 kcal mol^{-1} and contains a contribution by β-hydrogen abstraction: $k_{2,THF}$ = 4.6 × 10^6 M^{-1} s^{-1},[10] $k_{2-\beta-C-H}$ = 1.8 × 10^5 M^{-1} s^{-1} (β-C—H is equal to c-C$_6$H$_{11}$—H), and $k_{2-\alpha-C-H}$ = 4.4 × 10^6 M^{-1} s^{-1} to give ξ = 0.96. Since $(\Delta\Delta H_{solv})_{app}$ = −13, $\Delta_3 H_{obs}$(β-C—H) decreases from 14 to 11 kcal mol^{-1}. [g] Experimentally $\Delta_7 H_{obs}$ = −81 kcal mol^{-1}. With ξ = 0.96 (see footnote f) and $\Delta_7 H_{obs}$(β-C—H) = −54 kcal mol^{-1} in a polar solvent (see footnote i). [h] For an apolar solvent $\Delta_7 H_{obs} - \Delta_3 H_{obs}$ = −88 kcal mol^{-1}, which eliminates the solvation enthalpy contribution (see footnote i). [i] In ethyl acetate $\Delta_3 H_{obs}$ = −8, BDE(C—H) = 89, and $\Delta_7 H_{obs}$ = −67 kcal mol^{-1} to give BDE(C—O) = 34 kcal mol^{-1} in a polar medium. The $\Delta(\Delta_7 H_{obs} - \Delta_3 H_{obs})$ between a polar (ethyl acetate) and an apolar (isooctane) solvent of +8 kcal mol^{-1} reflects twice the difference in solvation enthalpy between TEMPO and R-TEMPO.

(1,4-cyclohexadiene, CHD) with known BDE and reaction rate constant (eq 2), reducing the global lifetime of the *tert*-butoxyl radicals. The observed enthalpy ($\Delta_3 H_{obs}$) is a combination of two processes, the hydrogen abstraction from CHD ($\Delta_3 H_{CHD}$) and CHEX ($\Delta_3 H_{CHEX}$). With known rate constants, the heat contribution can be disentangled by using the rate fraction ratio (ξ).[11] Addition of TEMPO to this mixture does not change ξ since all the formed radicals are trapped quantitatively within the PAC time window.

The difference in solvation enthalpy between TEMPO and R-TEMPO can be neglected in hydrocarbon solvents, but it has to be taken into consideration in polar solvents.[6b] The PAC experiments with triethylamine (0.2 M) were repeated in ethyl acetate, leading to a BDE(C—O) that is 4 kcal mol^{-1} lower than the one determined in isooctane. This difference is due to loss of solvation enthalpy for TEMPO in the polar solvent (see eq 7). The BDE(C—O) in tetrahydrofuryl-TEMPO has been determined in neat THF. Since ethyl acetate and THF have similar polar properties (dipole moments: 1.78, 1.63 D, respectively), the intrinsic BDE(C—O) for THF—TEMPO increases from 44 (measured) to 48 kcal mol^{-1} (see Table 1).

A prerequisite for PAC is that the course of the radical reactions, within the PAC time domain, is known. Besides recombination (eq 6), disproportionation between TEMPO and R• can be envisaged. We are not aware of any pertinent rate data concerning the ratio for the two pathways. Recombination appears to be the major (if not the only) route since the results from another PAC study[13] regarding the reaction enthalpy of

(11) $\Delta_3 H_{obs}$ = $\xi\Delta_3 H_{CHD}$ + (1 − ξ)$\Delta_3 H_{CHEX}$; ξ = $k_{2,CHD}$[CHD]/{$k_{2,CHD}$[CHD] + $k_{2,CHEX}$[CHEX]}.

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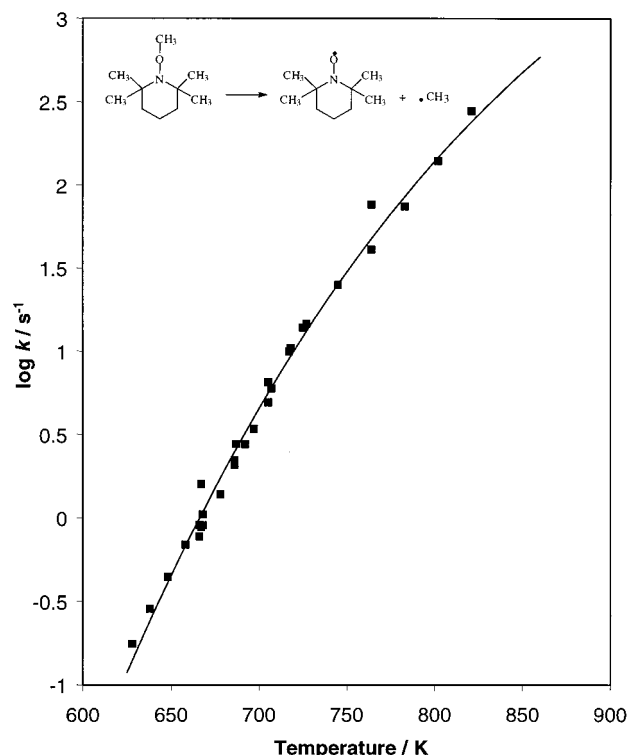

Figure 1. Experimental (VLPP, ■) and calculated (RRKM, solid line) rate constants for unimolecular decomposition of methyl-TEMPO. High-pressure rate constant: k s^{-1} = 10$^{15.3}$ exp(−45.8/RT).

the same radicals with molecular oxygen (for which only recombination occurs) could be linearly correlated with data given in Table 1. A recent study on trapping radical species at 294 K by TEMPO also revealed a high preference for recombination.[14]

Very Low Pressure Pyrolysis of Methyl-TEMPO. The BDE(C—O) in methyl-TEMPO has been investigated in the gas phase by means of very low pressure pyrolysis to avoid any effect of the solvent. At elevated temperatures and low pressures bimolecular reactions can be excluded. Methyl-TEMPO was chosen as the reagent because only one decomposition route exists. With other alkyl-substituted compounds, next to bond homolysis, a concerted elimination may occur (e.g., decomposition of ethyl-TEMPO directly into the hydroxyamine and ethene). The decay of the molecular ion was followed in the temperature region 550−850 K.

On the basis of the vibrational frequencies calculated by DFT, RRKM computations were performed to correct the experimental unimolecular rate constant for the falloff behavior with a fixed preexponential factor of 10$^{15.3}$. This value is typically for bond homolysis as has been shown for PhO—CH$_3$,[7] PhO—C$_2$H$_3$,[7] PhC(CH$_3$)$_2$—CH$_3$,[15a] and α-Br-acetophenone.[15b] The high-pressure Arrhenius expression for methyl-TEMPO obeys k s^{-1} = 10$^{15.3}$ exp(−45.8/RT) (see Figure 1). Hence, through BDE(C—O) = E_a + RT_m + ΔC_p(T_m − 298), where T_m is the average experimental temperature (700 K), and by considering ΔC_p negligible (as shown by DFT), the BDE(C—O) in methyl-TEMPO is calculated to be 47 ± 1 kcal mol^{-1} at 298 K.

DFT calculations at the B3LYP/6-31G(d,p) level resulted in a BDE(C—O) of 41.2 kcal mol^{-1}, 6 kcal mol^{-1} lower than the

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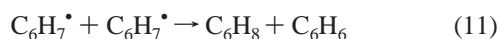
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experimental value. Virtually the same discrepancy is found for the BDE(O–H) in 2,2,6,6-tetramethyl-1-piperidinol (TEMPOH) between the experimental value (69.7 kcal mol^{-1})[16] and the one calculated by us (63.9 kcal mol^{-1}). Hence, DFT underestimates the dissociation enthalpies for O–H and C–O bonds as has been shown before with, e.g., phenols and aryl ethers.[7,17]

Interestingly, the difference between the BDE(O–H) in TEMPOH and the BDE(C–O) in methyl-TEMPO amounts to ca. 22 kcal mol^{-1}. Similar bond differences can be found between PhO–H[7] and PhO–CH$_3$,[18] and between CH$_3$O–H and CH$_3$O–CH$_3$,[19] suggesting that this is caused by the repulsion between the oxygen lone pair and the C–H bonding orbital.

Although a persistent radical at room temperature, TEMPO is completely converted at 600 K into an array of hydrocarbons with isobutene, ethene, and acetoxime ((CH$_3$)$_2$CNOH) as the major products. The thermal cracking pattern is quite similar to that obtained in a mass spectrometer at the standard ionization potential of 70 eV.

N-Alkoxyamines in Hydrogen-Donor Solvents. To compare the results obtained by PAC and VLPP, the thermal stability of *N*-alkoxyamines was studied in the liquid phase between 298 and 533 K with hydrogen-donor solvents (1,4-cyclohexadiene or 9,10-dihydroanthracene). These hydrocarbon solvents ensure an effective capping of the product radicals, thereby preventing reversibility (eq 9–11).[20]

$$R\text{-TEMPO} \rightarrow R^{\bullet} + \text{TEMPO} \tag{9}$$

$$R^{\bullet} + C_6H_8 \rightarrow RH + C_6H_7^{\bullet} \tag{10}$$

$$C_6H_7^{\bullet} + C_6H_7^{\bullet} \rightarrow C_6H_8 + C_6H_6 \tag{11}$$

Although these experiments (see Table 2) were not intended to derive the accurate Arrhenius parameters for eq 9, the rates of conversion can be used to compute the BDE(C–O)s. For cyclohexyl-TEMPO a good agreement is obtained with the PAC data. The rate constants for methyl-TEMPO are identical with those derived from the Arrhenius expression obtained by VLPP and therefore the bond enthalpies are quite similar. A discrepancy of almost 6 kcal mol^{-1} is found for THF–TEMPO between liquid-phase thermolysis and PAC. It is worthwhile to note that without the incorporation of the TEMPO solvation enthalpy (see Table 1), the difference would be reduced to 2 kcal mol^{-1}.

TEMPO in Hydrogen-Donor Solvents. During the *N*-alkoxyamine decomposition (vide supra) an appreciable amount of TEMPO was converted into the hydroxyamine (2,2,6,6-tetramethyl-1-piperidinol, TEMPOH) and the amine (2,2,6,6-tetramethylpiperidine, TEMPH). This phenomenon was further explored by thermolyzing TEMPO in various (hydrogen-donor) solvents (see Table 3). In diphenyl ether (DPE) or 2-propanol,

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Table 2. Thermal Stability of *N*-Alkoxyamines (R-TEMPO) in 1,4-Cyclohexadiene[a]

R	T (K)	conv (%)[b]	k (s^{-1})[c]	E_a (kcal mol^{-1})	BDE(C–O) (kcal mol^{-1})
C$_4$H$_7$O[d]	503	7	2.0 × 10^{-5}	43[e]	42[f]
	533	83	4.9 × 10^{-4}		
CH$_3$[d]	503	5	1.4 × 10^{-5}	46[g]	46[g]
	533	69	3.3 × 10^{-4}		
c-C$_6$H$_{11}$	488	19	5.9 × 10^{-5}	41[e]	40[f]
	495	27	8.7 × 10^{-5}		

[a] Reaction time: 1 h. In 9,10-dihydroanthracene similar results were obtained. [b] Conversion of R-TEMPO: 100 − 100([R-TEMPO]$_t$/[R-TEMPO]$_{t=0}$). [c] Calculated on the basis of converted *N*-alkoxyamines. [d] Since decomposition rates are quite similar, the experiments were performed with a mixture of THF–TEMPO and methyl-TEMPO in 1,4-cyclohexadiene. [e] log A/s^{-1} = 14.1.[22] [f] Exit barrier: 1 kcal mol^{-1} (see text). [g] The recombination between methyl and TEMPO can be regarded as a diffusion-controlled reaction, since the rate constant for a primary radical (1-nonyl) with TEMPO is already 1.2 × 10^9 M^{-1} s^{-1}.[3b] According to our VLPP gas-phase study the rate constants for methyl-TEMPO homolysis are 2.5 × 10^{-5} (503 K) and 3.3 × 10^{-4} s^{-1} (533 K), respectively, quite close to the liquid-phase values. Although the agreement may be fortuitous,[23] the same similarity was observed for *tert*-butyl peroxide homolysis.[25] Therefore, for methyl-TEMPO thermolysis in the liquid phase we have selected log A/s^{-1} = 15.3.

Table 3. Thermal Stability of TEMPO in Various (Hydrogen-Donor) Solvents

TEMPO:solvent[a]	T (K)	product yields (% on initial TEMPO)[b]		
		TEMPH	TEMPOH	TEMPO
AnH$_2$				
1:35[c]	322	6		56
1:50	398	21	38	44
1:50	423	51	35	27
1:30[d]	423	100	22	
1:40	465	100		
PhenH$_2$				
1:40	423	5	57	38
1,4-cyclohexadiene				
1:70[e]	298	8	49	43
1:85	321		78	22
1:66[f]	423	2	63	35
1:50[d]	423	69	18	13
diphenyl ether				
1:55[g]	423			100
1:85[h]	503	23	32	12
2-propanol				
1:300	425		1	99
ethylbenzene				
1:30	423	2	7	91
1:25[i]	423	21	17	62

[a] Molar ratio. Reaction time = 1 h. [b] The actual mass balance was ca. 80% in all cases. In view of the uncertainty of the response factors the mass balance was normalized to 100% (GC response factor of TEMPOH was taken equal to that for TEMPO; for TEMPH it was calculated on the basis of the number of carbon and oxygen atoms). [c] Reaction time = 23 h. [d] Addition of an equimolar amount of benzoic acid relative to TEMPO. [e] Reaction time = 3 h. [f] The yields (in %) of TEMPH, TEMPOH, and TEMPO after 2 h were 3, 70, and 27, and after 3 h they were 6, 63, and 31. [g] Addition of an equimolar amount of benzoic acid relative to TEMPO gave the same result. [h] 8% of methyl-TEMPO was obtained and an incomplete mass balance was observed. [i] Reaction time = 12 h.

solvents without any hydrogen-donating capacity, TEMPO is inert at 423 K. Only above 500 K the formation of methyl-TEMPO was observed. TEMPO can abstract a hydrogen from another molecule of TEMPO (e.g. the 3-position), followed by β-elimination yielding a methyl radical. Subsequent recombination gives methyl-TEMPO. In hydrogen-donor solvents a substantial reduction of TEMPO takes place.[26] The yield of the solvent dehydrogenation product (e.g. benzene from 1,4-cylohexadiene) was in all cases 1:2 with respect to TEMPOH

and 3:2 with respect to TEMPH. After 2 h at 423 K in AnH$_2$ the product yield did not significantly change with time, indicating that an equilibrium has been reached. By adding an equimolar amount of benzoic acid, a quantitative conversion of TEMPO into the amine occurred already within 1 h of reaction time at 423 K. The acid was shown to be effective only in the reduction of TEMPOH to TEMPH; addition of benzoic acid to TEMPO in DPE did not change the inertness.

The stability of TEMPO was also studied in neat ethylbenzene as a model for polystyrene. After 12 h at 423 K TEMPO was converted for 38% into TEMPOH and TEMPH (see Table 3). Taking into account that the polymerization usually lasts for many hours, it is reasonable to assume that in the last stages of the polymer growth, TEMPO is less effective. The yield of styrene agreed with TEMPO reduction products as was found with the other hydrogen-donor solvent. In another study it has been demonstrated that heating TEMPO in ethylbenzene at 393 K for 12 h yielded the recombination product (not quantified) between TEMPO and the 1-phenylethyl radical as was determined by NMR.[27] Under our conditions, at 423 K, the ethylbenzene−TEMPO adduct decomposes with a rate constant of ca. 0.1 s^{-1}, and even if the rate for disproportionation is around 1% relative to recombination, it can be shown by kinetic modeling that the final product after 12 h will be solely styrene. A similar behavior has been observed for cumyl and TEMPO at 353 K.[22]

Discussion

Thermal Stability of *N*-Alkoxyamines. This study demonstrates the thermally labile nature of the carbon−oxygen bonds in *N*-alkoxyamines (see Table 1). In fact, the combination of TEMPO and cyclohexadienyl radical yields a compound with a covalent bond of 18 kcal mol^{-1}, and consequently the half-life will be around 100 ms at room temperature. Although the decomposition rate is high, the time frame of the photoacoustic calorimetric method (less than 1 μs) prevents a convolution of the heat deposition by the forward (eq 6) and the reverse reaction.

The rates of thermal decomposition of some other *N*-alkoxyamines have been determined on the basis of product analysis by HPLC,[28] NMR detection,[29] or real time ESR.[22,30] The relationship between E_a for unimolecular dissociation and the BDE is rather straightforward for studies in the gas phase. An additional enthalpic contribution may be anticipated when reactions are studied in solution due to solvation of the reactant and/or the transition state.[23]

(21) Hawari, J. A.; Engel, P. S.; Griller, D. *Int. J. Chem. Kinet.* **1985**, *17*, 1215−1219.

(22) Kothe, T.; Marque, S.; Martschke, R.; Popov, M.; Fischer, H. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1553−1559.

(23) The rate constant for homolysis of bibenzyl into two benzyl radicals depends on the phase in which it has been derived: gas phase k s^{-1} = $10^{15.25}$ exp($-62.3/RT$), tetralin k s^{-1} = $10^{16.6}$ exp($-66.8/RT$), hence k_{gas}/k_{liquid} = 4 (500 K) and 1.9 (600 K).[24]

(24) Stein, S. E.; Robaugh, D. A.; Alfieri, A. D.; Miller, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 6567−6570.

(25) Benson, S. W.; Shaw, R. In *Organic Peroxides*; Swern, D., Ed.; Wiley-Interscience: New York, 1970.

(26) Upon standing, in the presence of (air) oxygen, both TEMPH and TEMPOH were slowly reoxidized to TEMPO. This reverse reaction may also be beneficial in living free radical polymerization.
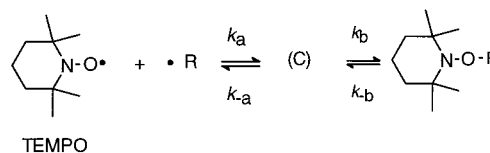
(27) Connolly, T. J.; Scaiano, J. C. *Tetrahedron Lett.* **1997**, *38*, 1133−1136.

(28) Skene, W. G.; Belt, S. T.; Connolly, T. J.; Hahn, P.; Scaiano, J. C. *Macromolecules* **1998**, *31*, 9103−9105.

(29) Li, I.; Howell, B. A.; Matyjaszewski, K.; Shigemoto, T.; Smith, P. B.; Priddy, D. B. *Macromolecules* **1995**, *28*, 6692−6693.

(30) Veregin, R. P. N.; Georges, M. K.; Hamer, G. K.; Kazmaier, P. M. *Macromolecules* **1995**, *28*, 4391−4398.

Scheme 1

From the kinetic data, the carbon−oxygen bond dissociation enthalpies at 298 K have been derived in the following way. For the reverse reaction (see Scheme 1), the trapping of the radical R$^\bullet$ (cumyl, benzyl) with TEMPO, an apparent activation enthalpy of about 1 kcal mol^{-1} has been determined,[22,31] which deviates from the temperature dependence found for near-diffusion-limited reactions (3−4 kcal mol^{-1}).

This phenomenon has been explained by considering that upon reversible encounter (k_a, k_{-a}) of the two radical species, a short-lived intermediate (C) is formed. Subsequent rearrangement, through an activated process, renders R-TEMPO. At sufficiently low temperatures the rate expression for product formation is given by d[R-TEMPO]/dt = k_f[R$^\bullet$][TEMPO] with k_f = $k_a k_b/(k_{-a} + k_b)$. Since k_a is a known diffusion-controlled rate constant, and k_f has been determined experimentally, k_{-a} and k_b can be obtained by kinetic simulation.[32] On the basis of the foregoing, and provided that the rate for scavenging of R$^\bullet$ and/or TEMPO is fast enough,[33] the BDE(C−O) in the *N*-alkoxyamine can be calculated from the measured activation enthalpy for k_{-b} by subtracting 1 kcal mol^{-1}.

In Table 4, (recalculated) literature values for the BDE(C−O) in *N*-alkoxyamines are presented, along with the results of this work. Some data[29,30] are not obtained under conditions of kinetic isolation and therefore most likely are in error. Other studies did recognize the presence of the persistent radical effect.[22,28]

On the basis of our data, excluding THF and triethylamine, a plot of the BDE(C−O) vs the BDE(C−H) results in a linear correlation of BDE(C−O) = 1.04BDE(C−H) − 62.1 kcal mol^{-1} (see Figure 2) and spans a wide range of almost 30 kcal mol^{-1}.

The other recalculated data (see Table 4) nicely fit this relation. According to the Pauling equation[34] the BDE consists of covalent and ionic contributions. From the slope of almost one in the correlation we can conclude that the variation in the electronegativity between the C−O and the C−H bonds remains essentially constant throughout this series of compounds. This correlation can be quite beneficial to predict the carbon−oxygen bonds in various TEMPO-based *N*-alkoxyamines using the known BDE(C−H) for the hydrocarbon. For example, in the living polymerization of styrene, the carbon−oxygen bond is

(31) Chateauneuf, J.; Lusztyk, J.; Ingold, K. U. *J. Org. Chem.* **1988**, *53*, 1629−1632.

(32) For example, the termination rate constant for two cumyl radicals is given by (4×10^{11}) exp($-3.4/RT$) M^{-1} s^{-1}, while the k_f for cumyl and TEMPO is (2.5×10^8) exp($-0.88/RT$) M^{-1} s^{-1}. If one accepts A_{-a}/A_b = 10^3, the entropy gain from the complex (C) into two radical species is always much higher than a rearrangement inside the solvent cage; fitting yields $E_{a,-a} - E_{a,b}$ = 2.7 kcal mol^{-1}. Hence, with $E_{a,a}$ of 3.4 kcal mol^{-1}, the enthalpy level for the TS of the rearrangement into R-TEMPO is 0.7 kcal mol^{-1} above that for the two separated species R$^\bullet$ and TEMPO. Hence, the slowness of the TEMPO trapping reaction is due to an entropic effect. Indeed, in the same solvent, k_f decreases by a factor of 20 between 9,10-dihydroanthracenyl and cyclohexadienyl while the overall reaction enthalpy remains the same.[3c]

(33) The kinetic expression for decomposition of the *N*-alkoxyamine obeys d[R-TEMPO]/dt = ($k_{-a}k_{-b}/(k_{-a} + k_b)$)[R-TEMPO] − ($k_a k_b/(k_{-a} + k_b)$)[R$^\bullet$][TEMPO]. When upon formation R$^\bullet$ is scavanged, i.e., v_{10} is larger than v_a, d[R-TEMPO]/dt = k_d[R-TEMPO], with k_d = ($k_{-a}k_{-b}/(k_{-a} + k_b)$). Using the ratio for k_{-a}/k_b as derived in ref 32, k_d = k_{-b}.

(34) Pauling, L. *The Nature of the Chemical Bond*, 3rd ed.; Cornell University Press: Ithaca, NY, 1960.

Table 4. BDE(C−O) in *N*-Alkoxyamines (R-TEMPO)

R	E_a (kcal mol^{-1})	BDE(C−O)^a (kcal mol^{-1})	ref
CH$_3$		47	this work
c-C$_6$H$_{11}$		40	this work^b
C$_6$H$_7$		18	this work^b
C$_6$H$_5$CH$_2$	32.6^c	32	28
C$_6$H$_5$CHCH$_3$	24.2^d	33	29^e
C$_6$H$_5$CHCH$_3$	28.4^f	34	29^e
C$_6$H$_5$CHCH$_3$	30.7^g	30	28
C$_6$H$_5$CHCH$_3$	31.1	27	30
C$_6$H$_5$C(CH$_3$)$_2$	27.3	26	22
C$_6$H$_5$C(CH$_3$)$_2$	27.2^h	26	28
C$_4$H$_7$O		48	this work^b
(CH$_3$CH$_2$)$_2$NCHCH$_3$		38	this work^b

^{a} At 298 K, the BDEs were recalculated from the rate expression by using log A/s^{-1} = 14.09^{22} and applying an enthalpic contribution of −1 kcal mol^{-1}.^{30} ΔC_p is assumed to be zero. ^{b} See Table 1. ^{c} Reported log A/s^{-1} = 13.6. ^{d} Solvent: DMSO-d_6. ^{e} In this report log A values of 9.1 and 10.9 were derived, values quite unexpected for bond homolysis. ^{f} Solvent: trichlorobenzene. ^{g} Reported log A/s^{-1} = 13.7. ^{h} Reported log A/s^{-1} = 14.0.
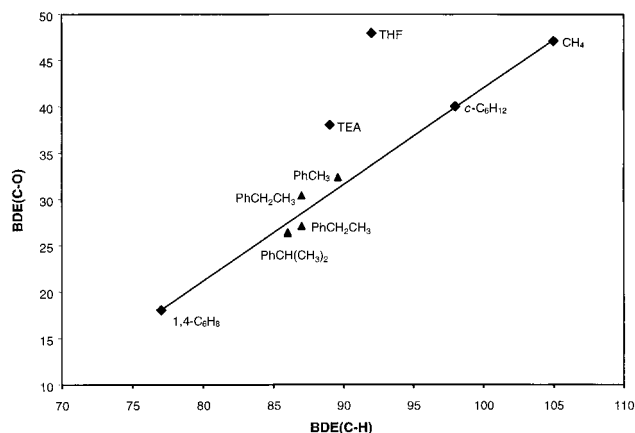

Figure 2. Relation between BDE(C−O) in *N*-alkoxyamines and BDE-(C−H) in the corresponding hydrocarbons (◆, this work; ▲, literature) in kcal mol^{-1}: BDE(C−O) = 1.04BDE(C−H) − 62.1, omitting THF and TEA (triethylamine). Entries 5 and 6 of Table 4 are not displayed. The auxiliary values for the BDE(C−H) are (in kcal mol^{-1}) 105 for CH$_4$ (Berkowitz, J.; Ellison, G. B.; Gutman, D. *J. Phys. Chem.* **1994**, *98*, 2744−2765), 87 for PhC*H*$_2$CH$_3$, 86 for PhC*H*(CH$_3$)$_2$ (Santoro, D.; Korth, H.-G.; Mulder, P. In preparation), and 89.6 for PhCH$_3$ (Tsang, W. In *Energetics of Organic Free Radicals*; Simoes, M. A., Greenberg, A., Liebman, F., Eds.; Chapman & Hall: London, 1996; pp 22−58).
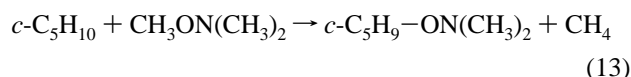
calculated to be 28 kcal mol^{-1} for the intermediate trapped polymer chain by TEMPO,^{35} in satisfactory agreement with experimental data (see Table 4).

The Anomeric Effect and the BDE(C−O) in *N*-Alkoxyamines. For *N*-alkoxyamines with a heteroelement in the α-position (O in THF and N in triethylamine), the BDE(C−O)s deviate markedly (i.e. a stronger bond is formed) from the correlation (see Figure 2). The PAC results show that the α-carbon−hydrogen bond in THF is ca. 6 kcal mol^{-1} weaker relative to that in cyclohexane (see Table 1). Conversely, in the corresponding TEMPO derivatives, the BDE(C−O) with THF is 8 kcal mol^{-1} stronger, hence the relative change amounts to 14 kcal mol^{-1}. This phenomenon is caused by two opposing interactions: the anomeric effect^{36} and the stabilization of the radical center. The anomeric effect is present in the ground state *N*-alkoxyamine, and encompasses the interaction of the n$_\pi$

(35) Taking ethylbenzene as the model compound for polystyrene (see Figure 2).

(36) Gorenstein, D. G. *Chem. Rev.* **1987**, *87*, 1047−1077.

orbital (HOMO) of the endocyclic oxygen (in THF) with the adjacent σ^* orbital (LUMO) of the exocyclic carbon−oxygen bond. As a result, the heat of formation is lowered. The anomeric effect is not present in THF itself, since the n$_\pi$−σ^* (C−H) interaction is much weaker. The decrease in the BDE(C−H) in THF relative to cyclohexane results from the interaction of the radical center with the endocyclic oxygen. To support our observations we have performed some additional DFT model calculations on (derivatives of) THF and cyclopentane. With the 6-31G(d,p) basis set, BDE(C−H) for the α-C−H in THF is found to be 3.1 kcal mol^{-1} weaker relative to cyclopentane. Next, the reaction enthalpies for the isodesmic reactions (12 and 13) have been calculated as (in kcal mol^{-1}) $\Delta_{12}H$ = −14.1 and $\Delta_{13}H$ = −8.5.

$$\text{THF} + \text{CH}_3\text{ON(CH}_3)_2 \rightarrow \text{THF−ON(CH}_3)_2 + \text{CH}_4 \quad (12)$$

$$c\text{-C}_5\text{H}_{10} + \text{CH}_3\text{ON(CH}_3)_2 \rightarrow c\text{-C}_5\text{H}_9\text{−ON(CH}_3)_2 + \text{CH}_4 \quad (13)$$

The anomeric stabilization enthalpy,^{37} $\Delta_{12}H − \Delta_{13}H$, becomes −5.6 kcal mol^{-1}, which is still quite separated from the experimental value of −14 kcal mol^{-1} (provided that the calculated model is adequate). More detailed calculations and experiments are needed to disclose the various electronic contributions. In any case, the carbon−oxygen bond dissociation enthalpy in *N*-alkoxyamines can be strongly influenced by the nature of the substitutent attached to the carbon carrying the nitroxide group.

Reduction of TEMPO to 2,2,6,6-Tetramethylpiperidine. The reduction (deoxygenation) of TEMPO to 2,2,6,6-tetramethylpiperidine (TEMPH) by hydrogen donor solvents appears to be a facile reaction. It is well documented that the nitroxide can be converted into TEMPOH by a number of reducing agents such as ascorbic acid,^{38} thiophenols,^{39} and organometallic hydrides.^{40}

The reaction of TEMPO with HMR$_3$ reducing agents (M = Si, Ge, Sn)^{40} yields TEMPOH and TEMPH. TEMPOH is supposed to be formed by hydrogen atom abstraction from the hydride. Subsequently, the (Me$_3$Si)$_3$Si$^\bullet$ radical recombines with TEMPO, and this adduct decomposes in such a way that the oxygen is transferred from nitrogen to the silicon to give TEMPH and a siloxane derivative. If the same mechanism would hold for hydrogen donors such as AnH$_2$, the oxygen is shuttled from TEMPO to the 9,10-dihydroantracenyl moiety to yield anthrone and TEMPH (see Scheme 2).^{41}

(37) The difference in the heat of formation, $\Delta\Delta_f H$, between α- and β-X-THF provides a direct way to establish the anomeric stabilization. According to DFT, with X = ON(CH$_3$)$_2$, $\Delta\Delta_f H$ = −7.0 kcal mol^{-1}, and with X = OCH$_3$, $\Delta\Delta_f H$ = −6.8 kcal mol^{-1}. The DFT calculated structures reveal the following molecular features: the bond lengths for (Me)$_2$NO−THF and (Me)$_2$NO−c-C$_5$H$_9$ are 1.4077 and 1.4205 Å, respectively. According to the MO description of the anomeric effect, the exocyclic carbon−oxygen bond is expected to be longer due to the antibonding orbital interaction. The Mulliken charges are the following: for (Me)$_2$NO−THF and THF, endocyclic O (−0.5065 and −0.48635), α-C (0.5265, 0.2877 and 0.2486, 0.2478), and exocyclic O (−0.4204) and N (−0.2248); for (Me)$_2$NO−c-C$_5$H$_9$ and cyclopentane, C (0.2820 and −0.0014), exocyclic O (−0.4309), and N(−0.2129). DFT predicts a stronger charge interaction in (Me)$_2$NO−THF relative to (Me)$_2$NO−c-C$_5$H$_9$.

(38) Aurich, H. G. In *Nitrones, Nitronates and Nitroxides*; Patai, S., Rappoport, Z., Eds.; Interscience: New York, 1989; pp 351−354.

(39) Carloni, P.; Damiani, E.; Iacussi, M.; Greci, L.; Stipa, P.; Cauzi, D.; Rizzoli, C.; Sgarabotto, P. *Tetrahedron* **1995**, *51*, 12445−12452.

(40) Lucarini, M.; Marchesi, E.; Pedulli, G. F.; Chatgilialoglu, C. *J. Org. Chem.* **1998**, *63*, 1687−1693.

(41) Jensen et al. noticed that Ar$_2$NO$^\bullet$ (Ar = 4-octylphenyl) is reduced to the amine during the autoxidation of hexadecane at 393 K.^{42} Thermal decomposition of Ar$_2$NOR is believed to play a key role in the regeneration of the amine.

Scheme 2
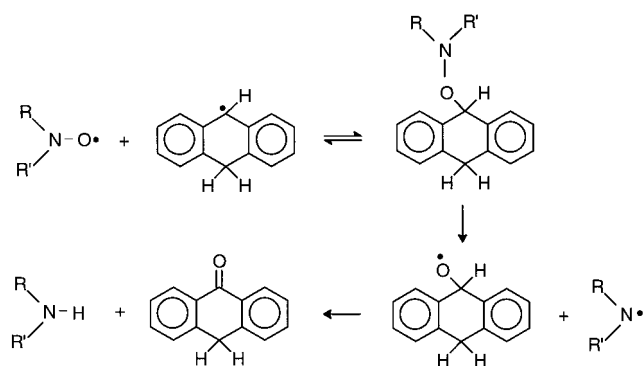
However, anthrone was never found as the reaction product. Besides, due to the low thermal stability of *N*-alkoxyamines (vide supra) other reactions than the carbon–oxygen homolysis may well be excluded.

Rüchardt et al. reported the quantitative reduction of nitrosobenzene to aniline in AnH$_2$ at 483 K.[43] The authors suggested that phenylhydroxyamine is the intermediate (although not identified), generated by hydrogen abstraction from the solvent. Next, a hydrogen from AnH$_2$ is transferred to the phenylhydroxyamine, to give the aminyl radical and water elimination in a novel bimolecular transfer hydrogenolysis. However, it seems unlikely that the phenylhydroxyamine (or the TEMPOH) can be reduced in this way since it requires the addition of a hydrogen atom to a quite unreactive oxygen site. Consequently this reaction will be very slow, if it takes place at all.

Our rationale for the reduction mechanism involves an ionic pathway. First, a hydrogen atom is transferred from the solvent to TEMPO, second TEMPOH is converted by an acid-catalyzed reaction, and after water elimination, the nitrenium ion abstracts a hydride from AnH$_2$ (see Scheme 3) to give TEMPH. A similar deoxygenation mechanism has been suggested for the acid treatment of the hydroxyamine derived from indoline-1-oxyl.[44] The applied solvents are good hydrogen atom and hydride ion donors as has been reported before.[45] The proton is recycled in the rapid conversion of the anthracenylic cation into anthracene. This mechanism is corroborated by the observations that addition

Scheme 3

of benzoic acid increases the rate of conversion of TEMPOH into TEMPH in hydrogen-donor solvents.

Assuming that the hydrogen abstraction by TEMPO from the donor solvent is the rate-determining step, then the differences in the rates of conversion (see Table 3) should correlate with carbon–hydrogen bond dissociation enthalpies in AnH$_2$, PhenH$_2$, and 1,4-cyclohexadiene. Our results showed that this is not the case.[46] The hydrogen abstraction reactions by another nitroxide, (CF$_3$)$_2$NO$^\bullet$, with a variety of hydrogen donors have been studied previously.[48] It has been found that overall kinetic parameters display an unusual pattern: low-frequency factors (around log A/M^{-1} s$^{-1} = 5$) and activation enthalpies unrelated to the reaction enthalpies. Analogous to the encounter of TEMPO with radicals, the hydrogen-transfer reaction may well proceed through a preequilibrium involving an intermediate complex. However, a detailed kinetic study is required to unravel the ultimate mechanism(s).

Conclusions

A simple relation holds between the BDE(C–O) for *N*-alkoxyamines and the BDE(C–H) for the parent hydrocarbons. Large deviations were found for carbon-centered radicals with heteroelements in the α-position, caused by an anomeric effect.

Due to the high reactivity of TEMPO toward hydrogen donors and taking into consideration the large number of abstractable hydrogens in free radical polymerization systems, the consumption of TEMPO is most likely and, consequently, a source of increasing polydispersity.
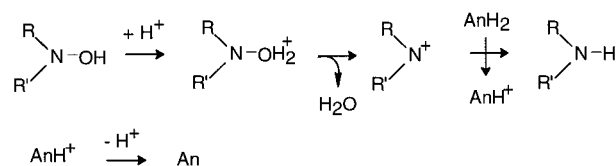
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(43) Rüchardt, C.; Gerst, M.; Ebenhoch, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1406–1430.
(44) Greci, L. *Tetrahedron* **1983**, *39*, 667–681.
(45) Dorrestijn, E.; Kranenburg, M.; Ciriano, M. V.; Mulder, P. *J. Org. Chem.* **1999**, *64*, 3012–3018.

(46) Rate constants for hydrogen abstraction, k_{abs}, by TEMPO from polysubstituted methylbenzenes have been determined by ESR.[47] At 408 K, with *p*-xylene, $k_{abst} = 0.94 \times 10^{-6}$ M^{-1} s^{-1}. For ethylbenzene (see Table 3) at 432 K, $k_{abst} = 1.8 \times 10^{-5}$ M^{-1} s^{-1}. On a per hydrogen basis the rate constant ratio is 60, which cannot be explained by the difference in reaction temperature or an expected small difference in reaction enthalpy.
(47) Opeida, I. A.; Matvienko, A. G.; Ostrovskaya, O. Z. *Kinet. Catal.* **1995**, *36*, 441.
(48) Ingold, K. U.; Doba, T. *J. Am. Chem. Soc.* **1984**, *106*, 3958–3963.