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Catalytic Chain-Breaking Pyridinol Antioxidants

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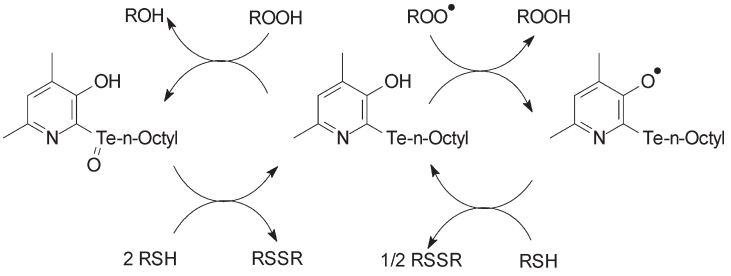

The synthesis of 3-pyridinols carrying alkyltelluro, alkylseleno, and alkylthio groups is described together with a detailed kinetic, thermodynamic, and mechanistic study of their antioxidant activity. When assayed for their capacity to inhibit azo-initiated peroxidation of linoleic acid in a water/chlorobenzene two-phase system, tellurium-containing 3-pyridinols were readily regenerable by *N*-acetylcysteine contained in the aqueous phase. The best inhibitors quenched peroxyl radicals more efficiently than α-tocopherol, and the duration of inhibition was limited only by the availability of the thiol reducing agent. In homogeneous phase, inhibition of styrene autoxidation absolute rate constants k_{inh} for quenching of peroxyl radical were as large as 1×10^7 M^{-1} s^{-1}, thus outperforming the best phenolic antioxidants including α-tocopherol. Tellurium-containing 3-pyridinols could be quantitatively regenerated in homogeneous phase by *N*-*tert*-butoxycarbonyl cysteine methyl ester, a lipid-soluble analogue of *N*-acetylcysteine. In the presence of an excess of the thiol, a catalytic mode of action was observed, similar to the one in the two-phase system. Overall, compounds bearing the alkyltelluro moiety *ortho* to the OH group were much more effective antioxidants than the corresponding *para* isomers. The origin of the high reactivity of these compounds was explored using pulse-radiolysis thermodynamic measurements, and a mechanism for their unusual antioxidant activity was proposed. The tellurium-containing 3-pyridinols were also found to catalyze reduction of hydrogen peroxide in the presence of thiol reducing agents, thereby acting as multifunctional (preventive and chain-breaking) catalytic antioxidants.

Introduction

The majority of chain-breaking antioxidants, both in Nature[1] and in man-made materials,[2] are phenolic. The antioxidant activity of these compounds stems from their ability to transfer the phenolic hydrogen to lipidperoxyl radicals much faster than the chain-propagating H-atom transfer step of lipid peroxidation. It is well-known that electron-donating *ortho* and *para* substituents in the phenolic moiety weaken the O−H bond[3] and thus increase the rate of

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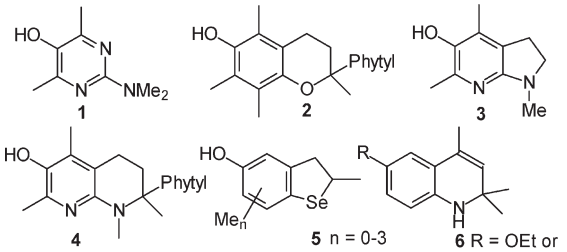
hydrogen atom transfer. However, improving the antioxidant activity of phenolic compounds along these lines will be successful only until the ionization potential of the compounds (which is also decreased by introduction of electron-donating groups) becomes so low[4] that the material will be consumed in a spontaneous electron-transfer reaction with molecular oxygen. Recently, by incorporating one or two nitrogens into the hydroxyaromatic ring, the groups of Pratt and Valgimigli found a way to circumvent the problem with the low ionization potential. Thus, whereas the O−H bond dissociation enthalpies (BDEs) of substituted 5-pyrimidinols and 3-pyridinols differed only marginally from those of the corresponding phenols, the ionization potentials were substantially higher. The O−H bond of 5-pyrimidinol **1** (78.2 kcal mol^{-1}) has almost the same strength as that of α-tocopherol (**2**; 78.3 kcal mol^{-1}), but the calculated ionization potential is 7.7 kcal mol^{-1} higher (167.0 kcal mol^{-1}).[5] Furthermore, as judged by the capacity to inhibit autoxidation of styrene, pyrimidinol **1** (k_{inh} = 8.6 × 10^6 M^{-1} s^{-1}) transfers its phenolic hydrogen atom to peroxyl radicals almost three times as fast as α-tocopherol (k_{inh} = 3.2 × 10^6 M^{-1} s^{-1}).[4] It has been hypothesized that this rate enhancement is due to polar effects in the transition state of the atom-transfer reaction.[6] Incorporation of an electron-donating amino substituent *para* to the hydroxyl group in the 3-pyridinol scaffold in a fused five-membered ring (compound **3**) resulted in the most effective phenolic chain-breaking antioxidant reported to date. Its ionization potential is 7.0 kcal mol^{-1} lower than calculated for α-tocopherol, and therefore it slowly decomposes when exposed to atmospheric oxygen. As a result of the 2.8 kcal mol^{-1} weaker O−H BDE of compound **3** compared to that of α-tocopherol, the reactivity toward peroxyl radicals is an impressive 88-fold higher (k_{inh} = 280 × 10^6 M^{-1} s^{-1}).[7,8] The synthesis and antioxidative properties of more vitamin E-like derivatives of this kind,[9] such as the naphthyridinol **4**, have recently been described.[10]



α-Tocopherol, the most reactive component of vitamin E, is known to trap two peroxyl radicals before it is converted into nonradical products. Nature has therefore arranged for its regeneration to allow for a catalytic mode of action of the antioxidant. In biological membranes this process is thought to occur by donation of a hydrogen atom from ascorbate ($AscH^-$) to the α-tocopheroxyl radical at the lipid−aqueous interphase (eq 1).[11−14]

$$\alpha\text{-TO}^{\bullet} + \text{AscH}^- \rightarrow \alpha\text{-TOH} + \text{Asc}^{\bullet -} \quad (1)$$

The tripeptide glutathione (GSH) is present in much higher concentrations than ascorbate in human plasma. It is known to act as a biological antioxidant and reducing agent both by one-electron (hydrogen atom) and two-electron (e.g., as a cofactor for the glutathione peroxidase enzymes) chemistry. However, early studies by Barclay[15] showed that GSH is incapable of regenerating α-tocopherol from the α-tocopheroxyl radical in simple model systems. In our search for other chain-breaking antioxidants that could perform in a catalytic fashion in the presence of thiols, we recently found that 2,3-dihydrobenzo[*b*]selenophene-5-ols **5**[16] and ethoxyquins **6**[17] were regenerable by *N*-acetylcysteine when assayed for their capacity to inhibit azo-initiated peroxidation of linoleic acid in a two-phase system. Considering that none of these antioxidants quenched peroxyl radicals as efficiently as α-tocopherol, we thought it would be interesting to try to modify the efficient pyridinol antioxidants in such a way that they could also act in a catalytic fashion in the presence of stoichiometric amounts of a thiol reducing agent. In this paper we report on the synthesis of 3-pyridinols carrying organosulfur organoselenium, and organotellurium substituents. Their inhibition of autoxidation in a two-phase system and in a purely lipid environment is described, and a mechanism is proposed for the observed catalytic mode of action.[18]

Results and Discussion

Synthesis. For introduction of chalcogens into the 3-pyridinol scaffold, it was thought that halogenated derivatives, which are commercially available with some variety, could serve as suitable starting materials. On treatment with 3 equiv of *t*-BuLi in dry THF at −78 °C, 6-bromo-3-pyridinol produced a solution of the corresponding 6,*O*-dilithiated species (Scheme 1). For preparation of the octyltelluro derivative **7a**, it was found most convenient to add finely ground elemental tellurium to the organolithium and then allow the insertion product to air-oxidize to the corresponding ditelluride. Subsequent borohydride reduction of crude ditelluride and alkylation with octyl bromide afforded compound **7a** in 66% overall yield. Selenide **7b** and sulfide **7c**

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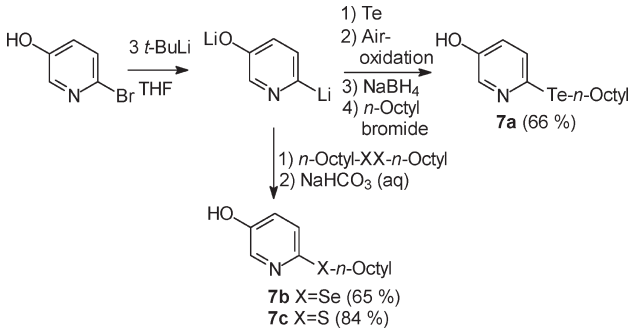
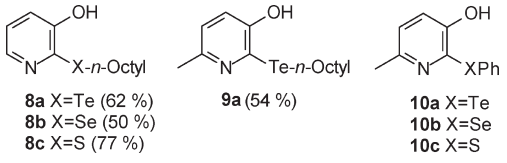
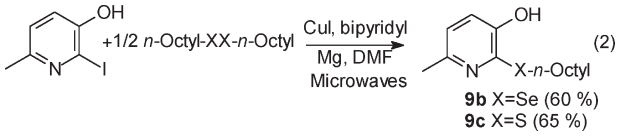
SCHEME 1. Organolithium Approach to Compounds 7



were prepared in 65% and 84% yields, respectively, by treatment of the organolithium with readily available dioctyl diselenide and dioctyl disulfide. Compounds **8a**−**8c** were analogously prepared from 2-bromo-3-pyridinol and telluride **9a** from 2-iodo-6-methyl-3-pyridinol.

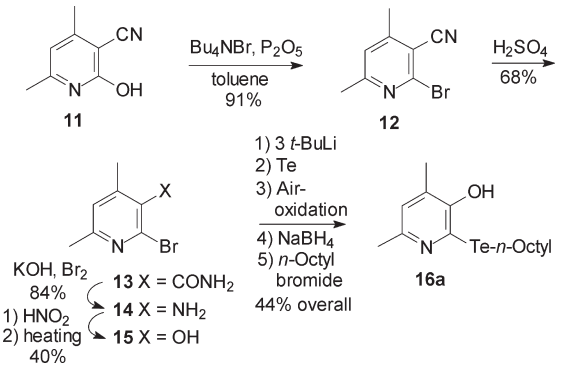


Selenide **9b** and sulfide **9c** were conveniently prepared by using a microwave-induced, copper-catalyzed coupling of aryl halides with diselenides and disulfides we developed some time ago (eq 2).[19]

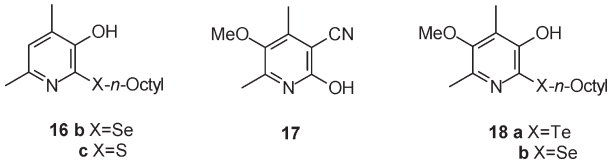


Compounds **10a**−**c** carrying an arylchalcogeno group next to the hydroxyl were all described in our report on the coupling reaction.[19] Introduction of additional methyl groups into the 3-pyridinol scaffold was more demanding from a synthetic point of view. It occurred to us that a cyano group in the 3-position of the pyridine could serve as a source of a pyridinol via a short series of transformations involving hydrolysis to an amide, Hofmann rearrangement, and diazotization/aromatic nucleophilic substitution. Shown in Scheme 2 is the preparation of a 2,6-dimethylated derivative **16a** from the commercially available 3-cyano-2-pyridinol **11**. 2-Pyridinol to 2-bromopyridine conversion was induced in high yield by P_2O_5 and tetrabutylammonium bromide in refluxing toluene.[20] Hydrolysis of nitrile **12** in concentrated sulfuric acid provided the corresponding amide **13** in 68% yield. Hofmann rearrangement was induced in 84% yield by treatment with bromine in an alkaline solution, and the resulting amine **14** was diazotized in water to provide 3-pyridinol **15** in a modest yield (40%). Then, by using the methodologies outlined in Scheme 1, octyltelluro (**16a** 44% yield), octylseleno (**16b**, 60%), and octylthio groups (**16c**, 35%) were introduced into the 2-position. In an attempt to increase the electron density on tellurium by introduction of

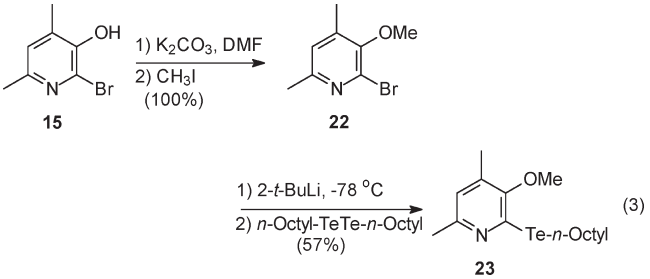
SCHEME 2. Preparation of Compound 16a



a *p*-methoxy group, 3-cyano-5-methoxy-4,6-dimethyl-2-pyridinol (**17**; which is present as the 2-pyridone tautomer) was prepared by cyclocondensation of 3-methoxypentane-2,4-dione with 2-cyanoacetamide[21] and taken through the steps described in Scheme 2 to provide telluride **18a**.



Yield-wise the two syntheses did not differ very much. However, it was noted that compound **18a** had a tendency to decompose more readily than compound **16a** during handling, purification, and storage. Selenide **18b** was prepared in 64% yield from the corresponding 2-bromopyridine in analogy with the procedure for compound **7b** (Scheme 1). To find the optimal positioning of the chalcogen moiety (*ortho* or *para* with respect to the pyridinol), compounds **21a**−**c** were prepared as outlined in Scheme 3. 3-Aminopyridine **19** was an intermediate in the conversion of nitrile **17** to compounds **18**. Diazotization and hypophosphorous acid reduction (37%) followed by boron tribromide induced *O*-demethylation (78%) afforded bromopyridinol **20**, which was converted into telluride **21a** and selenide **21b** using lithiation methodology. As a control for the mechanistic studies, we wanted access to a chalcogen-containing pyridine that could no longer act as a hydrogen atom donor. Bromopyridinol **15** was therefore first *O*-methylated with methyl iodide and the octyltelluro group installed following lithiation and reaction with dioctyl ditelluride (eq 3, compound **23**).



To study the antioxidative capacity of telluroxides, some of the tellurium-containing pyridinols (**8a** and **16b**) were

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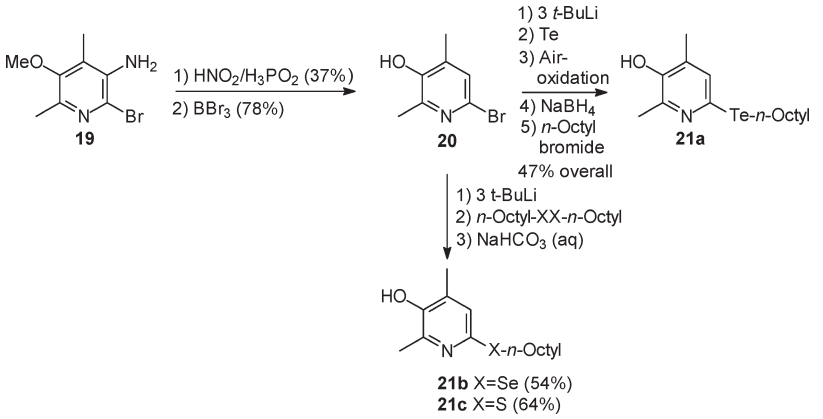
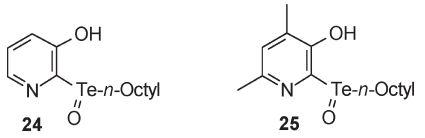
SCHEME 3. Preparation of Compounds 21



treated with a slight excess of *tert*-butyl hydroperoxide in methanol. The polar compounds **24** and **25**, isolated after evaporation of all volatiles under reduced pressure, were difficult to purify and characterize. For example, peaks in the ^{1}H NMR spectrum were extremely broad, which could be indicative of ongoing exchange processes or oligomerization. Mass spectral analysis was also inconclusive. In fact, the strongest indication of the identity of the compounds comes from reduction of the crude telluroxide with sodium disulfite, which always cleanly returned the corresponding alkyl pyridyl telluride.



Inhibition Studies in a Two-Phase System. Azo-initiated peroxidation of linoleic acid or derivatives thereof has frequently been used for antioxidant studies. Some time ago we designed a two-phase variant that allows the study of lipid-soluble antioxidant regeneration by water-soluble co-antioxidants.[22] In the experimental setup (see Supporting Information, Figure S1), linoleic acid and the antioxidant to be evaluated were vigorously stirred in chlorobenzene at 42 °C with an aqueous solution of *N*-acetylcysteine (NAC). 2,2′-Azobis(2,4-dimethylvaleronitrile) (AMVN) was added as an initiator in the organic phase, and the progress of peroxidation was monitored by HPLC by following the conjugated diene hydroperoxide formation. The inhibited rate of peroxidation, R_{inh}, was determined by least-squares methods from absorbance/time plots, while the duration of the inhibited phase, T_{inh}, was determined graphically as the cross-point for the inhibited and the uninhibited lines (see Figure 1). Whether NAC was present in the aqueous phase or not, α-tocopherol, which we used as a control, inhibited peroxidation of linoleic acid for almost the same time as in the lipid phase (Table 1, bottom). Thus, it is essentially not regenerable under the conditions used. The capacity of the chalcogen-containing pyridinol antioxidants to inhibit peroxidation is summarized in Table 1. Since, according to our previous experience, this approach provides the most evident indication of regenerability and catalytic behavior, the two-phase system served to screen all of the compounds and identify the best performing structural architectures, which were subsequently subjected to more detailed kinetic investigation. In the absence of *N*-acetylcysteine, all organotellurium compounds failed to inhibit peroxidation of linoleic acid. This is because organotelluriums are rapidly oxidized by residual linoleic acid hydroperoxide present in commercial samples of the acid, and the resulting telluroxides are poor chain-breaking antioxidants (vide infra). Pyridinols carrying octylseleno substituents often show a longer inhibition time if NAC is present in the aqueous phase (up to a 2-fold increase; compounds **7b**, **8b**, **9b**, **10b**, **16b**, **18b**, **21b**). Thus, they are regenerable to some extent and notably more so than the corresponding organosulfur compounds. However, even if electron-donating substituents are introduced in order to lower the O−H bond dissociation enthalpy, the organoselenium and organosulfur compounds often turn out to be poor quenchers of peroxyl radicals with R_{inh} values in the range of 45−328 μM h^{-1}.

The two 3-pyridinols **7a** and **8a**, carrying octyltelluro groups *para* and *ortho* to the hydroxyl, respectively, inhibited peroxidation with similar rates (32 vs 27 mM h^{-1}), but the former was clearly inferior in terms of inhibition time (70 vs 200 min) in the presence of NAC. Organotellurium catalyst **9a** inhibited peroxidation as efficiently as α-tocopherol with an inhibition time exceeding 360 min. Thus, regenerability was also improved by introduction of the methyl group. Phenyltelluro derivative **10a** performed poorer (T_{inh} = 280 min) than its octyltelluro counterpart in this respect. 4,6-Dimethylated 3-pyridinol derivative **16a**, carrying an octyltelluro group in position 2, quenched peroxyl radicals three times as efficiently as α-tocopherol (R_{inh} = 8 μM h^{-1}) in the presence of *N*-acetylcysteine. Regenerability was also excellent (T_{inh} > 400 min). Again, chain-breaking capacity and regenerability of the corresponding organoselenium and sulfur compounds **16b** and **16c** could not match those of the organotellurium derivative. Organotellurium **18a**, prepared in analogy with **16a**, showed similar antioxidant characteristics and clearly outperformed its selenium analogue **18b**. Compounds **21** are isomeric to compounds **16**, but the organochalcogen and 6-methyl groups were swapped. As noted above with compounds **7a** and **8a**, a close (*ortho*) arrangement of octyltelluro and hydroxyl groups in the

(22) Vessman, K.; Ekström, M.; Berglund, M.; Andersson, C.-M.; Engman, L. *J. Org. Chem.* **1995**, *60*, 4461–4467.

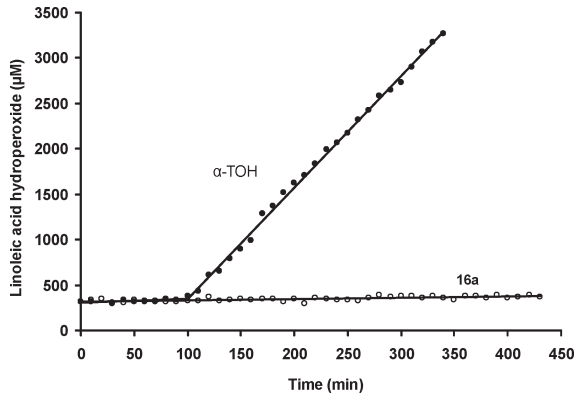


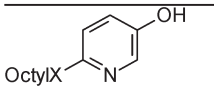
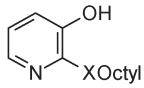
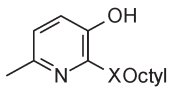
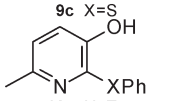
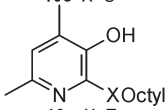
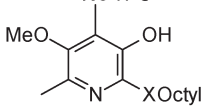
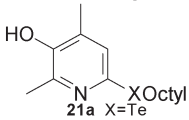
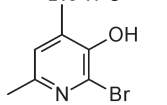
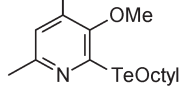
FIGURE 1. Peroxidation traces (linoleic acid hydroperoxide concentration vs time) recorded using compound **16a** (40 μM) or α-TOH (40 μM) as antioxidants in the chlorobenzene layer in the presence of NAC (1 mM) in the aqueous phase.

pyridinol is much preferred over the distant when it comes to regenerability. Bromopyridinol **15**, which was tested as a chalcogen-free reference antioxidant, did not inhibit peroxidation at all under the conditions of the assay. Obviously an octyltelluro group in the *ortho* position has a considerable effect on the reactivity. Compound **23**, the *O*-metylated analogue of our most potent regenerable antioxidant **16a**, showed only a limited inhibiting effect indicating that hydroxylic hydrogen atom transfer to peroxyl radicals is the prevailing antioxidant mechanism. NAC is needed to keep the compound in the reduced divalent state where it may quench peroxyl radicals either by hydrogen atom transfer (HAT) or by electron transfer (ET). Whereas HAT would be impaired by *O*-methylation, ET would still be possible; however, the resulting radical cation does not undergo effective reduction by aqueous thiol.

The peroxidation traces in Figure 1 show that compound **16a** can clearly outperform α-tocopherol when it comes to the duration of the inhibited phase. In fact, the limitation is the availability of the thiol reducing agent, and T_{inh} decreases in a more or less linear fashion to the limiting value under nonregenerating conditions as the NAC concentration is lowered (see Supporting Information, Figure S2). While keeping the concentration of *N*-acetylcysteine constant (1 mM), the concentration of antioxidant **16a** was lowered from the 40 μM used in the standard assay. The inhibition of peroxidation did not change at the 20 μM level, decreased at 10 μM (T_{inh} = 310 min), and could not be observed at the 5 μM level. Sampling of the aqueous (instead of the chlorobenzene) phase at intervals during peroxidation and analysis by reversed phase HPLC showed that the thiol/disulfide ratio decreased linearly with time until complete consumption of *N*-acetylcysteine after ca. 400 min (Figure 2).

Inhibition Studies in Homogeneous Phase. To achieve a deeper insight into the antioxidant behavior of alkyltelluro-substituted 3-pyridinols and into the mechanisms underlying both their surprising reactivity toward peroxyl radicals and their catalytic behavior, we investigated the inhibition of homogeneous-phase autoxidation of styrene in chlorobenzene (or acetonitrile), initiated by thermal decomposition of 2,2′-azobisisobutyronitrile (AIBN) at 303 K. Under such robust and well established conditions described by the usual eqs 4−9,[4] kinetics of oxygen consumption was monitored in a custom-built differential oxygen-uptake apparatus that has been previously described in detail.[23] Compounds **7a**, **8a**, and

TABLE 1. Inhibited Rate of Linoleic Acid Peroxidation (R_{inh}) and Inhibition Times (T_{inh}) for Antioxidants and Reference Compounds Tested in the Two-Phase Model

antioxidant (40 μM)	R_{inh}[a] (μM/h)	T_{inh}[b] (min)	without *N*-acetylcysteine (1 mM) in the aqueous phase: R_{inh}[a] (μM/h)	T_{inh}[b] (min)
				
7a X=Te	32	70	542	0
7b X=Se	163	200	119	100
7c X=S	115	130	121	110
				
8a X=Te	27	200	726	0
8b X=Se	120	150	152	90
8c X=S	203	140	115	120
				
9a X=Te	23	>360	652	0
9b X=Se	65	170	57	80
9c X=S	45	130	68	90
				
10a X=Te	27	280	627	0
10b X=Se	231	170	85	80
10c X=S	328	140	166	110
				
16a X=Te	8 ± 2	>400	600	0
16b X=Se	73	130	58	70
16c X=S	88	70	99	70
				
18a X=Te	8 ± 2	>400	479	0
18b X=Se	45	110	54	60
				
21a X=Te	27	50	490	0
21b X=Se	75	90	78	70
21c X=S	82	70	78	70
				
15	584	0	613	0
				
23	45	60	677	0
α-Tocopherol (**2**)	24 ± 2	90	24 ± 2	80

[a]Rate of peroxidation during the inhibited phase (uninhibited rate ca. 650 μM h^{-1}). Data for potent catalysts are mean ± SD for triplicates. Estimated errors for poorer catalysts are ±20%. [b]Inhibited phase of peroxidation. Reactions were monitored for 400 min. Estimated errors are ±5%.

(23) Amorati, R.; Pedulli, G. F.; Valgimigli, L.; Attanasi, O. A.; Filippone, P.; Fiorucci, C.; Saladino, R. *J. Chem. Soc., Perkin Trans. 2* **2001**, 2142–2146.

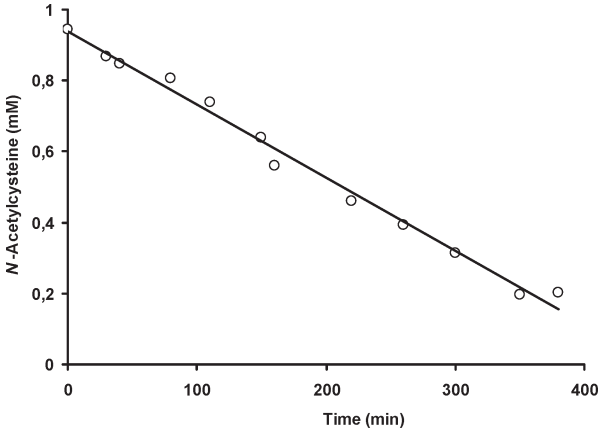


FIGURE 2. Concentration of *N*-acetylcysteine in the aqueous phase with time during a normal peroxidation experiment using antioxidant **16a**.

16a and the telluroxides **24** and **25** were chosen as representative of the structural diversity contained in the type of pyridinols of this study.

$$\text{initiator} \xrightarrow{R_i} R^\bullet \quad (4)$$

$$R^\bullet + O_2 \rightarrow ROO^\bullet \quad (5)$$

$$ROO^\bullet + RH \xrightarrow{k_p} ROOH + R^\bullet \quad (6)$$

$$ROO^\bullet + ROO^\bullet \xrightarrow{2k_t} \text{non-radical products} \quad (7)$$

$$ROO^\bullet + ArOH \xrightarrow{k_{inh}} ROOH + ArO^\bullet \quad (8)$$

$$ROO^\bullet + ArO^\bullet \rightarrow \text{non-radical products} \quad (9)$$

Each of compounds **7a**, **8a**, and **16a** produced a neat inhibited period in the autoxidation of 4.3 M styrene in chlorobenzene from which slope the absolute k_{inh} for reaction with peroxyl radicals was obtained as detailed in Table 2. Both compounds with the octyltelluro moiety *ortho* to the -OH function (**8a** and **16a**) displayed a remarkable antioxidant behavior, being able to quench peroxyl radicals approximately 3 times faster than the reference antioxidant α-tocopherol, confirming and extending our preliminary results. Interestingly, compound **7a**, carrying the octyltelluro moiety *para* to the -OH, resulted in a k_{inh} of "only" $\sim 0.8 \times 10^6$ M^{-1} s^{-1}, i.e., one order of magnitude lower than the value recorded for the isomeric **8a**.

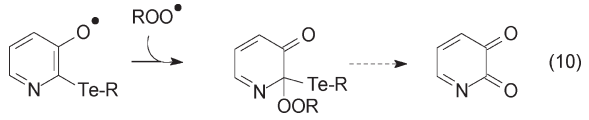
Despite the high efficiency in trapping peroxyl radicals, the stoichiometric factor *n*, i.e. the number of peroxyl radicals trapped by 1 molecule of antioxidant, as observed from the length of the inhibition period, was in the range 0.3−0.5 for the three pyridinols, largely below the ideal value $n = 2$ produced by α-tocopherol and other phenolic antioxidants. This suggests that either the reaction with peroxyl radicals follows a mechanism substantially different from the well-known behavior of conventional phenolic and pyri(mi)dinolic antixidants or the alkyltelluro-pyridinol is rapidly consumed during the course of autoxidation in a side reaction, to produce the corresponding telluroxides unable to inhibit the autoxidation or with limited antioxidant activity.

TABLE 2. Absolute Rate Constants k_{inh} and Stoichiometric Factors *n* for Inhibition of Homogeneous-Phase Autoxidation of 4.3 M Styrene at 303 K by Selected Pyridinols and Reference Compounds[a]

	chlorobenzene		acetonitrile	
	k_{inh} (M^{-1} s^{-1})	*n*	k_{inh} (M^{-1} s^{-1})	*n*
7a	$(7.5 \pm 0.9) \times 10^5$	0.3 ± 0.1	$(1.9 \pm 0.3) \times 10^5$	0.3 ± 0.1
8a	$(1.0 \pm 0.3) \times 10^7$	0.5 ± 0.1	$(2.9 \pm 0.3) \times 10^6$	0.5 ± 0.1
16a	$(9.2 \pm 2.0) \times 10^6$	0.4 ± 0.1		
24	< 100		< 100	
25	< 100		< 100	
26	< 1000[b]			
27	2.2×10^4[b]			
28	2.9×10^5[b]	2.0		
29	1.6×10^7[c]	2.0		
α-TOC	3.2×10^6[d]	2.0	6.5×10^5	2.0

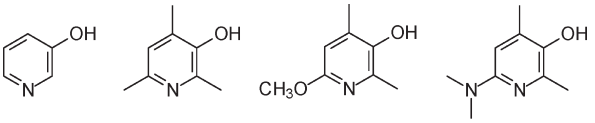
[a]Data are mean ± SD, each measurement in triplicate. [b]Reference value from ref 8. [c]Reference value from ref 7. [d]Reference value from ref 4.

To confirm this last assumption, we investigated the antioxidant capacity of telluroxides **24** and **25**. No inhibition or retardation of styrene autoxidation was observed, allowing us to estimate $k_{inh} < 10^3$ M^{-1} s^{-1} for these compounds. In our preliminary communication, we observed that during inhibition of styrene autoxidation by **16a**, at the end of the inhibited period, the rate of oxygen consumption was still retarded as compared with an uninhibited autoxidation under identical conditions.[18] We tentatively attribute this effect to styryl (alkyl) radical trapping by quinonoid products (eq 10) formed by detelluration of the antioxidant.



(10)

The very high reactivity of compounds **7a**, **8a**, and **16a** was indeed surprising and can be compared to those previously measured for pyridinols **26**−**29**.Telluro-pyridinol **16a** is approximately 400 times more reactive than structurally related compound **27**, carrying a methyl in place of the *o*-octyltelluro group. Since the reactivity of pyridinols toward peroxyl radicals is dictated by the capacity of substituents to lower the BDE_{OH},[5,7] the high reactivity of alkyltelluro-pyridinols would imply either that they react by a conceptually different mechanism related to the presence of the chalcogen (e.g., by electron transfer from tellurium lone pairs to peroxyl radical) or that the alkyltelluro group has a strong electron-donating character, lowering the BDE_{OH}.



26 **27** **28** **29**

The drop in reactivity observed for all investigated compounds on changing the solvent from apolar chlorobenzene to polar and H-bonding acetonitrile (Table 2) is exactly what was expected for regular phenolic or pyridinolic compounds reacting by HAT or proton coupled electron transfer (PCET) to the peroxyl radicals.[24]

(24) Valgimigli, L.; Banks, J. T.; Lusztyk, J.; Ingold, K. U. *J. Org. Chem.* **1999**, *64*, 3381–3383.

Thermodynamic Properties. The scarce data on the electronic properties of alkyltelluride substituents prompted us to measure the BDE_{OH} of compounds **7a** and **8a** in comparison with unsubstituted 3-pyridinol **26**. Unfortunately, the telluro-pyridinols were unstable to UV irradiation, and the low persistency of the corresponding 3-pyridinoxyl radicals prevented the use of the radical equilibration EPR-approach.[6] We therefore turned to electrochemical cycles in water. According to this approach the BDE_{OH} (kJ/mol) is obtained from eq 11, where $E°$ is the standard reduction potential of the pyridinoxyl radical, pK_a is the O−H pK_a of the pyridinol, and C is a constant that depends on the family of compounds and the solvent, accounting for the entropy and solvation terms.

$$BDE_{OH} = 96.48\,E° + 5.70\,pK_a + C \qquad (11)$$

In this work, the standard reduction potentials of the anions from **7a**−**c** and **8a**−**c** were measured in water by pulse radiolysis from equilibration with a reference reductant (4-iodophenol $E° = 0.82$ V vs NHE and phenol $E° = 0.79$ V vs NHE) at pH 12 (where the compound is mostly in its dissociated form), and the constant C previously found for phenols (232 kJ/mol)[25] was used. Results reported in Table 3 show that the *para* alkyltelluro group has a strong electron-donating character, inducing a BDE_{OH} lowering in water (−6.6 kcal mol^{-1}) higher than that of *para* MeO (−5.6 kcal mol^{-1} in water[3a]), but lower than Me_2N- (−14.0 kcal mol^{-1} in water[3a]). These measurements provide a satisfying explanation for the reactivity of compound **7a**. However, they do not explain the much higher reactivity of the isomeric **8a** (not significantly different in reactivity than **16a**). Indeed the BDE_{OH} values for *ortho* (**8a**) and *para* (**7a**) alkyltellurium pyridinols were almost identical.

It can be noticed that while in water at pH 12 the standard potentials of all investigated compounds (in their dissociated form) are approximately the same, in acetonitrile the ease of oxidation of the parent chalcogen-containing pyridinols follows the trend Te > Se > S. This indicates that the *ortho* and *para* alkyl-chalcogenide substituent effects are virtually identical with respect to the redox properties of dissociated pyridinols. However, for the nondissociated pyridinols, the chalcogen-dependent trend indicates that the chalcogen is directly involved in the redox process rather than just being a remote substituent.

Catalytic Activity in Homogenous Phase. In our preliminary report[18] we indicated that addition of 1−2 equiv of alkylmercaptans to the autoxidation of styrene (at 303 K in chlorobenzene) inhibited by **16a** had little effect on the length of the inhibition period. In contrast, an inhibition period corresponding to $n = 2$ was observed by adding to **16a** *N*-*tert*-butoxycarbonyl cysteine methyl ester (LipCys), a lipid-soluble analogue of *N*-acetylcysteine. We attributed this to complete suppression of oxidation at tellurium and partial regeneration of the pyridinol from the corresponding aryloxyl radical; in other words, we attributed it to catalytic antioxidant activity of **16a** even in homogeneous solution. As depicted in Figure 3, the inhibition time τ for compound **16a** could be extended well beyond the value corresponding to $n = 2$ recorded for α-tocopherol simply by adding increasing amounts of LipCys. The lengths of τ varied linearly with the concentration of LipCys (Figure 3B) as observed previously in our two-phase system, and the limiting factor for the duration of inhibition was the availability of thiol. However, in order to discriminate the antioxidant effect of **16a** from that of LipCys itself, we could not increase the amount of thiol much more. Conversely, in the presence of LipCys, τ was almost independent of the initial concentration of **16a** (see Supporting Information, Figure S3), confirming a true catalytic behavior of **16a**.

TABLE 3. Thermodynamic Data for Selected Pyridinols from Pulse Radiolysis Equilibration Measurements in Water at pH 12 ($E°$) and Cyclic Voltammetry in Acetonitrile (E_p) at 298 K

compound	pK_a[a]	$E°$ [V] vs NHE	BDE_{OH} [kJ/mol]	E_p [V] vs NHE
7a	9.1	0.80	361	1.05
7b	8.8	0.81	360	1.31
7c	8.7	0.79	358	1.40
8a	9.3	0.78	360	1.05
8b	9.0	0.82	362	1.25
8c	9.7	0.80	364	1.32
26	9.1	1.06[b]	386	1.58

[a]Acidity of the OH group in water. The pK_a values for protonation of the pyridine ring are as follows: **7a**, 2.6; **7b**, 2.5; **7c**, 2.6; **8a**, 3.0; **8b**, 2.5; **8c**, ≤2; **26**, 5.3. [b]Reference value from ref 26.

While the inhibition time for α-tocopherol was unaffected by addition of LipCys within experimental error,[18] also the simpler pyridinol **8a**, carrying the octyltelluro moiety in the *ortho* position, could be effectively regenerated by the thiol, as judged from the extension of τ. Again, τ was proportional to the initial concentration of LipCys (Figure 4) and there was no apparent upper limit, provided a sufficient amount of LipCys was added to the system. Interestingly, its corresponding telluroxide **24**, which was unable to inhibit styrene autoxidation in the absence of thiol, showed almost identical inhibition characteristics as **8a** in the presence of LipCys (Figure 4), clearly suggesting that the role of the thiol includes reduction of telluroxide to the parent telluride. Conversely, only modest catalytic behavior was observed for the *para* isomer **7a** and significantly larger amounts of LipCys were needed to extend its inhibition time up to the value corresponding to $n = 2$. Qualitatively, the behavior in homogeneous chlorobenzene solution paralleled our experience in the two-phase system.

To further test the ability of octyltelluro-pyridinols and their corresponding oxides to act in a catalytic fashion and to be fully regenerated by LipCys, we performed a series of styrene autoxidations inhibited initially only by the organotelluriums, followed by the injection of LipCys in the autoxidating mixture after the end of inhibition, i.e., when the pyridinol antioxidant had already been consumed and the autoxidation was running uninhibited. As exemplified in Figure 5, any of the three pyridinols was fully regenerated by LipCys and the pyridinol acted in catalytic fashion, exactly as it would have done by adding the thiol at the beginning of the autoxidation experiment. By this approach, with compounds **8a** and **16a**, it was possible to extend indefinitely the inhibition time, simply by adding aliquots of LypCys at regular time intervals (see Supporting Information, Figure S4). The catalytic efficiency of the tellurium-containing pyridinols, n(SH), can be expressed as the number of radical chains interrupted by each molecule of thiol, given by eq 12, where τ is the length of the inhibition period after subtracting

(25) Malmström, J.; Jonsson, M.; Cotgreave, I. A.; Hammarström, L.; Sjödin, M.; Engman, L. *J. Am. Chem. Soc.* **2001**, *123*, 3434–3440.

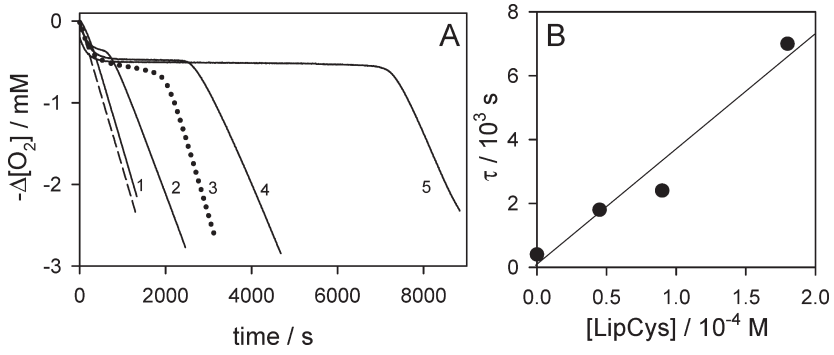


FIGURE 3. (A) Typical oxygen uptake kinetic traces during homogeneous phase autoxidation of styrene (4.3 M) in chlorobenzene, initiated by AIBN (0.05 M) at 303 K, in the absence of inhibitors (slashed line) and inhibited by (1) *N-tert*-butoxycarbonyl cysteine methyl ester (LipCys) 9.0×10^{-5}M; (2) **16a** 1.3×10^{-5} M; (3) α-TOH 6.3×10^{-6} M; (4) **16a** 6.3×10^{-6} M + LipCys 9.0×10^{-5} M; (5) **16a** 6.3×10^{-6} M + LipCys 1.8×10^{-4}M. (B) Inhibition times τ obtained with **16a** 6.3×10^{-6} M, as a function of the initial concentration of LipCys.

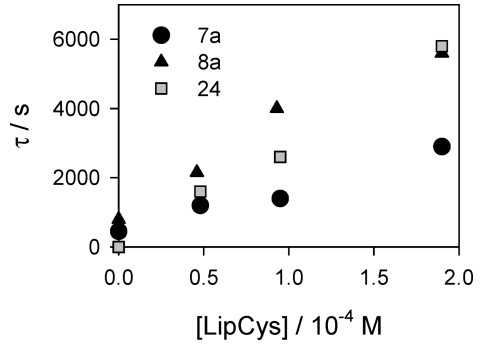


FIGURE 4. Length of the inhibited period observed during styrene autoxidation in the presence of organotelluriums **7a**, **8a**, and **24** (6.3×10^{-6} M) with increasing amounts of *N-tert*-butoxycarbonyl cysteine methyl ester (LipCys).

the intrinsic τ of the pyridinol alone, and R_i is the initiation rate, measured as reported in the experimental section (8.9×10^{-9} M s^{-1}). The values of n(SH) recorded in homogeneous phase were 0.11 ± 0.03, 0.25 ± 0.08, 0.26 ± 0.06, 0.27 ± 0.07, and 0.37 ± 0.03 for compounds **7a**, **8a**, **16a**, **24**, and **25**, respectively. Efficiencies lower than unity clearly indicate that a fraction of the thiol is consumed in reactions not leading to chain termination.

$$n(\mathrm{SH}) = (R_i\tau)/[\mathrm{SH}] \qquad (12)$$

For comparison, the catalytic efficiency in the two-phase system can be calculated by comparing the inhibition time recorded with α-tocopherol (T_{inh} = 80 min at 40 μM and known to quench two peroxyl radicals) with those using octyltelluro-pyridinols in the presence of 1 mM NAC. By using T_{inh} = 420 min for compound **16a**, one could calculate the catalytic efficiency as 0.42, which is just slightly higher than that recorded under homogeneous phase conditions. This specific aspect would be of relevance not only to understand the mechanism of regeneration but also to balance the antioxidant versus pro-oxidant (thiol depletion) behavior in biological systems.

Catalytic Decomposition of Hydroperoxides. From our inhibition studies in homogeneous phase and in the two-phase system it is clear that pyridinols carrying alkyltelluro groups are readily oxidized to the corresponding telluroxides

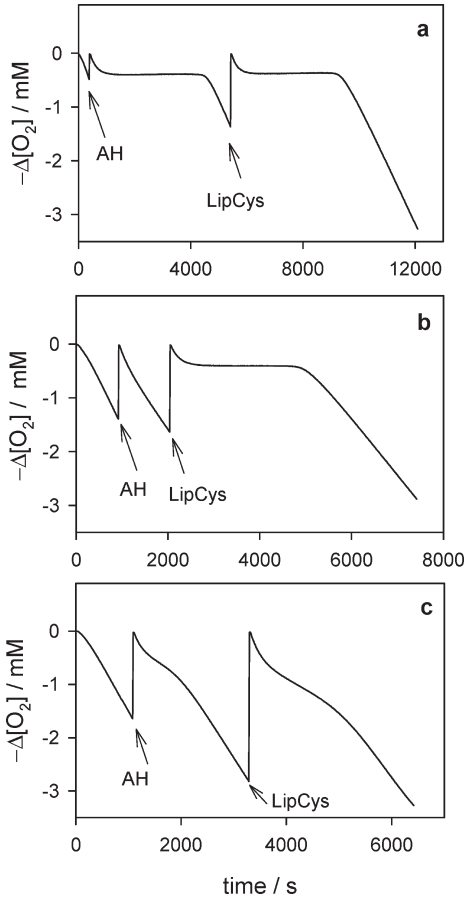


FIGURE 5. Oxygen consumption recorded during the autoxidation of styrene without inhibitors and after the injection of the organotellurium pyridinols (AH, 1.0×10^{-4} M, first arrow), followed by the injection of LipCys (9.5×10^{-5} M, second arrow). The pyridinols were **8a** (a), **24** (b), and **7a** (c).

and these species are readily reduced by thiol to regenerate the parent telluride. This facile redox cycling allows for their use as peroxide decomposers. In fact, they mimic the action of the selenium-containing glutathione peroxidase enzymes (GPx). To compare the efficiency of this catalysis, we measured the initial rate of reduction of hydrogen peroxide (v_0) by monitoring the formation of diphenyl disulfide from thiophenol by UV spectroscopy at 305 nm as described

(26) Das, T. N.; Neta, P. *J. Phys. Chem. A* **1998**, *102*, 7081–7085.

TABLE 4. Thiol Peroxidase Activity of Tellurium-Containing 3-Pyridinols

antioxidant	thiol peroxidase activity[a] (μM min^{-1})
7a	4.8 ± 1.1
8a	7.8 ± 1.0
9a	6.5 ± 0.5
10a	1.5 ± 0.1
16a	15.4 ± 2.2
18a	17.8 ± 3.0
21a	9.8 ± 1.8
diphenyl diselenide (PhSeSePh)	0.7 ± 0.2

[a]Initial rate of hydrogen peroxide reduction in the presence of thiophenol and antioxidant. Data are mean ± SD for triplicates.

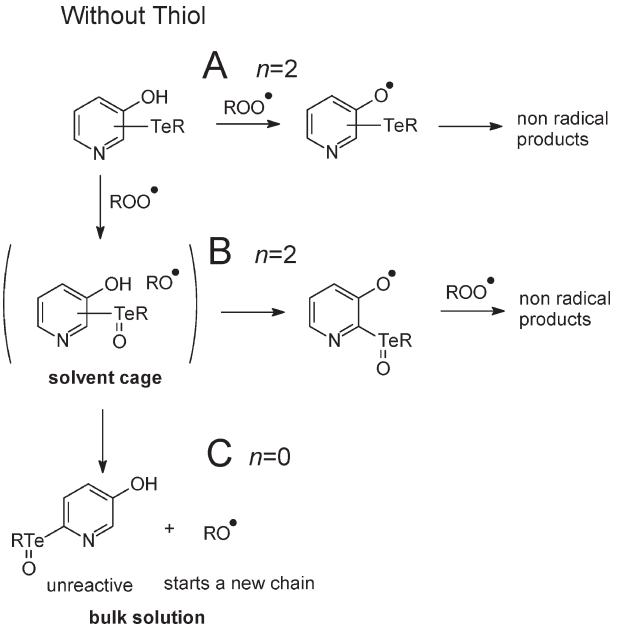
by Tomoda.[27] Initial rates recorded for the reduction of hydrogen peroxide (3.75 mM) in methanol by thiophenol (1 mM) in the presence of several organotellurium compounds (0.01 mM) as recorded by UV spectroscopy at 305 nm are shown in Table 4. For comparison, the thiol peroxidase activity of diphenyl diselenide under these conditions was only 0.67 μM min^{-1}. Reduction of hydrogen peroxide (or alkyl-hyroperoxides) involves, in the rate-determining step, nucleophilic attack of tellurium on oxygen.[28] Both electronic and steric effects are therefore expected to influence the catalytic performance. Considering that all compounds in Table 2 contain an electron-withdrawing pyridyl group, it is not surprising that the observed thiol peroxidase activities cannot match those recorded with the most efficient organotellurium catalysts studied in this system (a value of 199 μM min^{-1} was recorded for the alkyl 4-aminophenyl telluride obtained by replacing oxygen for tellurium in ethoxyquin).[17]

The most active pyridinol compound **18**, carrying a methoxy group *para* to tellurium, was roughly an order of magnitude less active than this compound. However, it is noteworthy that all tellurium compounds investigated showed a thiol peroxidase activity higher than that recorded for diphenyl diselenide, which has often been used as a standard in measurements of this kind.

Mechanistic Considerations. Pyridinols have been shown to express their chain-breaking antioxidant activity following the well-known mechanism of quenching chain-carrying peroxyl radicals by HAT or PCET to yield a phenoxyl radical that would quickly trap a second peroxyl radical, thereby breaking two oxidation chains (eqs 8 and 9). The rate-determining inhibition (eq 8) is characterized by a rate constant k_{inh} that would depend on the BDE of the O−H moiety and would be decreased by inter- and intramolecular H-bonding to any hydrogen bond acceptor. However, our kinetic measurements indicated that pyridinols bearing the alkyltelluro substituent *ortho* to the OH are largely more reactive than their *para* isomers, despite the identical value of BDE_{OH} (in water).

Interestingly, they were also more regenerable by NAC in the two-phase system or by LipCys in chlorobenzene. Mechanisms leading to regeneration of the parent antioxidant by a co-antioxidant have been rationalized for phenols, both in organic solution[29] and in heterogeneous aqueous environments.[13,14] Coherently, we suggested it to occur either by HAT from the thiol to the pyridinoxyl radical (in chlorobenzene) or via electron transfer from thiol to phenoxyl radical at or near the aqueous-lipid interphase, accompanied by transfer of a proton to produce disulfide. However, no higher efficiency would be justified for *ortho* versus *para* tellurides: clearly both the antioxidant and the co-antioxidant activities of these compounds must involve a distinct mechanism for *ortho* tellurides that is not accessible to the *para* isomers.

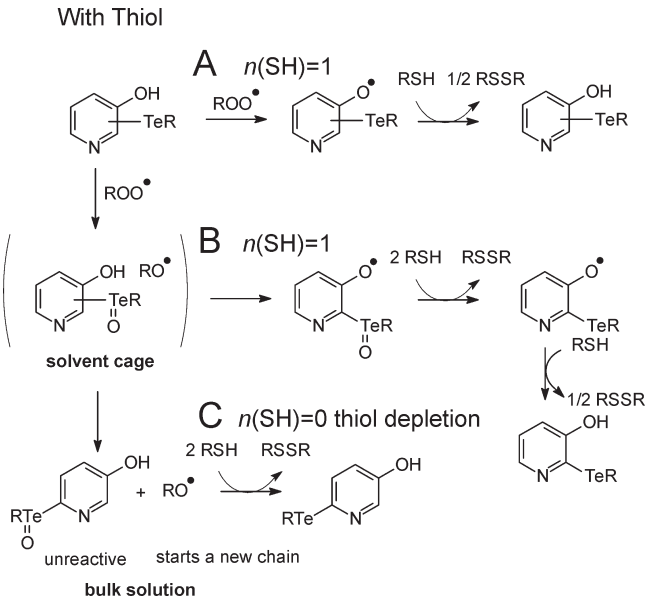
SCHEME 4. Reactions Involved in the Antioxidant Behaviour of Alkyltelluro-pyridinols in the Absence of NAC, LipCys, or Other Thiol Co-antioxidants



Our studies with telluroxides suggested that they form during the inhibited phase of peroxidation both in homogeneous phase and in the two-phase system and that they are effectively reduced to the corresponding tellurides by thiols present in the systems. Regarding their formation, we suggest it to occur by two distinct pathways: oxidation by hydroperoxides present in the oxidizable substrate already at the beginning of autoxidation and oxygen atom transfer from chain-carrying peroxyl radical during the inhibited time of the autoxidation (Scheme 4). The former reaction is mainly responsible for the negligible inhibition time observed in hydroperoxide-rich substrates such as linoleic acid (vide supra); however, it is also the basis for an additional mode of antioxidant behavior: the preventive, GPx-like activity. The second pathway, oxygen atom transfer from peroxyl radicals, could in fact provide an explanation for the unusually high antioxidant activity of pyridinols carrying an alkyltelluro group in the *ortho* position. Oxygen transfer from peroxyl radicals to tellurides is a fast reaction known to proceed with a rate constant as large as 10^8 M^{-1} s^{-1} with diphenyltelluride.[30] We suggest that this reaction competes

(27) Iwaoka, M.; Tomoda, S. *J. Am. Chem. Soc.* **1994**, *116*, 2557–2561.
(28) Engman, L.; Stern, D.; Pelcman, M. *J. Org. Chem.* **1994**, *59*, 1973–1979.
(29) (a) Amorati, R.; Ferroni, F.; Lucarini, M.; Pedulli, G. F.; Valgimigli, L. *J. Org. Chem.* **2002**, *67*, 9295–9303. (b) Amorati, R.; Ferroni, F.; Pedulli, G. F; Valgimigli, L. *J. Org. Chem.* **2003**, *68*, 9654–9658.
(30) Engman, L.; Persson, J.; Merenyi, G.; Lind, J. *Organometallics* **1995**, *14*, 3641–3648.

SCHEME 5. Reactions Involved in the Antioxidant Behaviour of Alkyltelluro-pyridinols in the Presence of NAC or LipCys as Co-antioxidants



with hydrogen atom transfer from the pyridinol to peroxyl radicals and might actually be the key difference between pyridinols carrying the alkyltelluro group *ortho* and *para* to the OH as illustrated in Schemes 4 and 5. In the presence of LipCys, phenoxyl radicals and telluroxides are reduced to the parent phenols and tellurides respsctively (Scheme 5).

Whereas path A in Schemes 4 and 5 describes the usual mechanism for the antioxidant activity of phenol-like compounds (including pyridinols), path B (in competition with path C) would be available only for pyridinols carrying an *o*-alkyltelluro group. Oxidation of Te to Te=O would increase the BDE_{OH} by about 10 kcal mol^{-1},[31] significantly reducing the reactivity of the pyridinol; however, the peroxyl radical would be turned into a much more reactive alkoxyl radical ($BDE_{ROO\text{-}H}$ ~88 kcal mol^{-1} vs $BDE_{RO\text{-}H}$ ~105 kcal mol^{-1}), able to abstract the phenolic H-atom in the solvent cage. Escape of the alkoxyl radical into the bulk solution (path C) would however start a new oxidative chain, thereby reducing the stoichiometric factor in the absence of thiol co-antioxidant (Scheme 4) or decreasing the catalytic efficiency in the presence of the thiol (Scheme 5). The observed stoichiometric factors n of 0.3−0.5 for the investigated pyridinols and their catalytic efficiency n(SH) of 0.2−0.4 is indicative of the relative relevance of path C.

As indicated, path B would not be available for *p*-alkyltelluro-pyridinols, which would react by a combination of path A (effective antioxidant behavior) and path C (unproductive consumption of antioxidant and co-antioxidant).

Conclusion

The above results demonstrate that 3-pyridinols suitably substituted with organyltelluro groups can act as catalysts not only for the reduction of peroxyl radicals (chain-breaking antioxidant activity) but also for decomposition of hydroperoxides (preventive antioxidant activity) in the presence of stoichiometric amounts of thiol reducing agents. Regarding their reaction with peroxyl radicals, compounds carrying the organyltelluro group *ortho* to the hydroxyl show a significantly higher reactivity than expected on the basis of the usual mechanism involved in peroxyl-radical quenching by phenols or pyridinols. This has been explained by a novel peculiar mechanism that deserves further investigation. At present, the catalytic efficiency in terms of thiol consumption was lower than unity both in homogeneous solution and in the two-phase system. However, our ongoing research suggests that it depends on the experimental conditions, and this issue will be addressed in detail in future work. We feel that our catalytic multifunctional antioxidants would be useful tools in the research related to disorders involving free-radical-mediated damage (after appropriate toxicological evaluation) and in the development of novel stabilizing agents for man-made and natural materials during processing and use.

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Supporting Information Available: All experimental details including ^{1}H and ^{13}C NMR spectra of compounds prepared; results of autoxidation experiments cited in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

(31) This value was estimated by assuming that the strength of the intramolecular H-bond between OH and Te=O groups is similar to that involving the S=O group (7−11 kcal mol^{-1}), reported in: Korth, H.-G.; de Heer, M. I.; Mulder, P. *J. Phys. Chem. A* **2002**, *106*, 8779−8789. The S=O group also increases the BDE_{OH} by ~0.4 kcal mol^{-1} because of its electronic effects: Amorati, R.; Fumo, M. G.; Menichetti, S.; Mugnaini, V.; Pedulli, G. F. *J. Org. Chem.* **2006**, *71*, 6325−6332.