Bond Dissociation Energies of the N−H Bond and Rate Constants for the Reaction with Alkyl, Alkoxyl, and Peroxyl Radicals of Phenothiazines and Related Compounds

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Abstract: The results of a detailed thermodynamic and kinetic investigation on the homolytic reactivity of phenothiazine, phenoxazine, and phenoselenazine, of several substituted phenothiazines, and of related tricyclic aromatic amines are reported. All these compounds give, by hydrogen atom abstraction from the N−H group, persistent aminyl radicals. Equilibration of each of these radicals with the parent amine and a reference compound having an easily abstractable hydrogen allowed us to determine, by using EPR spectroscopy, the N−H Bond Dissociation Energies (BDE) of the amines. These are characterized by low BDE values (in some cases lower than the O−H bond strength of α-tocopherol, i.e 78.3 kcal/mol) and therefore are very good hydrogen atom transfer reagents. To check the efficiency of tricyclic amines as antioxidants and as polymerization inhibitors, absolute rate constants were determined for their reaction with alkyl, alkoxyl, and peroxyl radicals by using competitive techniques in the first two cases and by autoxidation studies under controlled conditions in the last one. All amines have been found to be highly reactive toward these radicals which makes them very good autoxidation and polymerization inhibitors.

Introduction

Phenothiazines and related derivatives are commonly used in medicinal chemistry for their neuroleptic and antihistaminic properties; indeed, molecules bearing the phenothiazine nucleus such as promazine, chlorpromazine, triflupromazine, prometazine, etc. are widely represented in pharmaceutics of current use.[1] Beside experiencing interesting pharmaceutical properties, phenothiazines and, more generally, tricyclic aromatic amines can act as antioxidants for a wide variety of easily oxidizable substrates including lubricants, rubber, polymers, and biological materials.[2−4] In particular phenothiazine has been found to inhibit the autoxidation of methyl linoleate and phenoxazine to retard lipid peroxidation in rat brain.[5] It has also been suggested that the pharmacological activity of phenothiazines might be somehow related to their antioxidant or radical trapping ability.[6] Another important application of phenothiazine and related compounds concerns their use as polymerization inhibitors to stop the reactions of radical polymerization which may take place during the preparation and workup of acrylic monomers or during their storage.[7,8]

The mechanism by which aromatic amines behave as autoxidation inhibitors in nonacidic media is believed to involve the initial transfer of a hydrogen atom from the amino group to the peroxyl radicals carrying on the autoxidative chain reaction (eq 1).

$$Ar_2N{-}H + ROO^{\bullet} \rightarrow Ar_2N^{\bullet} + ROOH \qquad (1)$$

In acidic media[9] an electron transfer to ROO• with formation of the radical cation of the amine has instead been suggested.

Despite the great potential and practical interest for this class of molecules not much is known about their homolytic reactivity and data available in the literature are often contradictory. We wish to report here the results of a detailed investigation aiming to assess the thermochemical and kinetic aspects of the reaction of phenotiazines and related tricyclic aromatic amines toward three common classes of free radicals: alkyl, alkoxyl, and peroxyl.

Beside phenothiazine (**1**), the molecules investigated in this study are phenoxazine (**2**), phenoselenazine (**3**), iminostilbene (**4**), diphenylamine (**5**), some ring-substituted phenothiazines (**6**−**10**), and the *N*-methylated cyclic amines **11**−**13**.

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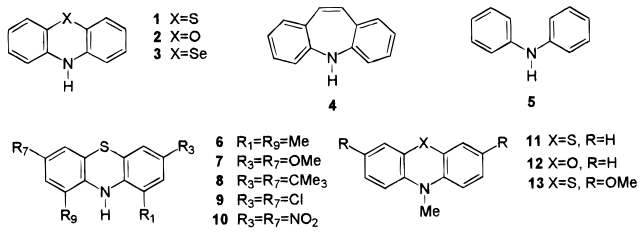
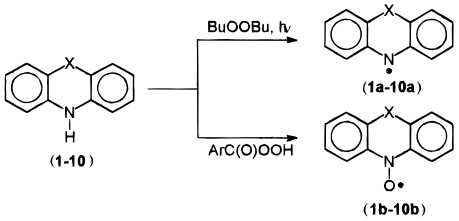


Results

When phenothiazine (**1**) was reacted with photolytically produced alkoxyl radicals in deoxygenated benzene solutions inside the cavity of an EPR spectrometer the only paramagnetic product observed was the aminyl radical (**1a**) originating from hydrogen abstraction from the N−H group.[10] This highly persistent radical is characterized by a nitrogen coupling constant of 7.08 G, two large proton splittings (2.80, 3.75 G) due to the coupling of the unpaired electron with the hydrogens in positions 1, 9 and 3, 7, two smaller splittings (1.02, 0.81 G) attributed to the hydrogens in 2, 8 and 4, 6, and a *g*-factor of 2.0046.

Oxidation of **1** with *m*-chloroperbenzoic acid afforded instead the corresponding nitroxide radical **1b** that cannot be mistaken for **1a** since it is characterized by a larger nitrogen (9.23 G) and smaller proton splittings (2.23 and 0.59 G for hydrogens 1, 3, 7, 9 and 2, 4, 6, 8, respectively) and a larger *g*-factor (2.0055).[11] A similar behavior was shown by the related amines **2**−**5** and by the ring-substituted phenothiazines **6**−**10**. The spectroscopic parameters measured for these radicals under the present conditions are reported in the Experimental Section and are in agreement with data previously reported[10] for the majority of them. In the case of the aminyl radical from iminostilbene (**4**), for which no experimental data could be found in the literature, the assignment of the hyperfine splitting constants to the ring protons was made by analogy with those for the radicals derived from **1** and **2**.

These experiments show that, in nonpolar aprotic media, the reaction of aromatic amines with alkoxyl radicals leads to hydrogen abstraction from the N−H bond to form stable and persistent aminyl radicals. Hydrogen abstraction is also the key step in the reaction sequences proposed to explain both the antioxidant power[3,4] and the ability to act as polymerization inhibitor[7,8] of these compounds. Since one of the more important factors determining the ease of this reaction is the N−H bond strength, we have first measured the nitrogen−hydrogen bond dissociation energies for derivatives **1**−**10**.



Bond Dissociation Energies of the N−H Bond. These were determined by an equilibration method that recently has been extensively used in our laboratory for the measurement of the BDE values of the O−H bond of phenols.[12−14] In the present case the method consists of measuring the equilibrium constants for the hydrogen atom transfer reaction (eq 1) from an amine to a reference radical (A$^\bullet$) by using EPR spectroscopy.

$$\mathrm{BuOOBu} \xrightarrow{h\nu} 2\mathrm{BuO}^\bullet \quad (2)$$

$$\mathrm{BuO}^\bullet + \mathrm{Ar_2NH} \rightarrow \mathrm{BuOH} + \mathrm{Ar_2N}^\bullet \quad (3)$$

$$\mathrm{BuO}^\bullet + \mathrm{AH} \rightarrow \mathrm{BuOH} + \mathrm{A}^\bullet \quad (4)$$

$$\mathrm{Ar_2NH} + \mathrm{A}^\bullet \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} \mathrm{Ar_2N}^\bullet + \mathrm{AH} \quad (5)$$

$$2\mathrm{Ar_2N}^\bullet \xrightarrow{2k_t} \text{products} \quad (6)$$

$$2\mathrm{A}^\bullet \xrightarrow{2k'_t} \text{products} \quad (7)$$

$$\mathrm{Ar_2N}^\bullet + \mathrm{A}^\bullet \xrightarrow{2k''_t} \text{products} \quad (8)$$

The reference compound AH may be either a phenol or another amine whose, previously calibrated, O−H or N−H BDE value does not differ by more than 2.5 kcal mol^{-1} from that of the investigated amine. The two equilibrating radicals were generated, within the cavity of an EPR spectrometer, by continuous photolysis of deoxygenated benzene solutions containing the amine and the reference compound together with a small amount of the radical photoinitiator di-*tert*-butyl peroxide. The overall reaction scheme is shown in eqs 2−8.

The molar ratio of the two equilibrating radicals [Ar$_2$N$^\bullet$]/[A$^\bullet$] was obtained from the EPR spectra either by double integration of appropriate lines or by comparison with computer-simulated spectra when the lines from the two species strongly overlapped. The equilibrium constant, K_5, was determined by introducing in eq 9

$$K_5 = \frac{[\mathrm{Ar_2N}^\bullet][\mathrm{AH}]_0}{[\mathrm{A}^\bullet][\mathrm{Ar_2NH}]_0} \quad (9)$$

the initial concentrations of amine, [Ar$_2$NH]$_0$, and reference compound, [AH]$_0$. To ensure that at the time of measurement no significant depletion of amine and AH has occurred, high concentrations of the reactants (0.1−1 M) were used.

Since the values given by eq 9 represent the equilibrium constant K_5 only if the hydrogen transfer reaction (eq 5) takes place rapidly relative to the decay of the aminyl radicals (eqs 6−8),[13] different experimental conditions were employed by changing either the initial concentrations of Ar$_2$NH and AH or the rate of initiation by using different amounts of peroxide or by partially cutting off the light. In all these measurements the same value of the equilibrium constant for any given couple of compounds was obtained within experimental error. In those cases where the Ar$_2$N$^\bullet$ and A$^\bullet$ radicals were so persistent (for instance with the couple phenoxazine−BHA shown in Figure 1) that after interrupting the irradiation no appreciable decay of the EPR signals was observed for hours, the condition that equilibration is faster than decay was obviously guaranteed.

The BDE's were calculated from the equilibrium constants by means of eq 10 obtained assuming that the entropy change

$$\mathrm{BDE(Ar_2N-H)} = \mathrm{BDE(A-H)} + \Delta H^\circ \cong \mathrm{BDE(A-H)} - RT\ln K_5 \quad (10)$$

ΔS° for the hydrogen transfer reaction is negligible. Since the

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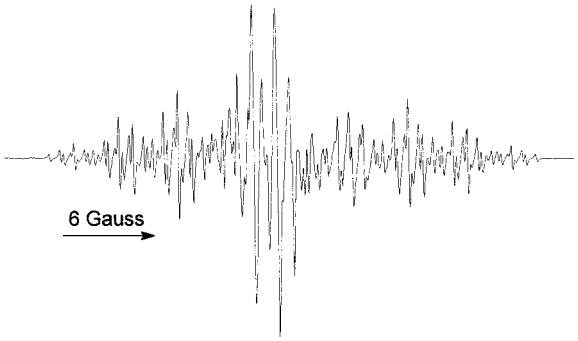

Figure 1. Room temperature EPR spectrum of the radicals obtained from a benzene solution of phenoxazine (**2**) (1×10^{-2} M) and 2,6-di-*tert*-butyl-4-methoxyphenol (BHA) (5.4×10^{-2} M) containing some di-*tert*-butyl peroxide (0.1 M), irradiated for a few seconds.

Table 1. Bond Dissociation Energies of Aromatic Amines in Benzene Solutions

amine	R_1, R_9	R_3, R_7	BDE/kcal mol^{-1}	ref 15
1			79.3 ± 0.3	82.3
2			77.2 ± 0.3	79.7
3			80.4 ± 0.4	
4			82.4 ± 0.5	84.6
5			85.8 ± 0.7	87.5
6	Me		77.7 ± 0.4	
7		OMe	76.2 ± 0.3	
8		CMe_3	78.1 ± 0.4	
9		Cl	79.8 ± 0.4	
10		NO_2	81.0 ± 1.0	

validity of this assumption is not warranted, especially when the equilibrating couple is made by an amine and a phenol, we studied the temperature dependence of the equilibrium constant K_5 in the case of the representative couple phenothiazine and α-tocopherol in the temperature range 290−345 K. The results of these measurements, $\Delta H^\circ = -1.13 \pm 0.83$ kcal mol^{-1} and $\Delta S^\circ = -1.25 \pm 2.98$ cal mol^{-1} K^{-1}, clearly indicate that the entropic contribution is so small that it can be safely neglected, similarly to what was previously found for equilibrating phenols.[12]

The BDE values obtained by the above procedure are collected in Table 1, which also reports for comparison some data available in the literature which were calculated by Bordwell and co-workers[15] from thermochemical cycles by using pK_a values and reversible oxidation potentials determined by cyclic voltammetry. The present values are lower by about 2 to 3 kcal/mol with respect to those data.

An examination of Table 1 and of its pictorial equivalent (Figure 2) shows that phenothiazine (**1**), phenoxazine (**2**), and, to a lesser extent, phenoselenazine (**3**) have low N−H bond dissociation energies even when compared with the most active radical trapping phenols such as α-tocopherol, galvinol, and 2,4,6-trimethoxyphenol. Amines lacking a heteroatom like iminostilbene (**4**) and diphenylamine (**5**) are instead characterized by stronger nitrogen−hydrogen bonds.

It is also worth pointing out that substitution of the ring hydrogens of phenothiazine with electron-donating groups significantly decreases the BDE value, while electron withdrawing groups make hydrogen abstraction more energetically demanding, similarly to what was observed with phenols.[13,16−20]

Reactivity toward Alkyl Radicals. The rate of hydrogen abstraction by primary alkyl radicals in benzene has been measured at 298 K by the radical clock method. This is based on competition kinetics between a known monomolecular process used as reference and the bimolecular reaction to be timed.[21] The competing monomolecular processes employed were the 5-hexo-cyclization of the 1-hexenyl radical,[22] $k_r = 2.3 \times 10^5$ s^{-1} at 298 K, the neophyl radical rearrangement,[23,24] $k_r = 1.1 \times 10^3$ s^{-1} at 298 K, and the similar 1,2-aryl migration of 2-methyl-2-(2-naphthyl)-1-propyl radical that has been recently calibrated in our laboratory[25] and which provided a rate constant of $k_r = 1.4 \times 10^4$ s^{-1} at 298 K, thus intermediate between those of the two other clocks employed.

$$Bu_3SnSnBu_3 \xrightarrow{h\nu} 2Bu_3Sn^\bullet \quad (11)$$

$$Bu_3Sn^\bullet + RBr \rightarrow Bu_3SnBr + R^\bullet \quad (12)$$

$$R^\bullet \xrightarrow{k_r} R'^\bullet \quad (13)$$

$$Ar_2NH + R^\bullet \xrightarrow{k_H} Ar_2N^\bullet + RH \quad (14)$$

$$Ar_2NH + R'^\bullet \rightarrow Ar_2N^\bullet + R'H \quad (15)$$

The alkyl radicals were generated by photolyzing oxygen free solutions of the corresponding bromide in the presence of hexabutyldistannane that were then left to react with the aromatic amines (eqs 11−15). Experimental conditions were chosen to avoid significant consumption of the phenothiazines during the reaction

$$k_H[Ar_2NH] = k_r\frac{[RH]}{[R'H]} \quad (16)$$

The reaction products RH and R′H were analyzed by means of GC and the rate constants for hydrogen abstraction, k_H, were obtained by using eq 16. When using the neophyl and the 2-methyl-2-(2-naphthyl)-1-propyl radical clocks, besides *tert*-butylbenzene and isobutylbenzene or 2-*tert*-butylnaphthalene and 2-isobutylnaphthalene, very minor side products, identified on the basis of their mass spectra as 1-phenyl-2-methylpropene and 1-(2-naphthyl)-2-methylpropene, respectively, were also detected. These are known to arise from disproportionation of the rearranged radicals R′•,[24,25] and their concentration has been considered in the denominator of eq 16 when calculating the rate constant for hydrogen abstraction from the amine. In all cases the measured product ratio was linear with the amino substrate concentration so that rate constants for hydrogen atom

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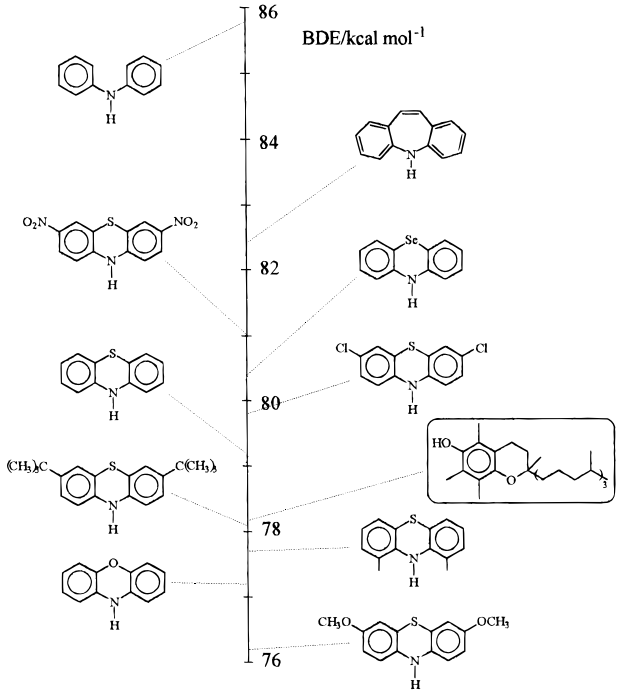

Figure 2. BDE values of the N−H bond of aromatic amines in benzene solution.

Table 2. Absolute Rate Constants for the Abstraction of the N−H Hydrogen Atom from Aromatic Amines by Primary Alkyl Radicals (R•) and the *tert*-Butoxyl Radical (Me_3CO•) at 298 K in Benzene Solution

amine	k_H (M^{-1} s^{-1}) (R•)	clock[a]	k_H (M^{-1} s^{-1}) (Me_3CO•)
1	6.0×10^4	β-L, H	2.3×10^9
2	4.8×10^5	H	1.1×10^9
3	2.2×10^4	N	1.1×10^9
4			7.8×10^8
5	1.3×10^6 [b]	N	
6	2.1×10^4	β-L	1.0×10^9
7	2.7×10^6	H	
8	8.0×10^4	β-L	1.9×10^9
9	3.6×10^4	β-L	
11	1.6×10^4	β-L	
12	1.1×10^5	H	
α-tocopherol	6.0×10^5 [c]		3.1×10^9 [d]

[a] H = 1-hexenyl; N = neophyl; β-L = 2-methyl-2-(2-naphthyl)-1-propyl radical. [b] Measured at 373 K (see ref 24). [c] Reference 26. [d] Reference 27.

abstraction could be obtained straightforwardly. With diphenylamine (**5**) data were taken from a previous paper by Burton et al.[24] reporting a kinetic study of the reaction of alkyl radicals with several 4-substituted diphenylamines.

The results of these measurements, reported in Table 2, show that phenothiazines and related compounds, being characterized by k_H values in the range 10^4-10^5 M^{-1} s^{-1}, are good trapping agents for alkyl radicals similar to the most effective phenols whose reactivity toward alkyl radicals has been recently measured in our laboratory by the same experimental technique.[26] For instance, the room temperature rate constants of hydrogen abstraction from α-tocopherol and 2,4,6-trimethylphenol in benzene are 6.0×10^5 and 6.4×10^4 M^{-1} s^{-1}, respectively.

To predict the efficiency of these aromatic amines as polymerization inhibitors these rate constants should be compared to the rate of addition of carbon-centered radicals to the double double bond of olefines. A large number of these data have been measured by Fischer and were found in the range 10^4-10^6 M^{-1} s^{-1}.[28] Since the rate constants for the addition to double bonds are comparable or larger than the rates of hydrogen transfer to alkyl radicals, only in a few cases can the polymerization be efficiently inhibited by small amounts of phenothiazines or phenols as stabilizing agents. This is in agreement with the reported finding[7,8] that the majority of these inhibitors are more efficient in the presence of some oxygen. Under these conditions, the few alkyl radicals spontaneously produced during the storage or distillation of the monomers will be transformed in the corresponding peroxyl radicals which will both add much more slowly to the double bonds and react much faster with phenothiazines or phenols.

It is also worth noting that the rate constant, k_H, for the abstraction of a hydrogen atom from the methyl group of the *N*-methylated amines **11**−**12** is similar to those measured for the hydrogen abstraction from the N−H group of amines **1**−**3** and **6**−**9**.

Reactivity toward Alkoxyl Radicals. The rate of hydrogen abstraction from the investigated aromatic amines by alkoxyl radicals has been studied by competition kinetics using the hydrogen abstraction from (TMS)SiH for which the rate constant for the reaction with *tert*-butoxyl radicals has been reported as 1×10^8 M^{-1} s^{-1}.[29] The *tert*-butoxyl radicals were generated by UV irradiation at 298 K of the reaction mixture containing di-*tert*-butyl peroxide, an internal standard, and different amounts of the silane and of the cyclic amine.

The mixture was analyzed by GC and CG-MS before and after irradiation and the desired rate constants were obtained from the loss of the starting hydrogen donors.[30] The results, reported in Table 2, clearly show that these molecules, consistently with their low values of N−H bond dissociation energies, are very reactive toward hydrogen abstraction by butoxyl radicals, their rate constants being similar to those measured for the most reactive phenols and close to the diffusion control limit.

$$BuO^{\bullet} + Ar_2NH \rightarrow BuOH + Ar_2N^{\bullet} \quad (17)$$

$$BuO^{\bullet} + (TMS)_3Si-H \rightarrow BuOH + (TMS)_3Si^{\bullet} \quad (18)$$

$$Ar_2N^{\bullet} \rightarrow \text{products} \quad (19)$$

$$(TMS)_3Si^{\bullet} \rightarrow \text{products} \quad (20)$$

In principle these measurements might be affected by the back formation of some amine from the aminyl radical by reaction with the silane (eq 21) which is a good hydrogen donor. Thus, the amount of residual amine actually determined might be larger and that of the silane lower than expected on the basis of reactions 17 and 18 only.

$$Ar_2N^{\bullet} + (TMS)_3Si-H \rightarrow Ar_2NH + (TMS)_3Si^{\bullet} \quad (21)$$

To check the importance of reaction 21, the evolution with time of the EPR signal of the phenothiazinyl radical (**1a**) was followed both in the absence and in the presence of $(TMS)_3SiH$.

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Since no substantial decay was found, also in the presence of silane up to a concentration ca. 0.1 M, we may be confident that the rate constants reported in Table 2 are correct.

$$BuO^{\bullet} + Ar_2NCH_3 \rightarrow BuOH + Ar_2NCH_2^{\bullet} \qquad (22)$$

No data are instead reported for the reaction of *tert*-butoxyl radicals with *N*-methylated amines (eq 22) since, in this case, hydrogen atom transfer from the silane to the aminoalkyl radical cannot be neglected.

Reactivity toward Peroxyl Radicals. The rate constants for the reaction of phenothiazines and related derivatives with peroxyl radicals (eq 23) were obtained by studying the inhibition by these compounds of the thermally initiated autoxidation of styrene and measuring the rate of oxygen uptake during the induction period where the autoxidation is strongly retarded by the aromatic amine.

$$ROO^{\bullet} + Ar_2NH \rightarrow ROOH + Ar_2N^{\bullet} \qquad (23)$$

The AIBN initiated autoxidation of styrene was carried out at 50 °C in a sealed quarz tube containing an air-saturated solution of styrene in benzene, in the presence of various amounts of the tricyclic compounds or of α-tocopherol, which was used as a reference chain breaking antioxidant. The reaction was allowed to occur inside the thermostated cavity of an EPR spectrometer and the oxygen consumption in solution was monitored by EPR, as described in previous papers,[31] by following the variation with time of the spectral line width of a nitroxide spin probe added to the solution. The spin probe employed was tetramethylpiperidine *N*-oxide (TEMPO), which was added to the reaction mixture in a concentration low enough (usually in the range 5×10^{-6} to 1×10^{-5} M) to avoid interference with the autoxidation. The three lines of TEMPO, which are initially broadened by Heisenberg spin exchange with molecular oxygen, become sharper as the concentration of oxygen decreases. Since both the EPR line width and the square root of the signal height are linearly related with the oxygen concentration in solution, the rate of oxygen consumption can be easily measured by this method. Experimentally, the signal intensity of the first spectral line of TEMPO was measured at fixed time intervals and was then converted into the molar concentration of dissolved oxygen by a calibration curve. An advantage of this method, besides its simplicity, is that the formation of transient paramagnetic species during the different stages of autoxidation may in some cases be directly detected.

As an example, Figure 3 shows the time dependence of the oxygen concentration during the initiated autoxidation of styrene in the presence of phenoxazine (**2**) as autoxidation inhibitor. A well-defined inhibition period is initially observed, whose length depends on the initiation rate, R_i, and on the concentration and stoichiometric factor n of the antioxidant,[32] the latter being the number of peroxyl radicals trapped by one molecule of antioxidant. The slope of the plot during the inhibition period, given by eq 24, provides the ratio of the rate constant for hydrogen abstraction by the peroxyl radicals (k_{inh}) and the rate constant for the propagation of the autoxidative chain reaction (k_p).

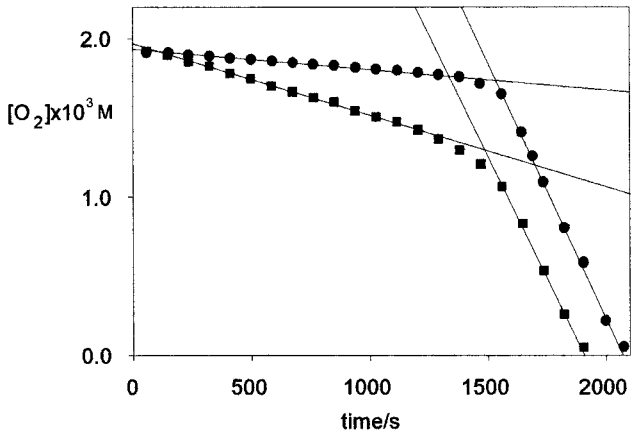

Figure 3. Oxygen consumption observed during the AIBN initiated autoxidation at 50 °C of styrene in benzene in the presence of 1.0×10^{-5} M phenoxazine **2** (●) and of its N-deuterated analogue.

$$\frac{-d[O_2]}{dt} = \frac{k_p R_i [\text{styrene}]}{n k_{inh} [Ar_2NH]} \qquad (24)$$

During autoxidation a broad EPR spectrum developed reaching a maximum approximately at the end of the induction period. The intensity of this spectrum remains constant during the period where oxygen is rapidly consumed and finally rapidly decays near the end of the autoxidation, when the concentration of oxygen becomes negligible. This spectrum could be unambiguously assigned to the nitroxide radical from the tricyclic amine, which reaches a concentration never larger than 15% of the concentration of the starting amine. Since its time evolution seems to indicate that the nitroxide is not responsible for the antioxidant activity of these amines, its role, if any, in the inhibition process is not clear.

The absolute values of the rate constant for the hydrogen atom abstraction by peroxyl radicals from the amines were obtained by comparing the rate of autoxidation of styrene in the presence of a given amine with that measured with α-tocopherol as inhibitor and using as reference for k_{inh}(α-TOH) the value of 3.2×10^6 M^{-1} s^{-1} reported at 30 °C by Ingold and co-workers.[16] Since, however, our measurements were performed at 50 °C, the above value was recalculated as 4.1×10^6 M^{-1} s^{-1} at the latter temperature by assuming a log A of 8 for this bimolecular reaction. The results of the determinations, reported in Table 3, show that phenothiazine is an excellent antioxidant being twice as fast as α-tocopherol in trapping peroxyl radicals and being characterized by a stoichiometric factor very close to two.

Even the other heteroaromatic amines behaved as extremely effective antioxidants. Indeed, phenoselenazine (**3**), which was the least active, showed about the same reactivity toward peroxyl radicals as α-tocopherol. Substitution of the protons in positions 3 and 7 with electron donors, such as methoxy and *tert*-butyl groups, makes the reaction with peroxyl radicals even faster.

In the case of iminostilbene (**4**) and diphenylamine (**5**), which behaved instead as relatively poor antioxidants, no induction period could be observed when they were used as inhibitors of styrene autoxidation. In these cases the inhibition rate constants were obtained by making measurements at different amine concentration and analyzing the data using the method proposed by Darley-Usmar et al.[33]

The most striking result was, however, obtained with phenoxazine (**2**) for which a rate constant as high as 2.9×10^7

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Table 3. Stoichiometric Factors, *n*, and Rate Constants for Hydrogen Atom Transfer to Peroxyl Radicals, k_{inh}, of Aromatic Amines Determined at 50 °C in Benzene Solution

amine	*n*	$k_{inh}/M^{-1}\ s^{-1}$	amine	*n*	$k_{inh}/M^{-1}\ s^{-1}$
1	1.8	8.8×10^6	**7**	2.0	5.0×10^7
2	5	2.9×10^7	**8**	1.6	1.2×10^7
3	2.5	3.2×10^6	**9**	1.8	5.1×10^6
4		3.7×10^4 [a]	**11**	- -	60[b]
5		1.5×10^4 [a]	α-tocopherol	2	4.1×10^6
6	1.7	$(1.4 \pm 0.7) \times 10^5$			

[a] Determined from the slope of the inhibited autoxidation by using the method of ref 33. [b] Determined from the oxidizability of **11** (see text). The value reported represents a higher limit for k_{inh}.

Table 4. Reversible Oxidation Potentials of Amines **1** and **7** and N-Alkylated Amines **11** and **13**, Measured in ACN vs SCE

	1	**7**	**11**	**13**
$E_{1/2}$(ox)/V	0.58	0.36	0.68	0.47

$M^{-1}\ s^{-1}$ was obtained (seven times larger than for α-tocopherol) and a stoichiometric factor of 5. At present we have no reasonable explanation of this value, since all other compounds show stoichiometric factors close to 2, as expected. This high value of *n* was always obtained when using solutions of the inhibitor freshly prepared, while with older samples lower values were sometime obtained, presumably because of depletion of **2** by air oxidation.

The very high values of k_{inh} obtained for tricyclic aromatic amines might suggest that some process other than hydrogen abstraction is responsible for their antioxidant activity. Particularly, electron transfer from amines to peroxyl radicals with formation of peroxyl anions and of the amine radical cations could be involved, even though benzene is not the more appropriate solvent for this process to take place. To check this possibility the autoxidation experiments were carried out in the presence of the *N*-methylated derivatives **11**−**13**. These compounds, having oxidation potentials (see Table 4) determined by cyclic voltammetry, very close to those of the parent protonated amines, should display a similar antioxidant activity if electron transfer is the key step in the inhibition reaction. Indeed, none of the *N*-methylated derivatives were able to inhibit the AIBN initiated autoxidation of styrene, when used in concentrations comparable to those of **1**−**10**, this indicating that the presence of the N−H hydrogen is a necessary prerequisite to observe antioxidant activity with these cyclic amines.

Additional support for the conclusion that k_{inh} represents the rate of hydrogen transfer from amines to peroxyl radicals was obtained by repeating styrene autoxidation experiments using N-deuterated phenoxazine as antioxidant. As shown in Figure 3, the deuterated compound is a worse inhibitor than the protonated one; from the slopes of the inhibited traces of oxygen consumption a deuterium kinetic isotope effect (k_H/k_D) of 4.2 was obtained, a value very close to that found by Ingold and co-workers for α-tocopherol.[16]

To obtain the value of the rate constant for hydrogen transfer from N-alkylated phenothiazine to peroxyl radicals we studied the autoxidation reaction of the *N*-methyl derivative **11** initiated by AIBN. From the rate of oxygen consumption, determined in benzene at 50 °C by the EPR method described above, we could obtain the oxidizability,[32] $k_p/(2k_t)^{1/2}$, of **11** as 3.5×10^{-3} $M^{-1/2}\ s^{-1/2}$. Here k_p, i.e., the rate constant of propagation, is the rate constant for hydrogen atom transfer from the oxidizable substrate **11** to the related peroxyl radical $Ar_2NCH_2OO^{\bullet}$, while $2k_t$ is the rate constant for the bimolecular decay of the peroxyl radicals from **11**. As an upper limit of the latter one it was assumed the rate constant reported[34] for benzylperoxyl radicals is $3 \times 10^8\ M^{-1}\ s^{-1}$, which gives $k_p = 60\ M^{-1}\ s^{-1}$, i.e., a value several orders of magnitude lower than that obtained for the arylamines **1**−**9**.

Discussion

The use of tricyclic heteroaromatic amines as both autoxidation and polymerization inhibitors has been described in the literature since 1950. This behavior can be well understood on the basis of the experimental data of Table 1 reporting the N−H bond dissociation energy values for this class of compounds. Actually bond strengths lower than 80 kcal mol^{-1} were always found, and with phenoxazine and some ring-substituted phenothiazines (**6**−**8**) the nitrogen−hydrogen bond is even weaker than the O−H bond in α-tocopherol (78.2 kcal mol^{-1}),[12,13] one of the more effective phenolic antioxidants known.

Besides the base structure, the presence of substituents in positions conjugated with the heterocyclic nitrogen also plays an important role in determining the strength of the N−H bond, electron-donating groups, such as alkyls or alkoxyls, producing a weakening of this bond and electron-withdrawing groups, such as chlorine and NO_2, a strengthening of the bond. This behavior, similar to that found in phenols, can be attributed to the conjugative effect of the substituent which leads to destabilization of the starting amine with electron donors and to stabilization of it with electron acceptors. The aminyl radical, formed by hydrogen atom abstraction from the amine, is expected to be slightly stabilized, through delocalization of the unpaired electron, by both donors and acceptors.[12−20]

Kinetically these amines exhibit an extraordinarily high reactivity toward peroxyl radicals, which makes them very good autoxidation inhibitors. Some of them are characterized by inhibition rate constants even larger than that of α-tocopherol. The data of Tables 2 and 3 allow us to rationalize also the reason phenothiazines are good polymerization inhibitors especially in the presence of small amounts of air. Under these conditions the oxygen present will react at a diffusion-controlled rate with the alkyl radicals spontaneously produced during the handling of monomeric olefines, transforming them into the corresponding peroxyl radicals which will both add more slowly to the double bonds to polymerize and react faster with phenothiazines.

A comparison of the rate constants for hydrogen abstraction from the tricyclic amines by peroxyl radicals and by primary alkyl radicals provides evidence that the exothermicity of the H-transfer is not the only important factor determining the rates of these processes. The rate constants for the reaction of the amines with peroxyl radicals (where a ROO−H bond having a strength of 89 kcal mol^{-1} is formed) are about 2 orders of magnitude larger than those for the reaction with primary alkyl radicals (where the RCH_2−H bond formed has a strength of 100 kcal mol^{-1}) despite the fact that the latter reaction is more exothermic by 11 kcal mol^{-1}.[35] The higher reactivity of peroxyl radicals toward the N−H bond of amines can be instead explained, according to the theory proposed by Zavitsas,[36] on the basis of the magnitude of the triplet repulsion terms in the transition state which will be lower for H atom transfer between oxygen and nitrogen rather than between oxygen and carbon. A lower energy of activation is expected in the former case

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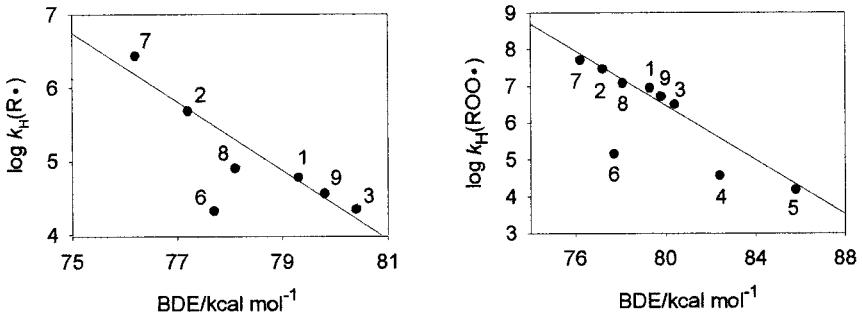

Figure 4. Plot of the logarithm of the rate constants for the hydrogen transfer from amines to alkyl (left) and peroxyl (right) radicals versus the corresponding N−H bond dissociation energies.

because the N−O antibonding repulsion would be low as a result of the weak R_2N-OOR bond (the BDE value is not known but is believed to be smaller than for the R_2N-OR bond, i.e., 30−40 kcal mol^{-1}).[37] On the other hand, the N−C antibonding repulsion should be important given the high BDE value of the NH_2-CH_3 bond (84.6 kcal mol^{-1}).

It is even more remarkable that the rate constant for hydrogen abstraction from the CH_3 group of the *N*-methylated phenothiazine **11** ($k_H \leq 60$ M^{-1} s^{-1}) by peroxyl radicals is instead about 3 orders of magnitude lower than that for the reaction with alkyl radicals ($k_H = 1.6 \times 10^4$ M^{-1} s^{-1}). This behavior, reversed with respect to the reactivity of the same radicals with phenothiazine **1**, can be explained by admitting that in this case the relative kinetic constants are basically determined by the exothermicity of the process, which is larger for the reaction with alkyl radicals, rather than by a different contribution to the transition state energy of the triplet repulsion term. This estimate is based on the reported BDE values for the RCH_2-CH_2R (86.6 kcal mol^{-1}) and RCH_2-OOR (72.6 kcal mol^{-1}) bonds[37] which, being of comparable strengths, are expected to give rise to antibonding repulsions of similar magnitude in the transition states of the two reactions.

Finally, to check if the kinetic constants for hydrogen transfer to peroxyl, alkyl, and alkoxyl radicals are linearly correlated with the corresponding bond dissociation energies as in phenolic antioxidants,[13,26] the logarithm of the rate constants for the reaction of these amines with the three classes of radicals was plotted against the N−H BDE values.

As shown in Figure 4, the correlation between kinetic and thermodynamic data is excellent when the attacking species are peroxyl and alkyl radicals, with a couple of exceptions, i.e., 1,9-dimethylphenothiazine (**6**) and iminostilbene (**4**) where steric crowding due to the methyl groups in the *peri* positions and the distorted geometry adopted to accommodate the seven-membered ring, respectively, are expected to slow the approach of the attacking radical to the N−H hydrogen atom. The same correlation does not hold with alkoxyl radicals whose reactivity toward phenothiazines seems independent of the energy of the bond to be broken (plot not shown). The more obvious explanation for this behavior is that the very high rate constants characterizing this reaction are essentially controlled by diffusion of the reactants in solution and therefore independent of the BDE of the N−H bond being broken.

Experimental Section

Materials. Solvents were of the highest purity grade commercially available and were used as received. Phenothiazine, phenoxazine, iminostilbene, diphenylamine, and 10-methylphenothiazine were purchased from Aldrich and were used as received. Phenoselenazine,[38] 3,7-dimethoxyphenothiazine,[39] 3,7-di-*tert*-butylphenothiazine,[40] 3,7-dichlorophenothiazine,[41] 3,7-dinitrophenothiazine,[42] and 10-methylphenoxazin,[43] were prepared according to literature procedures.

1,9-Dimethylphenothiazine. A solution of 1,1′-dimethyldiphenylamine (5 g; 0.025 mol) prepared as previously described,[44] sulfur (1.6 g; 0.05 mol), and iodine (0. 175 g; 0.7×10^{-3} mol) dissolved in 9 mL of *o*-dichlorobenzene is refluxed for 4 h, under inert atmosphere. During the reaction hydrogen sulfide develops. The *o*-dichlorobenzene is eliminated by distillation under reduced pressure (40 °C, 1 mbar). Column chromatography of the solid residue (eluant: acetone/pentane 1/12) affords 1,9-dimethylphenothiazine (1 g; 18%). Mp 129 °C. R_f 0.6. SM (70 eV): *m*/*e* (rel intensity) 227 (M^+, 100%), 194 ($M^+ - SH$, 95%). Anal. Calcd for $C_{14}H_{13}NS$: C 73.98; H 5.77; N 6.17. Found: C 73.89; H 5.84; N 6.11. NMR ^{1}H (200 MHz, $(CD_3)_2SO$), δ 7.1−6.4 (m, 6H), 6.2 (s, 1H), 2.3 (s, 6H). NMR ^{13}C (50.32 MHz; $(CD_3)_2SO$), δ 141 (2C), 129.7 (2CH), 125.1 (2CH), 123.3 (2C), 122.8 (2CH); 118.9 (2C), 16.9 ($2CH_3$).

10-Methyl-3,7-dimethoxyphenothiazine. Dimethyl sulfate (0.62 g; 4.9 mmol) is added to a dioxane solution (8 mL) containing 3,7-dimethoxyphenothiazine (0.4 g; 1.54 mmol) and potassium carbonate (1.55 g; 13.1 mmol). After this solution is stirred under reflux for 3.5 h, more dimethyl sulfate (0.4 g; 3.17 mmol) is added and the reaction mixture is refluxed for another 20 h. Then the mixture is poured into warm water (20m1) and stirred for 8 h. The precipitate formed is collected by filtration, dried, and purified by silica column chromatography (chloroform) to give 10-methyl-3,7-dimethoxyphenothiazine (0.18 g; 43%). Mp 168 °C. Calcd for $C_{15}H_{15}NO_2S$ (273): C 65.93; H 5.49; N 5.13. Found: C 65.72; H 5.56; N 5.07. NMR ^{1}H (100 MHz, DMSO), δ 6.79 (s, 6H), 3.68 (s, 6H), 3.20 (s, 3H). NMR ^{13}C (50.32 MHz, DMSO), δ 154.66 (2C), 139.36 (2C), 123.13 (2C), 114.70 (2CH), 112.79 (2CH), 112.41 (2CH), 55.44 ($2OC-H_3$), 35.08 (CH_3).

Kinetic Measurements. In a typical experiment 200 μL of a solution of the amine (0.1−1 M) containing either neophyl bromide or 6-bromo-1-hexene (0.005−0.01 M) and hexa-*n*-butylditin (0.01 M) was sealed in a quartz tube, after being deoxygenated by bubbling nitrogen. The reaction mixtures were then irradiated for 30−120 min at the desired temperature in a thermostated photoreactor, built in our laboratories, equipped with a 125 W high-pressure mercury lamp and the products were analyzed by gas chromatography. For each amine 4 to 7 measurements were made with different concentration and the reaction products ratio [UH]/[RH] was plotted versus the amine concentration to obtain the k_H/k_r ratio by linear regression of the experimental data.

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Autoxidation experiments were performed on air-saturated solutions of styrene (1.5−5.2 M) in benzene containing the desired amine (5×10^{-6} to 1×10^{-4} M), AIBN (1×10^{-3} to 4×10^{-2} M) as thermal initiator, and the stable nitroxide TEMPO (ca. 5×10^{-6} M). The solutions were introduced (ca. 200 μL) into a capillary tube with the internal diameter of ca. 1.85 mm and a second capillary tube (external diameter of 1.60 mm) sealed at one end was introduced into the sample tube to leave very little dead volume space.[31] The tube was sealed and put into the EPR cavity kept at 50 °C and the first spectrum was recorded after ca. 1 min to allow for temperature equilibration time. Initiation rates, R_i, were determined for each condition in preliminary experiments by the inhibitor method using α-tocopherol as reference antioxidant: $R_i = 2[\alpha\text{-tocopherol}]/\tau$.[16]

The EPR spectra were recorded on a Bruker ESP 300 spectrometer by using the following settings: microwave frequency 9.74 GHz, power 6.4 mW, modulation amplitude 0.7 G, center field 3320 G, sweep time 81 s, and time constant 81 ms.

For measuring the kinetic parameters for the reaction of *tert*-butoxyl radical with phenothiazine (and the related compounds investigated) solutions of di-*tert*-butyl peroxide (0.2−0.4 M), the tricyclic amine (ca. 1×10^{-2} M), tris(trimethylsilyl)silane (1 M) as reference hydrogen donor, and *tert*-butylbenzene as internal GC standard, in benzene, were degassed and sealed under nitrogen in quartz ampules. The reaction mixture was photolyzed at 298 K for 15-30 min in a thermostated photoreactor equipped with a 125 W high-pressure mercury lamp and the disappearance of the products was analyzed by GC. For each compound the results were averaged over 3−5 measurements with different amine/silane concentrations.

Determination of the BDE Values. Deoxygenated benzene solutions containing the amine under investigation (0.01−1 M), an appropriate reference phenol (0.1-1 M), and di-*tert*-butyl peroxide (0.1 M) were sealed under nitrogen in a suprasil quartz EPR tube sitting inside the thermostated cavity of an EPR spectrometer. Photolysis was carried out by focusing the unfiltered light from a 500 W high-pressure mercury lamp on the EPR cavity. The temperature was controlled with a standard variable-temperature accessory and was monitored before and after each run with a copper−constantan thermocouple.

The molar ratio of the two equilibrating radicals $[Ar_2N^\bullet]/[ArO^\bullet]$ was obtained from the EPR spectra and used to determine the equilibrium constant, K, by introducing in the equation $K = ([Ar_2N^\bullet][ArOH])/([Ar_2NH][ArO^\bullet])$, the initial concentrations of the reference phenol $[ArOH]_0$, and the amine under investigation $[Ar_2NH]_0$. Initial concentrations were chosen to avoid significative consumption during the course of the experiment.

Relative radical concentrations were determined by comparing the double integrals of at least two lines of the equilibrating species or, when strong line overlap was present, by comparison of the digitized experimental spectra with computer simulated ones. In these cases an iterative least-squares fitting procedure based on the systematic application of the Monte Carlo method was performed to obtain the experimental spectral parameters of the two species including their relative intensities.[12]

Cyclic Voltammetry. Oxidation potentials were measured in deoxygenated anhydrous acetonitrile containing tetrabutylammonium hexafluorophosphate (0.1 M) as supporting electrolyte and the amine (10^{-1} M). Cyclic voltammograms were recorded using a three-electrode potentiostat coupled to a digital acquisition system based on a personal computer. The voltammetric experiments were carried out in a standard cell fitted with a working platinum disk electrode (Tacussel EDI, diameter:2 mm), a platinum wire auxiliary, and a SCE reference electrode (Tacussel XR 110). The potentiostat and the dedicated software were designed by G. Gronchi and Y. Berchadsky in the "Laboratoire Structure et Réactivité des Espèces Paramagnétiques" and in the "Laboratoire d'Electrochimie Organique et d'Instrumentation" at the University of Aix-Marseille III.

ESR Spectral Parameters of the Aminyl (1a−10a) and Nitroxide Radicals (1b−10b). The following hyperfine splitting constants (expressed in gauss = 0.1 mT) and *g*-factors have been measured in benzene at room temperature. The assignment of the proton splittings to the various positions is based on those reported in the literature for aminyl[10] and nitroxide[11] radicals.

1a: 7.08 (N), 2.80 ($H_{1,9}$), 0.81 ($H_{2,8}$), 3.75 ($H_{3,7}$), 1.02 ($H_{4,6}$), *g* 2.0046. **2a**: 7.72 (N), 3.02 ($H_{1,9}$), 0.72 ($H_{2,8}$), 3.79 ($H_{3,7}$), 0.95 ($H_{4,6}$), *g* 2.0036. **3a**: 7.07 (N), 2.93 ($H_{1,9}$), 0.85 ($H_{2,8}$), 3.94 ($H_{3,7}$), 1.22 ($H_{4,6}$), *g* 2.0102. **4a**: 7.46 (N), 3.37 ($H_{1,10}$), 1.06 ($H_{2,9}$), 4.24 ($H_{3,8}$), 1.12 ($H_{4,7}$), 2.17 ($H_{5,6}$), *g* 2.0031. **5a**: 8.86 (N), 3.71 ($4H_o$), 1.53 ($4H_m$), 4.34 ($2H_p$), *g* 2.0032. **6a**: 6.67 (N), 2.00 (6H), 1.01 ($H_{2,8}$), 2.78 ($H_{3,7}$), 1.15 ($H_{4,6}$), *g* 2.0046. **7a**: 7.39 (N), 2.80 ($H_{1,9}$), 0.49 ($H_{2,8}$), 0.49 (6H), 1.02 ($H_{4,6}$), *g* 2.0046. **8a**: 7.40 (N), 2.80 ($H_{1,9}$), 0.82 ($H_{2,8}$), 0.15 (18H), 1.10 ($H_{4,6}$), *g* 2.0049. **9a**: 7.02 (N), 2.97 ($H_{1,9}$), 0.80 ($H_{2,8}$), 0.42 (2Cl), 1.13 ($H_{4,6}$), *g* 2.0052. **10a**: 6.11 (N), 1.85 ($H_{1,9}$), 0.15 ($H_{2,8}$), 1.71 (2N), 0.88 ($H_{4,6}$), *g* 2.0050.

1b: 9.23 (N), 2.23 ($H_{1,3,7,9}$), 0.59 ($H_{2,4,6,8}$), *g* 2.0055. **2b**: 8.97 (N), 2.39 ($H_{1,3,7,9}$), 0.51 ($H_{2,4,6,8}$), *g* 2.0050. **3b**: 9.30 (N), 2.16 ($H_{1,3,7,9}$), 0.65 ($H_{2,4,6,8}$), *g* 2.0070. **4b**: 12.61 (N), 1.51 ($H_{1,10}$), 0.50 ($H_{2,4,7,9}$), 1.71 ($H_{3,8}$), 0.69 ($H_{5,6}$), *g* 2.0058. **5b**: 9.65 (N), 1.90 ($4H_o$), 0.81 ($4H_o$), 1.82 ($2H_p$), *g* 2.0055.

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