

Mechanistic Insights into Oxidation of 2-Methyl-1-naphthol with Dioxygen: Autooxidation or a Spin-Forbidden Reaction?

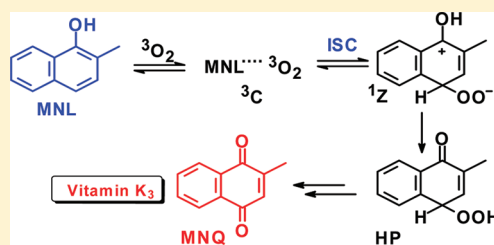
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 Supporting Information

ABSTRACT: Oxidation of 2-methyl-1-naphthol (MNL) with molecular oxygen proceeds efficiently under mild reaction conditions (3 atm O₂, 60–80 °C) in the absence of any catalyst or sensitizer and produces 2-methyl-1,4-naphthoquinone (MNQ, menadione, or vitamin K₃) with selectivity up to 80% in nonpolar solvents. ¹H NMR and ¹H, ¹H-COSY studies revealed the formation of 2-methyl-4-hydroperoxynaphthalene-1(4H)-one (HP) during the reaction course. Several mechanistic hypotheses, including conventional radical autooxidation, electron transfer mechanisms, photooxygenation, and thermal intersystem crossing (ISC), have been evaluated using spectroscopic, mass-spectrometric, spin-trapping, ¹⁸O₂ labeling, kinetic, and computational techniques. Several facts collectively implicate that ISC contributes significantly to MNL oxidation with O₂ at elevated pressure: (i) the reaction rate is unaffected by light; (ii) C–C-coupling dimers are practically absent; (iii) the reaction is first order in both MNL and O₂; (iv) the observed activation parameters ($\Delta H^\ddagger = 8.1 \text{ kcal mol}^{-1}$ and $\Delta S^\ddagger = -50 \text{ eu}$) are similar to those found for the spin-forbidden oxidation of helianthrene with ³O₂ (Seip, M.; Brauer, H.-D. *J. Am. Chem. Soc.* **1992**, *114*, 4486); and (v) the external heavy atom effect (2-fold increase of the reaction rate in iodobenzene) points to spin inversion in the rate-limiting step.



INTRODUCTION

The selective oxidation of organic compounds plays a central role in organic synthesis and biological systems. Molecular oxygen is the most attractive oxidant from both an economic and an environmental viewpoint. In recent years, oxidations with O₂ are among the most important topics in the fields of chemistry and biology, and great efforts have been made to understand mechanisms of its activation and to develop environmentally benign systems for the preparation of valuable oxygenated products.¹ It is well-known that direct reaction of O₂ in its ground triplet state (³O₂) with singlet organic molecules to give singlet products is a spin-forbidden process. The spin-conservation obstacle can be overcome by (1) involvement of ³O₂ in a radical chain process (autooxidation); (2) photochemical activation of either ³O₂ or an organic substrate and (3) interaction with paramagnetic transition metal ions.^{2–5}

However, there are a limited number of organic substrates, which can react spontaneously with ³O₂ in the dark in the absence of any catalyst at rather mild reaction conditions and produce products typical of ¹O₂ involvement.^{4,6–15} Some representatives are shown in Chart S1 in the Supporting Information (SI).

Nonelectron transfer spontaneous reactions that go against the spin conservation rule remain a matter of discussion because, in the absence of a redox mediator or light, one should find a mechanism that allows a triplet–singlet thermal intersystem crossing (ISC) either to transform the substrate into a triplet state or to transform ³O₂ to ¹O₂.

Barton et al. suggested a mechanism that involves radical addition of ³O₂ to an organic substrate (e.g., cisoid diene destabilized by strain or resonance) to give a triplet biradical followed by obligatory spin inversion by exchange and ring closure to yield endoperoxide.¹⁵ Evidence for biradicaloid intermediates in the oxidation of diallenes to cyclic peroxides was provided by spin-trapping experiments.⁹ Long-lived biradical intermediates have been detected using nitroso and nitron spin traps, and a rate-retarding effect of the radical scavenger, *tert*-butyl mercaptan, has been established.⁸ Recently, a detailed computational mechanistic study of two-state reactivity for the addition of both ¹O₂ and ³O₂ to acenes has been reported by Reddy and Bendikov.¹⁶ They have found that, starting from anthracene, acenes react with oxygen via a biradical stepwise mechanism; ISC from a triplet potential energy surface (PES) to a singlet PES is suggested for the reaction with ³O₂.

A mechanism of thermal ISC that involves the consecutive formation of a triplet collision complex and its conversion to a weakly bound singlet collision complex followed by the formation of zwitterion or perepoxide and their subsequent transformations to the reaction product, dione, was proposed by Turro and co-workers for the dark reaction between cyclic strained acetylene, 3,3,6,6-tetramethyl-1-thia-4-cycloheptyne (TMTCH,

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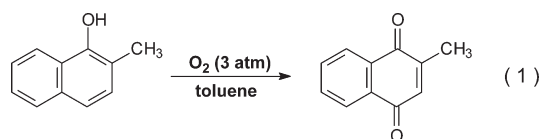
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Chart S1), and triplet oxygen.^{12a} Later on, Turro et al. provided evidence for the occurrence of two distinct mechanisms (zwitterionic and diradicaloid) in the reaction of triplet oxygen with ketenes.^{12b}

Seip and Brauer have revealed that helianthrene (HEL, Chart S1) can react with molecular oxygen in its ground triplet state to give endoperoxide (HELPO) in nonpolar solvents.¹⁴ A pronounced external heavy atom effect found for the dark HEL oxidation with ³O₂ (rate acceleration by a factor of 5.3 upon replacement of toluene for iodobenzene) allowed the authors to suggest a mechanism of thermal ISC.¹⁷ The rate-acceleration effect coupled with the lack of HELPO selectivity in methanol was rationalized in terms of the formation of a polar zwitterionic intermediate in the rate-limiting, spin-forbidden step.¹⁴

In 2006, Kholdeeva and Rossi found that oxidation of 2-methyl-1-naphthol (MNL) with molecular oxygen proceeds efficiently under mild reaction conditions (3 atm O₂, 20–80 °C) in the absence of any catalyst and produces 2-methyl-1,4-naphthoquinone (MNQ, menadione, or vitamin K₃)¹⁸ with the yield as high as 80–85%.¹⁹



It is well documented in the literature that high selectivity is not typical for autooxidation of phenolic compounds.²⁰ Normally, it requires a base and/or a catalyst (initiator), involves the formation of organic free radicals and results in a complex mixture of products, including benzoquinones, diphenols, diphenoquinones, hydroperoxides, quinols, polymeric species, tars, etc.

Given in mind the unusually high yields of MNQ in reaction (1) and potential significance of MNL oxidation for environmentally benign production of vitamin K₃,^{21,22} we aspired to gain insight into the mechanism of dioxygen activation and to the routes leading to the selective formation of MNQ. In the present work, we report a detailed mechanistic study of MNL oxidation with O₂, which includes thorough identification of the reaction products, probing the reaction intermediates by spin-trapping, ¹⁸O₂ labeling, computational, and some other techniques, study on the reaction kinetics, solvent effects, etc. Three alternative oxidation mechanisms (free radical autooxidation, cation radical autooxidation, and thermal ISC) are discussed in view of the experimental data obtained, and the choice in favor of a spin-forbidden reaction is grounded.

EXPERIMENTAL SECTION

Instrumentation and Methods. GC analyses were performed using Agilent 4890 D (capillary column CP-Sil 8 CB, 30 m × 0.53 mm) and modernized TSVET-500 (MDN-SS, 30 m × 0.25 mm) gas chromatographs equipped with a flame ionization detector. Gas chromatography-mass spectrometry (GC-MS) analyses of organic products were carried out using a HP 5973/6890 system (carrier gas He, 30 m × 0.25 mm cross-linked 5% PHME siloxane (0.25 μm coating) capillary column; HP-5MS) or VG-7070. Electrospray mass-spectrometry (ESI-MS) analysis was performed on a ThermoFinnigan LCQ Advanage. Electron paramagnetic resonance (EPR) spectra were recorded at room temperature using a Bruker ER-200D instrument. ¹H NMR spectra were run using AM 250 Bruker or Avance III 500

Bruker spectrometers. ¹H, ¹H-COSY NMR spectra were recorded on an Avance III 500 Bruker. Electronic absorption spectra were run using a Varian Cary 50 instrument. Transition metal content in initial MNL was determined by inductively coupled plasma emission spectroscopy (HORIBA Jobin Yvon Activa ICP-OES and iCAP 6500 ICP-AES).

Materials. 2-Methyl-1-naphthol (MNL, 98%, containing 2.6 ppm of V and <12.8 ppm of Fe, Mn and Co), 2-methyl-1,4-naphthoquinone (MNQ), 2,3,6-trimethylphenol (TMP), 2,6-di-*tert*-butyl-4-methylphenol (DTBP or ionol), hydroquinone (HQ), *tert*-butylhydroperoxide (TBHP, 4 M solution in decane), 2,2'-azobisisobutyronitrile (AIBN), 3,5-dibromo-4-nitrosobenzenesulfonic acid (DBNBS), 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO), tetramethylethylene (TME), and 2,2,6,6-tetramethylpiperidone (TEMP) were purchased from Sigma-Aldrich and used as received. ¹⁸O₂ (98.5 atom %), CDCl₃ (H₂O < 0.02%) and C₆D₆ (H₂O < 0.02%) were purchased from Euriso-top. 2,6-Di-*tert*-butyl-4-methyl-4-hydroperoxy-2,5-cyclohexadiene-1-one was prepared as described elsewhere.²³ Toluene was purified by distillation and dried over molecular sieves prior to use. The other reactants were obtained commercially and used without further purification.

Oxidation Runs and Products Analysis. MNL oxidations with O₂ were carried out in a special Pyrex glass static reactor under vigorous stirring (500 rpm). Normally, no protection from the daylight was used, with the exception of special experiments. Typical reaction conditions were as follows: [MNL] = 0.05–0.25 M; O₂ pressure, 3 atm; toluene, 3 mL; 60–80 °C. MNL oxidations at 1 atm of O₂ and room temperature were performed in glass vessels. Samples of the reaction mixture were withdrawn periodically during the reaction course by a syringe and analyzed. The oxidation products were identified by mass-spectrometry and ¹H NMR techniques. MNL and MNQ were quantified by GC using biphenyl as the internal standard. The results coincided with those obtained using ¹H NMR. The amount of a peroxo compound formed during the reaction course was determined by both iodometric titration and ¹H NMR. The assignment of signals was made based on the literature data and was confirmed by a ¹H, ¹H-COSY NMR spectrum of the reaction mixture. The amount of C–C coupling products, 4,4'-di(2-methyl-1-naphthol) (DNL) and 4,4'-di(2-methyl-1-naphthoquinone) (DNQ), was estimated from ¹H NMR spectra.

MNL oxidation products (MNQ, DNL, and DNQ) were isolated using preparative thin-layer chromatography on silica (toluene and toluene/ether (30:1) were used as eluents). The structure of the isolated compounds was confirmed by ¹H NMR, GC-MS, UV–vis (DNQ), and ESI-MS techniques.

4,4'-Di(2-methyl-1-naphthol) (DNL). ¹H NMR (250 MHz, CDCl₃): δ 2.46 (s, 6H, 2CH₃), 5.16 (s, 2H, 2OH), 7.23–7.32 (m, 4H, H^{6,6',7,7'}), 7.35 (d, 2H, H^{5,5'}), 7.42–7.48 (m, 2H, H^{3,3'}), 8.22 (d, 2H, H^{8,8'}). MS (ESI) *m/z* (relative int.): 315 (27, [MH]⁺), 314 (100, [MH–H]⁺), 313 (62, [MH–2H]⁺), 298 (5, [MH–OH]⁺), 285 (7, [MH–2CH₃]⁺), 257 (3, [MH–2COH]⁺), 242 (15, [MH–CH₃–2COH]⁺). GC-MS: 314 (100, [M]⁺), 298 (16, [M–O]⁺), 282 (10, [M–2O]⁺), 255 (6, [M–2O–CCH₃]⁺), 239 (9, [M–2O–CCH₃–HCH₃]⁺), 157 (4, [M–C₁₁H₉O]⁺).

4,4'-Di(2-methyl-1-naphthoquinone) (DNQ). ¹H NMR (250 MHz, CDCl₃): δ 2.23 (s, 6H, 2CH₃), 7.65–7.70 (m, 4H, H^{6,6',7,7'}), 7.85–7.90 (m, 2H, H^{5,5'}), 7.95 (s, 2H, H^{3,3'}), 8.33–8.37 (m, 2H, H^{8,8'}). MS (ESI) *m/z* (relative int.): 313 (100, [MH]⁺), 285 (8, [MH–2CO]⁺), 242 (52, [MH–CH₃–2CO]⁺). UV–vis: characteristic band λ_{max} = 490 nm.

Table 1. MNL Oxidation with Molecular Oxygen in Toluene

entry	[MNL], M	$P(\text{O}_2)$, atm	T , °C	time, h	MNL conversion, %	MNQ selectivity ^a (yield), %
1	0.1	1	20	30	0	
				480	98	20 (19) ^b
2	0.1	0.2 (air)	80	30	5	
3	0.1	1	80	7	3	
				30	55	44 (24)
4	0.1	2	80	7	21	71 (15)
				15	48	69 (33)
5	0.1	3	80	7	40	75 (30)
				20	86	74 (64) ^c
6	0.1	10	80	5	97	52 (50)
7	0.05	3	80	7	31	76 (23)
8	0.25	3	80	7	58	69 (40)
				13	90	67 (60)
9	0.05	3	100	7	47	68 (32)
10	0.05	3	60	10	12	80 (10)
				21	43	77 (33) ^d

^a GC yield based on MNL consumed. ^b C–C-coupling dimers, DNL and DNQ, formed in 20–25% yield each. ^c HP, DNL, and DNQ formed in 12, 4, and 2% yield, respectively. ^d The main byproduct was HP (ca. 10% yield).

2-Methyl-4-hydroperoxynaphthalene-1(4H)-one (HP). ¹H NMR (500 MHz, C₆D₆): δ 1.88 (t, 3H, CH₃), 4.87–4.91 (m, 1H, H⁴), 6.58 (dq, 1H, H³), 6.95–7.10 (m, 2H, H^{6,7}), 7.44 (d, 1H, H⁵), 7.82 (br. s, exch. 1H, OOH), 8.30 (d, 1H, H⁸).

Kinetic Study. The kinetic study was performed in a Pyrex glass static reactor or in a steel autoclave containing an internal Teflon beaker in the temperature range of 60–100 °C under vigorous stirring (500 rpm). Kinetic curves completely coincided at 250 or 500 rpm, thus indicating that the reaction is not controlled by diffusion of molecular oxygen. The reactions were carried out at 1–10 atm of O₂, MNL concentration of 0.05–0.25 M in 3 mL of a solvent (generally, toluene). Biphenyl (BP) was added to the reaction mixture as the internal standard for GC. Samples of the reaction mixture were taken periodically by a syringe and immediately analyzed by GC. The reaction rates were determined from the steady-state portions of kinetic curves after completion of the induction period. Each experiment was reproduced at least three times. The reproducibility of the reaction rates was within 7–10%.

Spin-Trap/Probe Experiments. Experiments with spin traps, DNBNS and DMPO, were carried out using a procedure similar to that described previously.²⁴ To a reaction mixture containing 0.4 mmol of MNL in 4 mL of toluene, 0.08 mmol of DNBNS was added at the beginning of the reaction or after completion of the induction period. The reaction mixture was kept at 3 atm of O₂ and 80 °C under vigorous stirring. DNBNS is poorly soluble in toluene, but the solubility increases upon heating. Aliquots of 500 μ L were withdrawn in 2, 4, and 6 h and were placed into a flat quartz cuvette. DMPO (0.12 mmol) was added to a mixture of 0.15 mmol of MNL in 3 mL of toluene, and the reaction mixture was kept under 3 atm of O₂ at 80 °C. Aliquots of 500 μ L were withdrawn immediately after addition of DMPO, in 10 min and 2 h and were used for EPR measurements. All EPR spectra were run at room temperature.

Experiments with TEMP were carried out at typical reaction conditions (3 atm of O₂, 80 °C). TEMP (0.06 mmol) was added to a reaction mixture containing 0.3 mmol of MNL in 3 mL of toluene at the beginning of the reaction or after completion of the

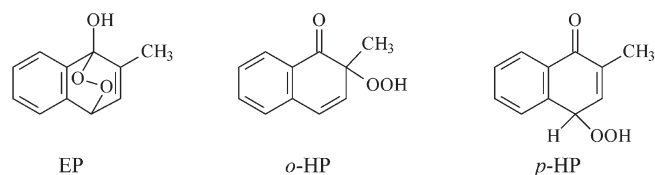
induction period (in ca. 1.5 h). The aliquots of 250 μ L were withdrawn after 30 min and 4 h and analyzed by EPR at room temperature. The experiment was carried out both in the dark and in the daylight.

¹⁸O₂ Labeling Experiments. The oxidation of MNL in the presence of labeling ¹⁸O₂ was performed under an atmosphere containing about 90% of ¹⁸O₂ (99.6% ¹⁸O enrichment) and 10% of Ar. The 50 mL reaction flask containing 0.1 mmol of MNL in 1 mL of C₆H₆ was filled up with ¹⁸O₂. The reaction was carried out at 80 °C and 1 atm of ¹⁸O₂ for 21 h. The isotopic composition of products was determined by GC-MS. Each sample was analyzed two times and m/z intensities of each peak were obtained by the integration of all scans of the peak. The degree of ¹⁸O incorporation into MNQ was calculated from the ratio of m/z 172/174 intensities in the mass spectra of MNQ.

Computational Details. Electronic structure calculations were performed with the ORCA program.²⁵ Structures were optimized at the B3LYP²⁶ level of the density functional theory (DFT) with polarized triple- ζ basis sets.²⁷ The convergence criteria for the SCF part are chosen to be 10^{−7} Hartree (Eh) in energy, 10^{−6} Eh for the change of elements of the density matrix and 10^{−6} Eh for the maximum element of the direct inversion of iterative subspace (DIIS) error. A geometry is considered to be converged when the change in energy is less than 10^{−6} Eh, the average force is smaller than 3 \times 10^{−5} Eh bohr^{−1}, and the maximum force is smaller than 10^{−4} Eh bohr^{−1}. All structures were verified as minima with numerical frequency calculations at the same level of theory. The zero-point energies were also obtained from these calculations. Optimized geometries, energies, and vibrational frequencies for all species are available in the SI.

RESULTS

Product Study. MNL conversions and corresponding MNQ yields/selectivities acquired in toluene as solvent at different reaction conditions are presented in Table 1. At 1 atm of O₂ and room temperature, the reaction proceeded very slowly (no detectable MNL conversion after 30 h). A 98% conversion was reached after 20 days if the reaction mixture was exposed to sun

Chart 1. Possible Structures for Peroxo Derivative Formed during MNL Oxidation

light, but no reaction occurred in the dark. ^1H NMR, UV–vis, and MS techniques identified C–C-coupling dimers, DNL and DNQ, as the major oxidation products. Both dimers formed in a 20–25% yield along with MNQ (ca. 20%) and unidentified tars. Monitoring of the oxidation process by iodometric titration revealed no peroxo compounds during the reaction course.

The dioxygen pressure strongly affected the reaction rate and the composition of products. While going from 1 to 3 atm of O_2 , the selectivity to MNQ improved significantly (Table 1, compare runs 3–5) and attained 75–80% at 3 atm, slightly depending on other reaction conditions (temperature, MNL concentration). Further increase of O_2 pressure resulted in a reduction of MNQ selectivity (52% at 10 atm, run 6), most likely due to over-oxidation processes. Importantly, MNQ overoxidation is negligible at 3 atm of O_2 , which ensures constant MNQ selectivity during the reaction course (see Table 1). The increase of MNL concentration from 0.05 to 0.25 M produced no dramatic decrease of MNQ selectivity, which contrasts with catalytic MNL oxidations reported in the literature.²¹

A characteristic feature of MNL oxidation at 3 atm of O_2 is that DNL and DNQ practically do not form (<5–6% at ca. 90% MNL conversion). Iodometric titration identified a peroxo compound formed during the reaction course. The ^1H NMR spectrum of the reaction mixture (Figure S1a) revealed, along with signals of MNL substrate and MNQ product, an additional set of signals, which evidently belongs to the peroxo compound. The total mass balance for MNL, MNQ, and peroxo compound was 92–95%. Importantly, the amount of the peroxo compound determined by titration and ^1H NMR spectroscopy was similar; the results of MNL and MNQ quantification from the GC and ^1H NMR data also coincided.

Three structures that could be supposed for the peroxo species formed during MNL oxidation are endoperoxide (EP), *ortho*-hydroperoxide (*o*-HP) and *para*-hydroperoxide (*p*-HP) (Chart 1).

After careful analysis of the literature data²⁸ (^1H NMR spectra of some representative peroxo compounds are given in Table S1 in the SI), we assigned the observed ^1H NMR spectrum to *p*-HP (hereinafter referred to as HP). The choice in favor of HP and not EP has been done based on, first of all, the presence of the signal at δ 7.82 (s, br. 1H) which is typical of the HOO-group (see examples in Table S1).^{28c,d} A marked difference in the chemical shifts of *peri*-protons, H^5 and H^8 (7.44 and 8.30 ppm, respectively), is also consistent with the structure of HP and can be explained by the presence of two completely different functional groups at C1 and C4 atoms in the HP molecule. A pronounced difference observed for the chemical shifts of H^4 and H^3 (4.90 and 6.58 ppm, respectively) allowed us to suppose that the HP is *p*-HP rather than *o*-HP because for *ortho*-quinol derivatives signals of H^4 and H^3 have more close chemical shifts.²⁹ Furthermore, for methyl-substituted hydroperoxides (the case of *o*-HP), a significant high field shift is expected for the signal of CH_3 -group bound to the C atom bearing peroxo

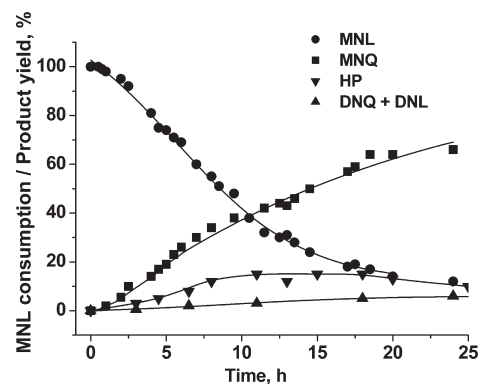


Figure 1. Substrate consumption and products accumulation during MNL oxidation. Reaction conditions: $[\text{MNL}] = 0.1 \text{ M}$, $P(\text{O}_2) = 3 \text{ atm}$, 3 mL of toluene, 80 °C.

group (see Table S1),^{28c,d} which, in effect, is not observed. The assignment of the ^1H NMR signals to *p*-HP was confirmed by ^1H , ^1H -COSY NMR technique (Figure S1b).

Attempts to isolate pure HP using TLC on silica failed because during the isolation process it decomposed rapidly, producing MNQ and some unidentified products. It should be noted that only alkyl-substituted *ortho*- and *para*-quinol derivatives, including hydroperoxides, have been described in the literature,³⁰ most likely, because nonsubstituted quinolic compounds are extremely prone to further transformations and thus can not be isolated.

$^{18}\text{O}_2$ Labeling Experiments. To probe further the reaction mechanism, MNL oxidation was carried out in the presence of $^{18}\text{O}_2$ (99.6 atom %, 1 atm.) at 80 °C (unfortunately, we had no technical possibility to perform the $^{18}\text{O}_2$ labeling experiment at elevated pressure). GC-MS analysis showed that the isotopic composition of MNQ determined from the ratio of signals at $m/z = 172$, 174, and 176 was constant during the reaction. Importantly, 98% of MNQ contained one ^{18}O atom bonded to C4 and only 2% of MNQ was labeled with two ^{18}O atoms at C1 and C4.

Kinetics Study. Typical kinetic profiles for MNL consumption and accumulation of the main products (MNQ, HP, and dimers) are shown in Figure 1. Kinetic curves for MNL and MNQ revealed a sigmoidal behavior. The kinetic curve for HP also had an induction period; then HP concentration became quasi constant and slightly decreased at high conversions, indicating an intermediate character of this product. The concentration of C–C-coupling products increased monotonically but did not exceed 5–6 mol %, even at 86–92% conversion.

Careful protection from the daylight did not affect the oxidation rate (Figure S2). Kinetic profiles obtained at different O_2 pressures and MNL concentrations are presented in Figures S3 and S4, respectively. The dependences of the oxidation rates (measured at the steady-state region of the kinetic curves) on the O_2 pressure and MNL concentration are shown in Figures 2a and 2b, respectively. The corresponding log/log plots are given in the insets.

One can see that the reaction is first order in both oxidant and substrate, i.e., the reaction rate obeys eq 2 at the steady state.

$$W = k_{\text{obs}}[\text{MNL}][\text{O}_2] \quad (2)$$

Assuming the concentration of dioxygen in toluene $3 \times 10^{-2} \text{ M}$ at 3 atm (ca. $1 \times 10^{-2} \text{ M}$ at 1 atm),^{2a,5,14} we estimated the value of bimolecular constant k_{obs} as $6.5 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ at 80 °C.

The reaction rate exhibited a typical Arrhenius dependence in the temperature range of 60–100 °C (Figure S5). The observed

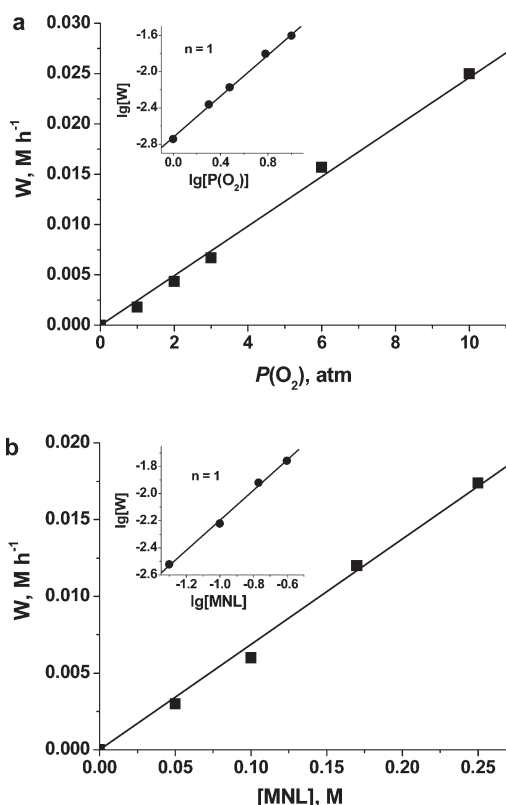


Figure 2. MNL oxidation rate (W) as a function of (a) O_2 pressure ($[\text{MNL}] = 0.1 \text{ M}$) and (b) MNL concentration ($P(\text{O}_2) = 3 \text{ atm}$). Reaction conditions: toluene 3 mL; 80°C .

activation energy E_a amounts to $8.6 \pm 1.4 \text{ kcal/mol}$. The activation parameters calculated from the corresponding Eyring plot (Figure S6) are $\Delta H^\ddagger = 8.1 \pm 0.6 \text{ kcal/mol}$ and $\Delta S^\ddagger = -50 \pm 7 \text{ eu}$.

Effects of Inhibitors and Initiators. To probe the reaction mechanism, the effects of conventional radical chain inhibitors (DTBP, HQ) and initiators (Co^{3+} , AIBN) on the MNL oxidation have been studied. The kinetic curves shown in Figure S7 clearly demonstrate that neither DTBP nor HQ, added in concentrations of 0.002–0.02 M, affect the reaction rate. GC measurements confirmed that no consumption of the radical scavengers occurred during the reaction course.

On the other hand, small additives of AIBN (its molecule easily splits into two radicals, initiating a radical chain process) led to acceleration of MNL oxidation (Figure 3a). In the presence of 3 mol % of AIBN, the rate of MNL consumption increased, and the induction period reduced, but at the same time the selectivity to MNQ decreased from 75 to 57%. On the contrary, the amount of dimeric byproduct, DNL and DNQ, increased significantly. 4-fold increase of the AIBN amount resulted in complete disappearance of the induction period, while the MNQ selectivity was reduced further and achieved only 52%.

It is precedented that traces of metals may dramatically change the rate and mechanism of oxidation reaction.³¹ Metal trace analysis (Fe, Mn, Co, and V) in the starting MNL reactant (see Experimental) revealed that the content of the transition metals was less than 12 ppm ($V < 3 \text{ ppm}$). To verify whether such amounts of metal impurity can influence MNL oxidation or not, we carried out experiments in the presence of the corresponding very small additives of cobalt(III), iron(III), and V(IV) acetylacetonates but found no effect on both the reaction rate and

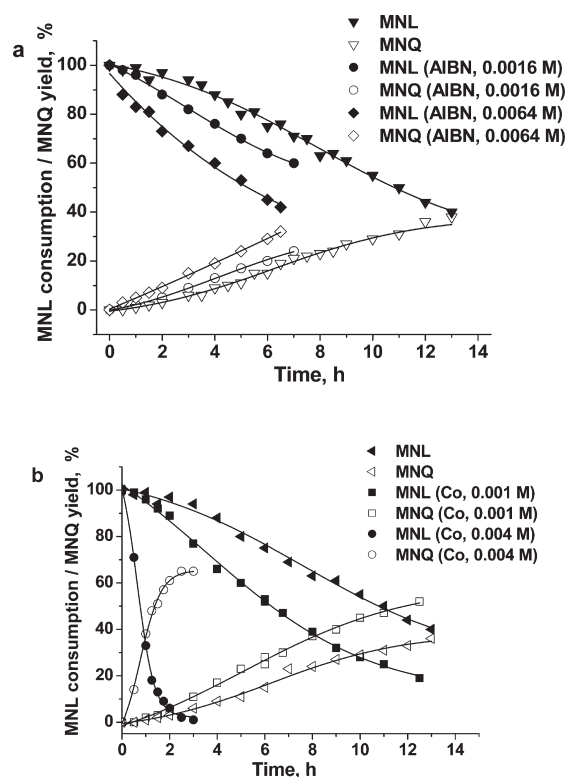


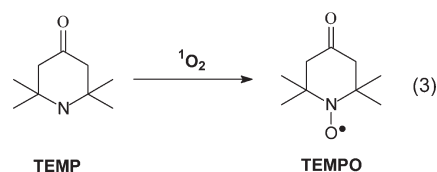
Figure 3. Effect of initiator, (a) AIBN and (b) $\text{Co}(\text{acac})_3$, on MNL oxidation. Reaction conditions: $[\text{MNL}] = 0.05 \text{ M}$, $P(\text{O}_2) = 3 \text{ atm}$, 3 mL of toluene, 80°C .

selectivity (Figure S8). At the same time, additives of $\text{Co}(\text{acac})_3$ in the amount of 0.001–0.004 M produced a significant rate acceleration effect (Figure 3b). Thus 0.004 M of $\text{Co}(\text{acac})_3$ allowed increasing the MNL oxidation rate by a factor of 12. Significantly, dimers DNL and DNQ were identified as the main byproduct, but no HP was detected during the reaction course. Hence, we may conclude that in order to produce an effect on MNL oxidation, metal concentration should be, at least, an order of magnitude higher than the maximal amount of metal, which might be introduced into reaction with MNL.

Spin Trap/Probe Experiments. Earlier, we demonstrated that naphthoxyl radicals formed during catalytic oxidation of MNL with H_2O_2 can be detected by EPR using spin trap DBNBS.²⁴ In contrast, no EPR signals were revealed during MNL oxidation with dioxygen in the presence of DBNBS (see Experimental Section for details). This implies that naphthoxyl radicals are not produced in a detectable amount during reaction with O_2 .

DMPO has been widely exploited for identification of $\text{HO}\cdot$, $\text{O}_2\cdot^-$, $\text{RO}\cdot$ and $\text{RO}_2\cdot$ radicals.³² We used this spin trap to probe the radicals formation during MNL oxidation with O_2 and found that the reaction mixture is EPR silent over all reaction course.

TEMP reacts easily with singlet oxygen producing stable nitroxyl radicals TEMPO (eq 3), which can be identified using EPR technique.³³



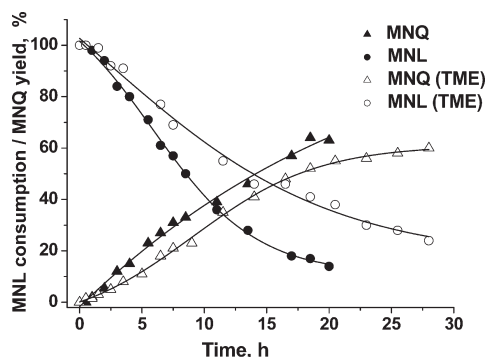


Figure 4. Effect of TME (2 M) on MNL oxidation. Reaction conditions: $[MNL] = 0.1$ M, $P(O_2) = 3$ atm, 3 mL of toluene, 80 °C.

When MNL oxidation was carried out in the presence of TEMP, no signals were detected in the EPR spectrum at the beginning of the reaction. However, after completion of the induction period, a signal consisting of a triplet with $a_N = 14.5$ G and $g = 2.006$ (Figure S9a), which is characteristic of TEMPO,³³ appeared. Careful protection of the reaction mixture from light before and during EPR measurements had no effect on the appearance of the EPR signal. When MNL was replaced for other phenols, TMP or DTBP, which do not react with O_2 at 3 atm in the absence of a catalyst, no EPR signal was detected. These results would allow suggesting that singlet oxygen was generated in the course of MNL oxidation with 3O_2 . Alternatively, HP formed in the course of MNL oxidation could react with TEMP to produce TEMPO. Indeed, we allowed TEMP to react with TBHP and found that the reaction proceeds even at room temperature, showing an EPR spectrum with the same parameters (Figure S9b). A similar EPR spectrum was registered after interaction of another hydroperoxide, 2,6-di-*tert*-butyl-4-methyl-4-hydroperoxy-2,5-cyclohexadiene-1-one, with TEMP at 80 °C. Hence, the EPR signal of TEMPO, which appeared during MNL oxidation, could be due to interaction of TEMP with either 1O_2 or HP formed in the course of the oxidation process.

TME is a known singlet oxygen acceptor; the rearranged allylic hydroperoxide is the main oxidation product formed in this reaction.^{12a,34a} Figure 4 shows that both MNL consumption and MNQ accumulation rate decreased proportionally in the presence of a 20-fold excess of TME. The selectivity of MNQ formation remained unchanged. GC-MS technique identified 2,2',3,3'-tetramethyloxirane and 2,3-dimethylbut-3-en-2-ol formed in the ratio of 2:1 along with MNL oxidation products. The epoxide could derive from the interaction of TME with HP formed during MNL oxidation,^{2,3} while the alcohol most likely originated from the allylic hydroperoxide, a characteristic product of TME and 1O_2 .^{12a,34a}

Effects of Sensitizers. Although MNL oxidation to MNQ with dioxygen proceeds efficiently in the dark, effects of different sensitizers have been assessed. Two sensitizers, which under the action of light transfer energy to triplet oxygen generating the singlet state (type II photosensitized oxygenation),³⁵ methylene blue (MB) and tetra-(*tert*-butyl)phthalocyanine (H_2Pc), were employed. The corresponding kinetic profiles are presented in Figure 5 (MB) and Figure S10 (H_2Pc). It is clear that both sensitizers increased significantly the MNL oxidation rate but reduced the selectivity of MNQ formation. Thus, the latter achieved only 30–35% in the presence of MB.

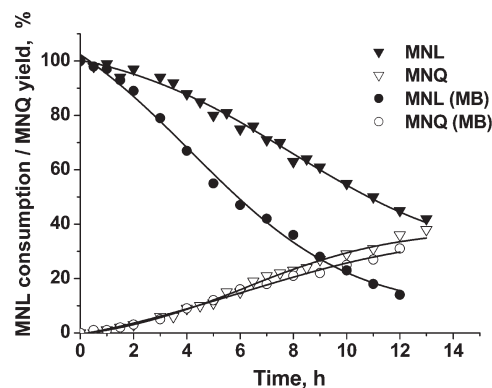


Figure 5. Effect of methylene blue (MB, 0.001 M) on MNL oxidation with O_2 . Reaction conditions: $[MNL] = 0.05$ M, $P(O_2) = 3$ atm, 3 mL of toluene, 80 °C.

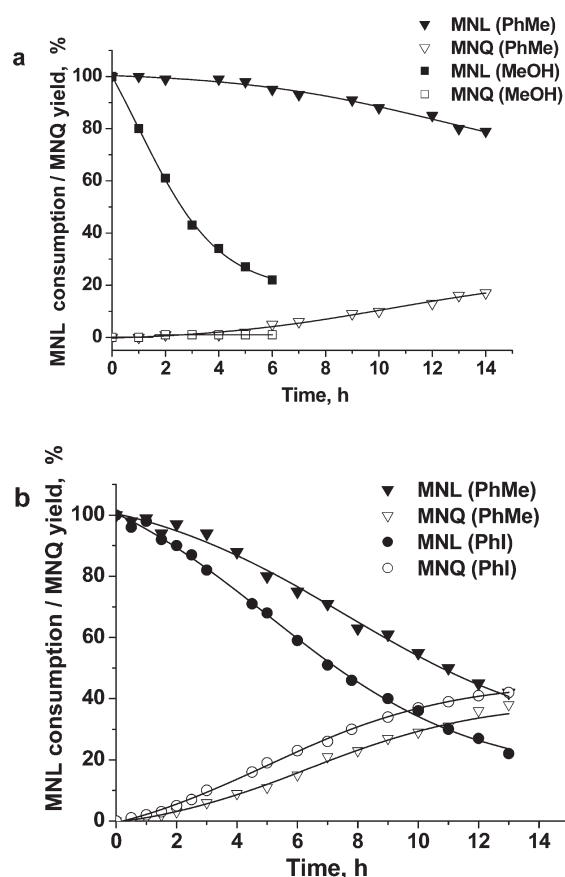


Figure 6. Effect of solvent nature on MNL oxidation: (a) methanol versus toluene, 60 °C and (b) iodobenzene versus toluene, 80 °C. Reaction conditions: $[MNL] = 0.05$ M, $P(O_2) = 3$ atm, solvent 3 mL.

MNQ in a triplet excited state (3MNQ) is known to operate through the type I photosensitization mechanism, which includes interaction of the excited sensitizer with substrate or solvent yielding radical ions capable of reacting with triplet oxygen to produce oxygenated products.³⁶ To check the possibility of autoacceleration of the MNL oxidation via such a mechanism, we studied MNL oxidation in the presence of 0.005 M MNQ. No influence on the reaction rate and selectivity was found (Figure S11).

Solvent and Base Effects. Both the rate and selectivity of MNL oxidation with O_2 depend dramatically on the nature of solvent used; only nonpolar solvents are suitable for the production of MNQ.^{19,21} Figure 6a shows the reaction profile in methanol in comparison with the reaction in toluene. The oxidation rate increased more than 10 times, but no MNQ was obtained. On the contrary, the reaction was very slow in acetonitrile and cyclohexanone. Additives of pyridine to toluene produced a rate-retarding effect.

Iodobenzene was employed as the reaction medium to probe the so-called “external heavy atom effect” (vide infra).^{14,17} Kinetic curves shown in Figure 6b reveal a ca. 2-fold increase of the MNL oxidation rate upon replacement of toluene for PhI. Importantly, the selectivity to MNQ remained at the same level as in toluene.

Small additives of water changed neither MNL oxidation rate nor its selectivity (Figure S12). The addition of a methanolic solution of tetrabutylammonium hydroxide (0.025 M, 95 μ L) resulted in immediate appearance of a dark brown color, which evidently indicated the formation of tars. After 15 min, MNL conversion was already 75%, but no MNQ was produced.

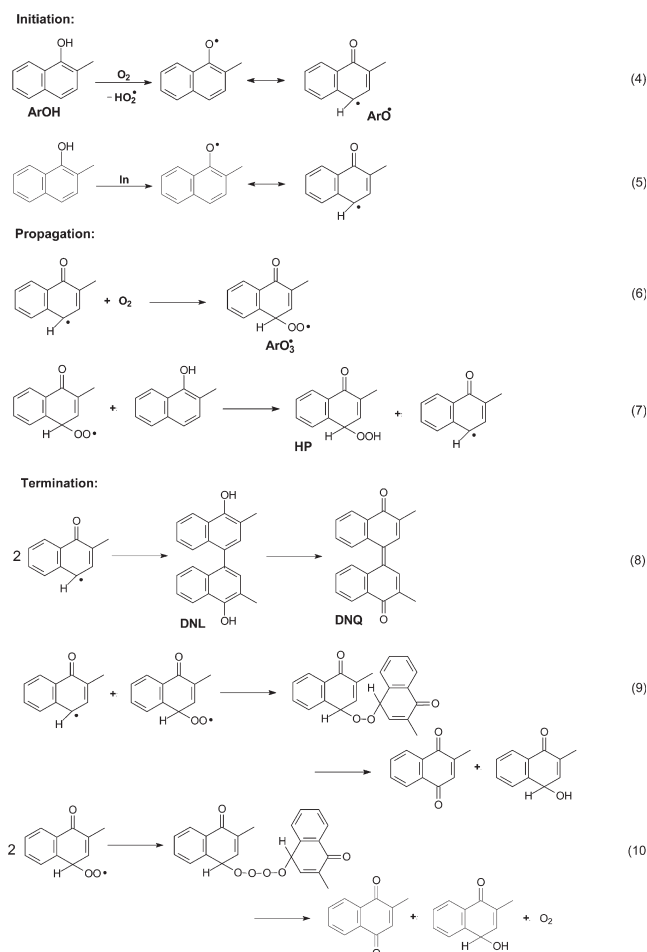
DISCUSSION

Free Radical Autoxidation Hypothesis. In the absence of light, metal ions, or bases, oxidation of phenols is usually a slow process.²⁰ Normally, phenol autoxidation proceeds via radical chain mechanism and involves the formation of aryloxy radicals at the first step followed by their numerous transformations (C–C and C–O coupling, peroxidation, etc.).²⁰ Autoxidation of some hindered phenols and naphthols leads to hydroperoxides as stable major products.^{23a,28a,28c,28d,37–39} Greenland et al. reported that 2,3,4-trimethylnaphthalen-1-ol (TMNL) easily reacts with dioxygen in the absence of catalysts or bases at atmospheric pressure and room temperature producing 4-hydroperoxy-2,3,4-trimethylnaphthalen-1-(4H)-one.^{28d} The extremely high reactivity of TMNL was rationalized in terms of a buttressing effect as a result of 4,5 *peri* interaction, which is relieved by the formation of an sp^3 carbon at C4 atom.^{28d} However, no mechanistic studies on the reaction of TMNL with O_2 were reported.

The peroxy compound revealed in the course of MNL oxidation was ascribed to HP (Chart 1) based on the 1H NMR and 1H , 1H -COSY data. On the basis of the general principles of autoxidation chemistry,^{2–4,20,40,41} we can display a hypothetical radical chain mechanism of MNL oxidation as a sequence of reactions 4–10 that lead to the formation of HP, MNQ and dimeric products.

Once naphthoxyl radical is formed, it can interact with another $ArO\bullet$ to afford dimeric naphthol (termination step 8) followed by further oxidation of DNL to DNQ. Alternatively, $ArO\bullet$ radical can be entrapped by molecular oxygen producing peroxy radical $ArO_3\bullet$ (propagation step 6), which then abstracts hydrogen atom from another $ArOH$ molecule to give $ArO\bullet$ and HP as a primary oxidation product (propagation step 7). MNQ could form due to chain termination (reactions 9 and 10) and/or in the course of further transformations of HP.

At room temperature and low oxygen pressure (1 atm), MNL oxidation is sensitive to sunlight, the selectivity to MNQ is low (20%) and C–C-coupling products form in considerable amounts (ca. 50% yield). These facts indicate a free radical autoxidation process with predominant chain termination via reaction 8.

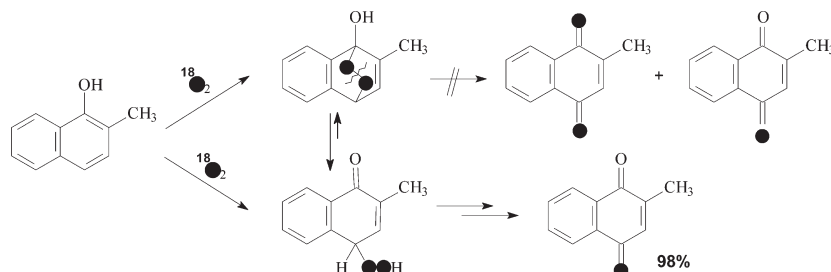


Does the same mechanism operate at elevated O_2 pressure? In contrast to the low pressure reaction, MNL oxidation at 3 atm of O_2 proceeds with the same rate in the dark and in the daylight (Figure S2), which excludes any photochemically induced reaction pathway and prejudice radical chain mechanism. The excellent reproducibility of the reaction rates observed for MNL oxidation is not typical for radical chain processes² and raises doubts on the autoxidation mechanism via reactions 4–10.

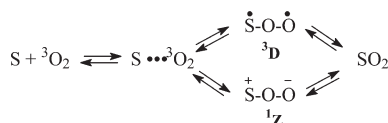
Radical chain mechanism can often be distinguished using special inhibitors and initiators.^{2–4} Thus the oxidation of 1-alkyl-2-naphthols was ascribed to radical chain autoxidation based on the rate-retarding effect of DTBP.³⁸ We found that additives of DTBP or HQ produce no effect on MNL oxidation by O_2 (Figure S7), and the inhibitors are not consumed in the course of the reaction. However, it is known that some authentic radical chain processes are unaffected by addition of scavengers when the chains are short and/or the rate constant for biomolecular radical scavenging is small relative to those for propagation.

MNL oxidation with O_2 can be accelerated markedly by the addition of initiators, e.g., AIBN or transition metal complex (Figure 3). However, this leads to a significant decrease of MNQ selectivity (52–55% with AIBN versus 76% without additives). Furthermore, DNL and DNQ appear among the oxidation products, indicating that naphthoxyl radicals are involved in the oxidation process initiated by the additives.

It is well-established that rates of liquid-phase autoxidation are independent of O_2 concentration when the chains are reasonably long, i.e., when the propagation steps dominate product formation.^{2–4} The value of oxygen pressure at which the passage

Scheme 2. Possible Routes to MNQ Suggested Based on $^{18}\text{O}_2$ Labeling Experiments

Thermal Intersystem Crossing. As was mentioned in the Introduction, in rare cases mechanisms of thermal ISC (spin inversion) operate in the oxidation of reactive organic substrates with triplet oxygen. Diradicaloid (^3D) or zwitterionic (^1Z) intermediates are supposed to be involved in such processes.^{8,9,11–16}



^3D intermediates are preceded mostly for transformations of nonpolar or low polar substrates. Such intermediates have been recognized by the action of radical scavengers and identified using EPR spin-trapping technique.^{8,9} In the light of the absence of effects of DTBP and HQ on the MNL oxidation rate coupled with the absence of EPR signals in the presence of DNBBS and DMPO, the formation of any long-lived diradicals in the title reaction seems to be unlikely. Yet, a diradicaloid intermediate would not account for the observed solvent effects.

Zwitterions are widely accepted as intermediates in reactions of singlet oxygen with organic substrates^{12,36,47,49} and have been suggested for a few spontaneous oxidations with triplet oxygen.^{12,14} Polar solvents favor the formation of such intermediates and thus increase the overall reaction rate⁵⁰ but, at the same time, act as nucleophiles, which causes side reactions and rearrangements of zwitterions, thus resulting in low reaction selectivity.^{14,36} This is exactly what was observed for both HEL¹⁴ and MNL oxidation in MeOH.

Turro et al. suggested the formation of zwitterion (or perepoxide) during the course of the spin-forbidden reaction between the strained acetylene TMTCH (Chart S1) and $^3\text{O}_2$.^{12a} They also proposed the generation of free singlet oxygen by decomposition of an intermediate oxygen–acetylene complex, thus producing the starting organic substrate:



However, theoretical calculations prejudiced thermal $^1\text{O}_2$ formation from $^3\text{O}_2$ and TMTCH via reaction sequence 12.⁵¹

To test for a possible formation of singlet oxygen in our system we performed MNL oxidation in the presence of TME, a known $^1\text{O}_2$ acceptor.³⁴ The rate of both MNL consumption and MNQ accumulation was notably reduced (Figure 4), but tetramethyloxirane predominated over 2,3-dimethylbut-3-en-2-ol among the TME oxidation products, indicating that the observed reactivity is, most likely, due to HP rather than $^1\text{O}_2$. Nevertheless, the formation of minor amounts of singlet oxygen cannot be ruled out completely.

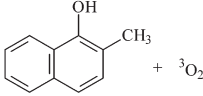
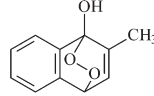
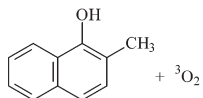
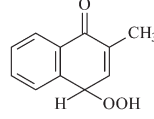
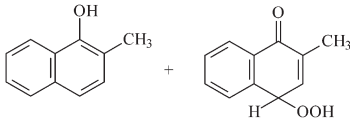
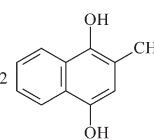
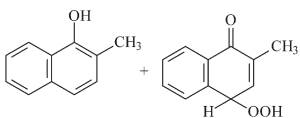
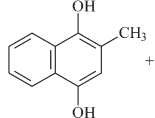
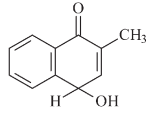
It is well-known that many condensed aromatic compounds interact with $^1\text{O}_2$ to afford endoperoxides which, in turn, can release singlet oxygen upon heating.^{34a,36,52,53} In principle, the appearance of singlet oxygen might be a manifestation of the EP formation in the course of MNL oxidation. Interconversions between hydroperoxides and endoperoxides are well-precedented in the literature.^{47,54,55} Highly activated phenols, such as 2,4-di-*tert*-butyl-5-methoxyphenol, were reported to react with $^1\text{O}_2$ to yield endoperoxides which readily transformed to stable hydroperoxides.⁵⁶ The photosensitized peroxidations of electron-rich aromatic compounds, including phenols, generally lead to the corresponding 4-hydroperoxy-2,5-cyclohexadienones as final products rather than to endoperoxides.^{47,57}

The results of the $^{18}\text{O}_2$ labeling experiments are compatible with the formation of MNQ either directly from HP or via EP intermediate followed by C–O cleavage of the latter to yield HP (Scheme 2). The very low ^{18}O labeling at C1 implies that, if EP were really involved in the oxidation process, homolytic cleavage of the endoperoxide O–O bond (the route suggested by Reddy and Bendikov for oxidation of nonpolar acenes to quinones)¹⁶ could not be a principal reaction pathway.

DFT calculations (Table 2, Entries 1 and 2) showed that the formation of EP from MNL and $^3\text{O}_2$ is thermodynamically unfavorable. Keeping in mind that MNL oxidation with O_2 has an activation barrier $E_a = 8.6 \text{ kcal mol}^{-1}$, it cannot proceed through an intermediate state that is $20.7 \text{ kcal mol}^{-1}$ above the reactants. For the same reason, singlet oxygen, which lies 22 kcal mol^{-1} higher than triplet oxygen,^{12a} cannot be not involved in the main reaction pathway leading to MNQ. Therefore, DFT calculations support our conclusion that HP rather than EP should be a predominant intermediate in the MNL oxidation. Some manifestations of $^1\text{O}_2$ (first of all, the presence of 2,3-dimethylbut-3-en-2-ol among the TME oxidation products) could be due to a dead-end, minor route leading to transformation of HP to EP followed by subsequent release of $^1\text{O}_2$ from the latter.

The following facts collectively support mechanism of thermal ISC that involves most likely the formation of a zwitterionic intermediate in the rate-limiting step of MNL oxidation with $^3\text{O}_2$. First, the reaction rates are the same in the dark and upon irradiation. Second, the lack of dimeric byproduct and adducts with spin traps indicate very low (if any) concentration of radical species. Third, the external heavy atom effect (enhancement of the reaction rate ca. 2 times upon replacing toluene for iodo-benzene) points out that spin inversion is involved in the rate-limiting step. Forth, the established rate law (first orders in O_2 and MNL) indicates that both O_2 and MNL are involved in the rate-limiting step. Fifth, the significant rate enhancement in

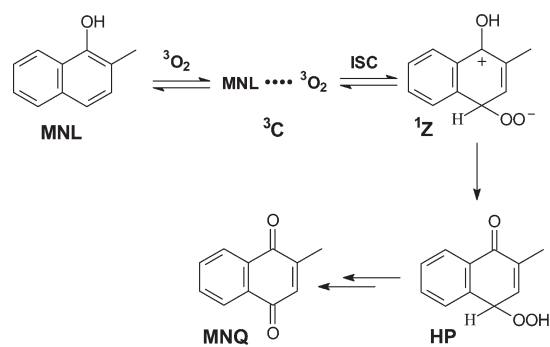
Table 2. Enthalpies of Some Possible Reactions Operating in MNL Oxidation, Calculated on the B3LYP/TZVP Level

Entry	Reagents	Products	ΔH , kcal/mol
1			20.7
2			-0.8
3		2 	-68.4
4		 + 	-55.2

methanol coupled with the lack of MNQ selectivity is consistent with a polar transition state, zwitterion (*vide supra*). Sixth, the activation parameters found for MNL oxidation ($\Delta H^\ddagger = 8.1 \text{ kcal mol}^{-1}$ and $\Delta S^\ddagger = -50 \text{ eu}$) are close to the corresponding parameters established for the spin-forbidden reaction of HEL with $^3\text{O}_2$ in toluene ($\Delta H^\ddagger = 10.2 \text{ kcal mol}^{-1}$ and $\Delta S^\ddagger = -39 \text{ eu}$);¹⁴ the negative value of the entropy is indicative of associative transition state developing in the course of addition of dioxygen to MNL. Seventh, the second-order rate constant estimated from the kinetic data ($6.5 \times 10^{-4} \text{ M}^{-1}\text{s}^{-1}$) has the same order of magnitude as the rate constant found for the reaction of HEL.¹⁴

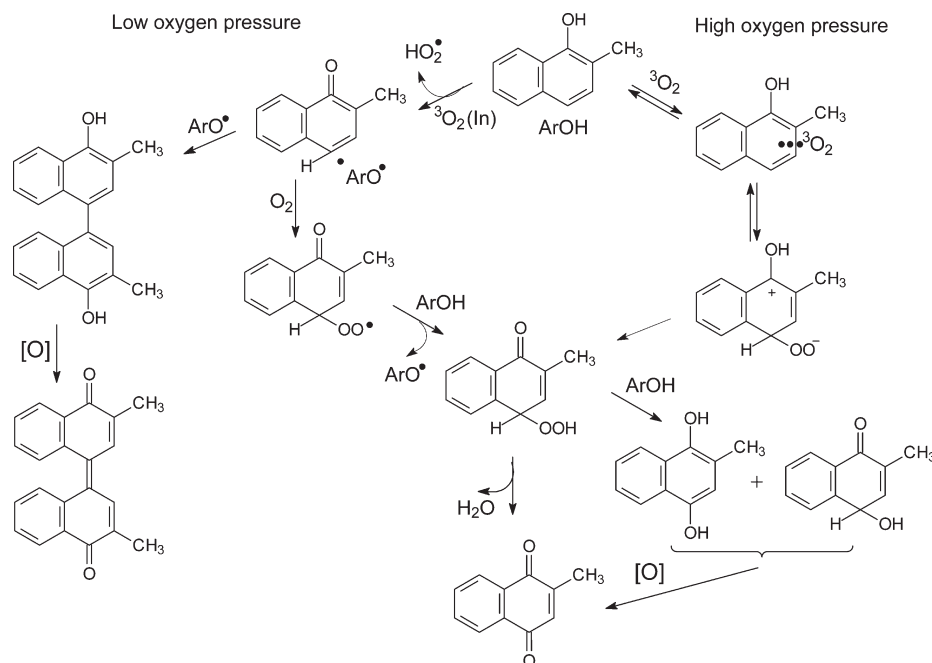
The common features established for the oxidation of HEL and MNL allowed us to suggest that ISC mechanism, similar to that proposed by Seip and Brauer,¹⁴ might be responsible for the selective transformation of MNL to HP (Scheme 3). This mechanism involves the formation of loosely bound complex ^3C formed by collision of MNL and $^3\text{O}_2$, which reacts directly in a spin-forbidden step under charge transfer from MNL to oxygen to yield zwitterion ^1Z which, in turn, transforms to HP.

The driving force for the spin-forbidden reactions is supposed to be either a strong strain in the substrate molecule,^{12,14,15} which reduces significantly in the product, or resonance effects.^{13,15} Salem et al. have demonstrated that spin inversion is favored by high ionic character in the singlet state involved in the transition.⁵⁸ The presence of electron-donating substituents in the substrate molecule might promote a favorable situation for spin-orbit coupling, i.e., a one-center $p_x \rightarrow p_y$ jump on an oxygen atom in a charge-transfer complex of $\text{MNL} + ^3\text{O}_2$.^{12a,b} In other words, the importance of charge transfer may increase with the enhanced donor strength of an electron-rich substrate (e.g., MNL) with a low ionization potential. Nonionizing HBA solvents, such as acetonitrile or cyclohexanone, should reduce

Scheme 3. Proposed Thermal ISC Mechanism for MNL Oxidation with O_2 

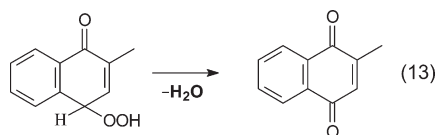
the electron-releasing strength of the OH group via hydrogen bonding, thus increasing the MNL ionization potential and decreasing the oxidation rate. Indeed, MNL oxidation was very slow in both these solvents. In the framework of such mechanism, the increasing amount of electron-donating substituent would increase the reaction rate. Indeed, TMNL spontaneously reacts with dioxygen in its ground state to form the corresponding hydroperoxide at ambient conditions (1 atm air, room temperature).^{28d}

Routes Leading to MNQ. Finally, we would like to discuss possible routes that could afford conversion of HP to MNQ. Different ways of transformation of the primary oxidation products, hydroperoxides, have been described in the literature.^{2-5,40} It was reported that 2- and 4-hydroperoxycyclohexadienones can be decomposed by alkali to the corresponding quinols.^{20b} However, additives of Bu_4NOH produced a strong negative effect on

Scheme 4. The Main Pathways Operating in MNL Oxidation with $^3\text{O}_2$ 

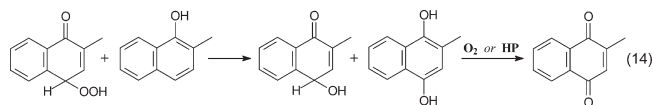
the MNQ yield. A bimolecular reaction between two HP molecules producing ArO^\bullet and ArO_3^\bullet radicals along with H_2O molecule seems unlikely because no indication of chain branching has been found using the radical scavengers and spin traps.

An alternative route to MNQ could be dehydration of HP via reaction 13.



Indeed dehydration of secondary hydroperoxides to produce unsaturated carbonyl compounds was reported in the literature.^{2,59} Such reactions are favored by the formation of conjugate $\text{C}=\text{O}$ and $\text{C}=\text{C}$ bonds.^{28a,59} Note, however, that suggesting reaction 13 as the only route from HP to MNQ one cannot explain the autocatalytic character of the kinetic curves, which is observed for MNL oxidation.

On the other hand, the autocatalytic behavior might be understood if we suppose that HP reacts with starting MNL to produce the two-electron oxidation products, naphthohydroquinone (MNHQ) and isoelectronic quinol (MNQL) (or alternatively, two MNHQ molecules), which are subsequently oxidized to the target MNQ (eq 14).



In this case, the observed sigmoidal-shaped character of the kinetic curves might be rationalized in terms of the establishment of a steady-state concentration of HP in the system. DFT calculations confirmed that the formation of such intermediate products from HP and MNL is reasonable from the thermodynamic point of view (Table 2, entries 3 and 4). The fact that

neither MNHQ nor MNQL were identified among the oxidation products was not surprising because such compounds are normally much more reactive substrates than parent phenols and undergo rapid oxidation to quinones.^{20,45} Additionally, we allowed MNL to react with a rather stable hydroperoxide, 2,6-di-*tert*-butyl-4-methyl-4-hydroperoxy-2,5-cyclohexadiene-1-one, and found that even at room temperature this reaction proceeds fast and produces MNQ among other oxidation products. Hence, the reaction sequence 14 seems to be reasonable. However, we cannot rule out completely that other routes of HP transformation to MNQ (first of all, dehydration) might contribute to the product formation.

Keeping in mind all the results collectively, we can suggest the following scheme of MNL transformations in the presence of dioxygen (Scheme 4).

CONCLUSIONS

We have studied here in detail the mechanism of unusual direct oxidation of MNL by triplet oxygen leading to the selective formation of MNQ, which is a valuable product, vitamin K_3 . The results obtained in this study have demonstrated that at elevated pressure (3 atm of O_2) neither photooxidation nor free radical (nor cation radical) autoxidation are the main mechanisms responsible for the formation of the target quinone.

The insensitivity of the reaction to light rules out any photo-oxygenation mechanism. Furthermore, the exposure to sunlight in the presence of type II photosensitizers leads to decreasing selectivity of MNQ formation. In turn, type I sensitizers do not affect the reaction at all.

The autocatalytic character of the reaction and the formation of hydroperoxide as an intermediate product, in principle, agree with the chain radical autoxidation mechanism, but the first reaction order in dioxygen coupled with the observed composition of products (minor amounts of dimeric DNL and DNQ)

conflict with each other in the framework of such a mechanism. The absence of rate-retarding effects of radical scavengers (DTBP, HQ) along with the negative results of the spin-trap experiments (DBNBS, DMPO) and the observed solvent effects do not support the conventional autoxidation mechanism as well. The radical autoxidation mechanism can be pushed by the addition of chain initiators, but the product composition changes significantly in favor of dimeric byproduct, which result from C–C coupling of naphthoxyl radicals.

Radical cation autoxidation mechanism is consistent with the first reaction order in O₂ and the absence of dimeric products. However, this mechanism can be eliminated as the main route leading to MNQ since no promotional effects of BP, MeCN, or MNQ, expected for this type of mechanism, were found and no superoxide was identified by EPR spin-trapping technique. We cannot completely exclude the SPLET mechanism for the reaction in MeOH, but such mechanism cannot be responsible for the selective transformation of MNL to MNQ that occurs only in nonpolar solvents.

After careful analysis of the literature and of our own results we came to the conclusion that a rare spin-forbidden process that involves thermal ISC (spin inversion) and, most likely, occurs via the formation of a zwitterionic intermediate in the rate-limiting step contributes significantly to the O₂-based selective oxidation of MNL to MNQ. This mechanism is supported by (i) the same reaction rates in the presence and in the absence of light; (ii) the lack of dimeric byproduct and independence of MNQ selectivity on the initial MNL concentration; (iii) the first reaction order in both substrate and oxidant; (iv) the observed rate constant and activation parameters close to those found for HEL oxidation with ³O₂; (v) the negative ΔS^\ddagger value indicative of associative mechanism; (vi) the enhancement of the reaction rate upon replacing toluene by iodobenzene (external heavy atom effect); and (vii) the significant increase of the reaction rate and the lack of selectivity to MNQ in MeOH compared to toluene. To the best of our knowledge, this is the first example demonstrating that the reaction of a phenolic compound with molecular oxygen can involve a spin-inversion step.

The mechanism of MNL oxidation can be altered by addition of initiators, bases, or type II sensitizers (the latter upon irradiation), but these additives lead to the loss of MNQ selectivity and the formation of dimeric and polymeric products. In the presence of radical initiators as well as at low O₂ pressure, radical chain autoxidation evidently competes with the dark spin-forbidden process. On the other hand, the radical cation autoxidation mechanism may contribute to the oxidation process at high pressures. In turn, basic additives and/or alcoholic solvents may facilitate electron transfer mechanisms. The delicate balance among all these mechanisms depends mainly on the dioxygen pressure and the solvent nature. The appropriate choice of the reaction conditions, first of all, the optimal O₂ pressure and the appropriate, nonpolar solvent, allows converting MNL to the target vitamin K₃ with high selectivity.

■ ASSOCIATED CONTENT

S Supporting Information. ¹H NMR and ¹H,¹H-COSY NMR data, kinetic data, effects of various additives, EPR spectra in the presence of TEMP, as well as optimized geometries, energies, and vibrational frequencies. This information is available free of charge via the Internet at <http://pubs.acs.org>.

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