

# Comprehensive Structural and Electronic Properties of 2-Azaadamantane *N*-Oxyl Derivatives Correlated with Their Catalytic Ability

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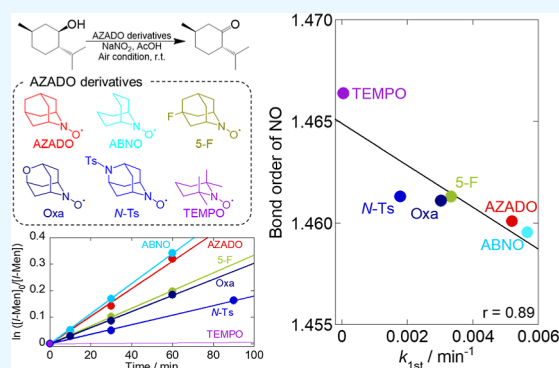
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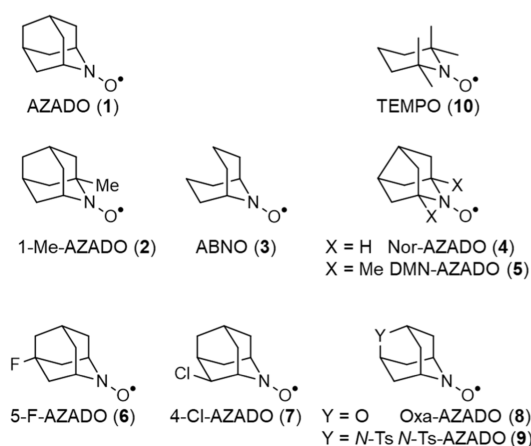
**ABSTRACT:** Herein, a comprehensive kinetic study is performed to compare the catalytic efficiency of 2-azaadamantane *N*-oxyl (AZADO) derivatives with that of 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO) used as radical catalysts in the aerobic oxidation of *l*-menthol. Furthermore, the correlation between the catalytic activity and structural/electronic parameters of AZADOs and TEMPO is elucidated. The reaction rate constants achieved with several AZADO derivatives exhibit moderate relationships with spectroscopic parameters, such as the hyperfine coupling constant of the N atom ( $A_N$ ) and NO stretching vibration frequency ( $\nu_{NO}$ ) observed in electron spin resonance and infrared spectra, respectively. The planarity C–(NO)–C angle ( $\varphi$ ) at the N atom, determined by density functional theory (DFT) calculations, also strongly correlates with the  $A_N$  and  $\nu_{NO}$ . Moreover, the bond order of NO, which strongly depends on the structural and electronic properties of NO radicals, correlates with radical activity; thus, the radical activity can be predicted by DFT calculations, thereby accelerating the synthesis of new AZADO derivatives without requiring alcohol oxidation experiments.



## INTRODUCTION

The development of highly efficient and selective oxidation catalysts is important in several fields, such as organic chemistry, natural product synthesis, and industrial chemistry. Stable nitroxyl radicals have recently attracted considerable attention as metal-free catalysts owing to their safety, environmental sustainability, and designability.<sup>1–3</sup> Although 2,2,6,6-tetramethylpiperidinyl *N*-oxyl (TEMPO) is a well-known organic radical catalyst with industrial applications, it is limited to the oxidation of primary alcohols.<sup>4–6</sup> To overcome this limitation, the stable 2-azaadamantane *N*-oxyl (AZADO) organic radical was developed as an efficient and selective catalyst for the oxidation of primary and secondary alcohols under mild conditions.<sup>7–12</sup> The difference in the catalytic activity of AZADO and TEMPO was explained as a steric effect arising from the existing bulky substitution of four methyl groups at the 2- and 6-positions. Although numerous AZADO derivatives (Scheme 1) have been synthesized and applied to AZADO-mediated catalytic oxidation, explaining their reactivity purely in terms of steric effects is challenging. A study of alcohol oxidation with 5-F AZADO revealed that the electronic interactions on the NO bond have a significant influence on the catalytic ability of AZADOs in oxidative reactions. Additionally, the oxoammonium ion, which is formed by the oxidation of AZADO, was identified as the active catalytic species.<sup>8</sup> Stahl et al. achieved efficient electrochemical oxidation of the alcohol beyond that of

## Scheme 1. Structure of AZADO Derivatives and TEMPO



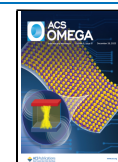
AZADO by tuning the oxidation potential of TEMPO.<sup>13</sup> If the catalytic activity of AZADO derivatives can be predicted

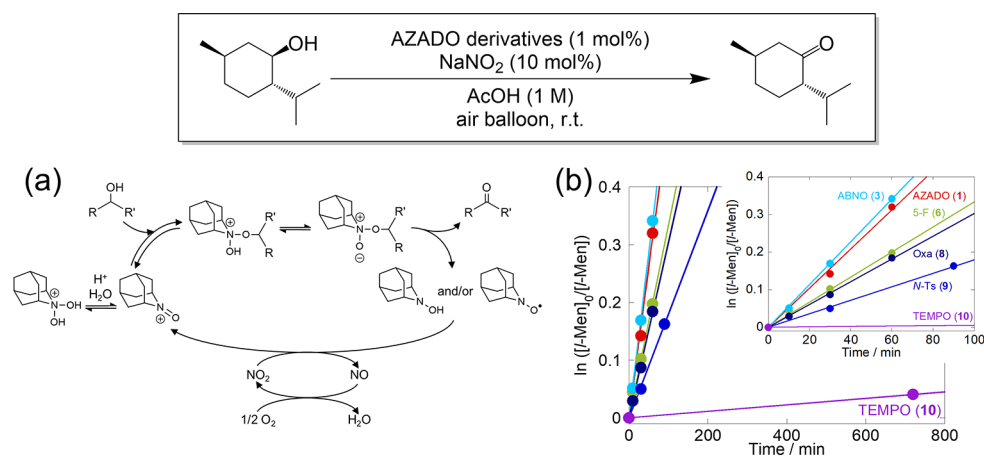
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**Figure 1.** Reaction condition of *l*-menthol oxidation using AZADOs: (a) plausible mechanism and (b) time profile of oxidation reaction.

**Table 1.** Observed Oxidation Rates, Hyperfine Coupling Constants of N Atoms ( $A_N$ ), and NO Stretching Wavenumbers ( $\nu_{NO}$ ), along with the Calculated Values of Planarity C–(NO)–C Angle ( $\varphi$ ) and Bond Order of NO in AZADO Derivatives, Including TEMPO

catalyst	observed		calculated <sup>f</sup>			
	$k_{1st} \times 10^{-3}/\text{min}^{-1a}$	hyperfine coupling constant of N atom ( $A_N$ )/mT	wavenumber of NO stretching ( $\nu_{NO}$ ) <sup>d</sup> /cm <sup>-1</sup>	planarity C–(NO)–C angle ( $\varphi$ ) <sup>g</sup> /degree	bond order of NO	
AZADO (1)	5.19	1.86065	1280.5	21.290	1.4628	
1-Me (2)	n.d. <sup>b</sup>	1.83179	1305.6	21.052	1.4632	
ABNO (3)	5.67	1.86087	1289.7 <sup>e</sup>	21.914	1.4621	
Nor (4)	n.d. <sup>b</sup>	1.79693	1297.9 <sup>e</sup>	20.127	1.4645	
DMN (5)	n.d. <sup>b</sup>	1.76962	1337.4	19.850	1.4656	
5-F (6)	3.34	1.79571 <sup>c</sup>	1283.4	21.219	1.4635	
4-Cl (7)	n.d. <sup>b</sup>	1.81260	1271.8	20.625	1.4632	
Oxa (8)	3.03	1.83402	1379.8	21.228	1.4635	
N-Ts (9)	1.79	1.84548	1356.7	21.522	1.4636	
TEMPO (10)	0.0556	1.59471	1339.3	16.500	1.4676	

<sup>a</sup>Calculated from *l*-menthol oxidation, obtained from *J. Org. Chem.* **2014**, *79*, 10256. <sup>b</sup>Not detected. <sup>c</sup>Hyperfine coupling constant of fluorine atom ( $A_F$ ) was also observed at 0.554538. <sup>d</sup>Measured by the attenuated total reflection (ATR) method. <sup>e</sup>Measured by thin film method in  $\text{CCl}_4$ . <sup>f</sup>Optimization, frequency calculation, and natural bond orbital (NBO) analysis of all compounds were performed using density functional theory (DFT) with the UB3-LYP functional and a 6-311+G(d) basis set using Gaussian 16. <sup>g</sup>As shown in Figure 2a.

using a systematic approach rather than the trial-and-error approach used to evaluate the oxidation, then the catalyst design can be more easily accomplished and the formation of novel radical materials is expected to be realized. To achieve this goal, the present study compares the catalytic activities of AZADOs and TEMPO obtained *via* spectroscopic measurements.

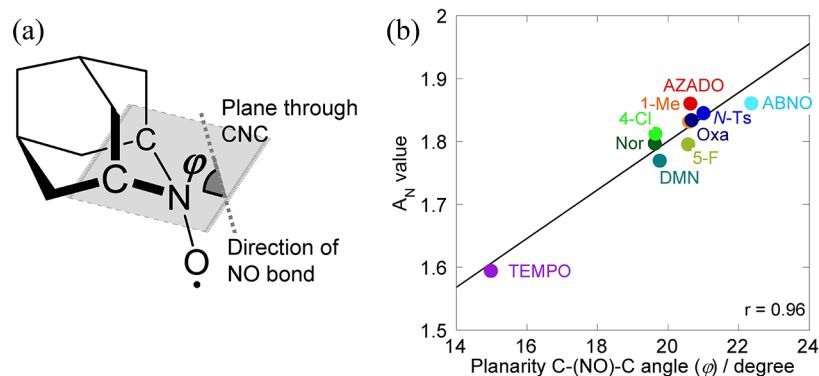
The reaction rate of *l*-menthol with AZADOs was analyzed as a pseudo-first-order reaction. We previously reported the oxidation of *l*-menthol by AZADOs and TEMPO.<sup>14</sup> The oxidation of *l*-menthol was catalyzed by AZADO derivatives (1, 3, 6, 8, and 9) or TEMPO (10) in acetic acid in the presence of the NOx generator sodium nitrite under ambient air conditions (Figure 1). Although the reaction proceeds under weakly acidic conditions, we have proposed a mechanism in which the hydrogen atom at the  $\alpha$ -position of the alcohol is withdrawn as a proton rather than a hydride (Figure 1a). This mechanism involves the oxidation of *l*-menthol by the catalytically active oxoammonium ion.<sup>15</sup> Subsequently, the nitroxyl radical and hydroxylamine formed in the alcohol oxidation step are reoxidized by NOx, thereby regenerating the active oxoammonium ion. Because this

oxidation proceeds under ambient air conditions,  $\text{O}_2$  should be in excess, and thus the amount of oxygen should be constant relative to the other chemical species, resulting in a pseudo-first-order reaction with respect to the amount of *l*-menthol. The reaction rate is expressed as follows

$$-\frac{d[l\text{-Men}]}{dt} = k[l\text{-Men}][\text{O}_2]_0 = k_{1st}[l\text{-Men}]$$

$$\therefore k_{1st} = k[\text{O}_2]_0$$

where  $k$  is the second-order-reaction rate constant,  $[l\text{-Men}]$  is the concentration of *l*-menthol, and  $[\text{O}_2]_0$  is the initial concentration of oxygen, respectively.<sup>16</sup> The pseudo-first-order rate constant ( $k_{1st}$ ) was evaluated based on the reduction in the amount of *l*-menthol measured by gas chromatography. The evaluated  $k_{1st}$  values for AZADOs are listed in Table 1. Notably, the  $k_{1st}$  value of AZADO and TEMPO ( $5.19 \times 10^{-3}$  and  $5.56 \times 10^{-5} \text{ min}^{-1}$ , respectively) differed by approximately 100-fold. Various AZADO derivatives exhibit significant differences. For example, ABNO (3) exhibits the fastest reaction rate ( $5.67 \times 10^{-3} \text{ min}^{-1}$ ), and the reaction rate of AZADO is similar to that of ABNO. N-Ts (9,  $1.79 \times 10^{-3}$



**Figure 2.** (a) Definition of planarity C-(NO)-C angle ( $\phi$ ) around the nitroxyl radical and (b) relationship between  $A_N$  and  $\phi$ .

$\text{min}^{-1}$ ) exhibited the slowest reaction, approximately 3 times slower than that of ABNO. A previous study found that this trend could not be explained simply by the relative oxidation potentials of AZADOs and TEMPO owing to the lack of correlation between their reaction rates.<sup>7</sup>

Moreover, steric effects should be taken into account; however, such effects have not yet been quantitatively measured, owing to the difficulty in quantitatively evaluating the steric effect. In contrast, the present study evaluated this effect from an experimental perspective. In particular, an evaluation of the effect of the electronic structure on the N atoms was conducted using the analysis of electron spin resonance (ESR), infrared (IR) absorption, and quantum chemical calculations, and the correlation between these data and the reaction rate was elucidated.

## RESULTS AND DISCUSSION

ESR is an effective technique for characterizing the properties of radicals.<sup>17</sup> ESR spectra provide information about the structural and electronic environments of the target radical. The hyperfine coupling constant of the N atom ( $A_N$ ) in nitroxyl radicals provides valuable insights into the electron density and hybrid orbitals of the N atoms. If a correlation between the reaction rate and hyperfine coupling constant can be established, then analysis of the hyperfine coupling data will allow the structure of AZADOs and the reaction rate to be correlated. Although ESR measurements of TEMPO have been reported, comprehensive ESR analyses of the AZADO derivatives are currently lacking. We therefore measured the ESR spectra of AZADO derivatives in a dichloromethane solution at room temperature. The spectra of all AZADO derivatives and the obtained parameters are shown in the Supporting Information (Figures S1–S10) and summarized in Table 1. As an example, the spectra of both AZADO and TEMPO show triplet signals characteristic of nitroxyl radicals, owing to the nuclear spin of nitrogen ( $I = 1$ ). The vertical axis of all spectra is normalized by the area, showing the line width difference as a height difference. The spectrum of TEMPO is sharper than that of the AZADO derivatives. Thus, the spectral shapes of AZADOs at various concentrations were confirmed and remained constant under our experimental conditions, thus indicating that the interactions between radicals can be ignored (Table S1). We believe that the main reason for the broad line width observed in the spectra of the AZADO derivatives is the poorly resolved hyperfine coupling of  $^1\text{H}$  nuclei; however, the  $g$ -values and  $A_N$  can be determined without reaction rate. By contrast,  $A_N$  values for AZADO (1.86

mT) and TEMPO (1.59 mT) differed significantly.  $A_N$ s are influenced by the difference in electron density on the N atom in AZADOs and the hyperconjugate effects on the NO  $\pi$ -bond (*vide infra*).<sup>18</sup> Based on this hypothesis, the reactivity of AZADO and TEMPO can be elucidated from the structure around the NO bond or by considering its electronic structure.

DFT is a very powerful tool in chemistry for calculating the conformational and bond properties of a given molecule, such as the electron and spin density of the atom, with high accuracy.<sup>19–24</sup> Rintoul et al. previously assigned the signals in the IR spectra of various nitroxyl radicals using DFT calculations.<sup>25</sup> Herein, DFT calculations of AZADOs and TEMPO were performed using the UB3-LYP functional and 6-311+G(d) basis set to investigate the conformational and electronic structures of AZADO derivatives.<sup>26</sup> Bond order was evaluated with the NBO program (version 3.1), which is a companion to Gaussian 16.<sup>27</sup>

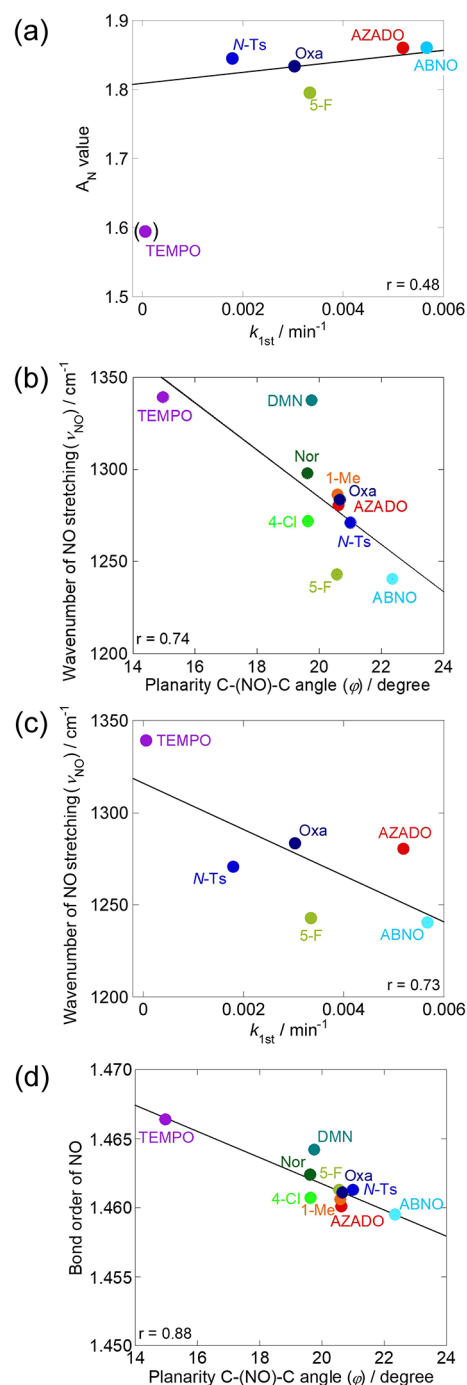
The most relevant structural parameter in nitroxyl radicals is typically  $\phi$ , which is an indicator of  $sp$  hybridization on the N atom. The  $\phi$  values of the AZADO derivatives are summarized in Table 1. The definition of  $\phi$  is shown in Figure 2a. Note that the contribution of the  $\pi$ -radical character increases as  $\phi$  decreases, owing to  $sp^2$  hybridization on the N atom. The  $\phi$  of TEMPO ( $16.50^\circ$ ) was approximately  $4.8^\circ$  smaller than that of AZADO ( $21.29^\circ$ ) owing to steric repulsion between the two methyl groups bonded to each carbon atom neighboring the nitrogen atom, resulting in a difference in the  $sp$  hybridization of the N atom. The  $\phi$  values of relatively high-strain AZADO derivatives, such as Nor (4) and DMN (5), also tended to be smaller. An excellent linear relationship was obtained between  $\phi$  and  $A_N$  values with  $r = 0.96$  (Figure 2b). The  $A_N$  value of the target atom depends strongly on the electron spin density of the N atom. The  $A_N$  value of nitroxyl radicals is approximated by the sum of the electron spin densities of the N and O atoms weighted by the Karplus–Fraenkel parameters.<sup>28</sup> This strong correlation between  $\phi$  and  $A_N$  suggests that both structural and electronic factors contribute strongly to  $\phi$ .

IR spectroscopy is a versatile method that can sensitively observe slight structural differences in the target compound while providing a unique fingerprint region in the spectrum of each analyte. Highly accurate assignments of IR spectral peaks have recently been achieved by using DFT calculations. Rintoul et al. reported the correlation between the structural environment of NO radicals and the wavenumber of the NO stretching vibration ( $\nu_{\text{NO}}$ ).<sup>25</sup> Currently, IR spectroscopic studies of NO radicals are limited and no comprehensive IR analyses of AZADO derivatives have been performed. We

assigned the  $\nu_{\text{NO}}$  of the AZADO derivatives by comparing the observed transition energy with that calculated using DFT (Figures S11–S20). Because the intensity of the NO stretching band is relatively weak, the ATR method was used to measure the fingerprint region of the AZADO derivatives with high sensitivity. However, the experimental results obtained using ABNO (3) and Nor (4) solutions were used, because they were comparable with the calculated values. The assigned  $\nu_{\text{NO}}$  values are listed in Table 1. Because the IR spectrum of TEMPO is available, it was compared to this spectrum to ensure that no discrepancies existed.

The correlation between the  $k_{1\text{st}}$  of the AZADO-mediated oxidation of *l*-menthol and the  $A_{\text{N}}$  values is plotted in Figure 3a. TEMPO is excluded from this linear approximation because the electronic properties of TEMPO differ from those of AZADO derivatives owing to steric effects around the NO radical. Nevertheless, no clear correlation ( $r = 0.48$ ) was observed between  $A_{\text{N}}$  and the  $k_{1\text{st}}$  of the AZADO derivatives. This loose quantitative trend between  $A_{\text{N}}$  and  $k_{1\text{st}}$  indicates that the oxidation mechanism is not well-explained by the only electronic factor of the NO radical. The relationship between  $\varphi$  and  $\nu_{\text{NO}}$  exhibited a moderate correlation ( $r = 0.74$ ) in all AZADOs, including TEMPO (Figure 3b). Qualitatively, this result can be reasonably explained as a weakening of the steric effect of the NO stretching vibration around the radical center owing to the widening of  $\varphi$ . The correlation between  $k_{1\text{st}}$  and  $\nu_{\text{NO}}$  (Figure 3c) shows a moderate relationship with  $r = 0.73$ . Although several studies have employed IR spectroscopy to estimate catalytic activity and elucidate its mechanism, most of these have evaluated catalyst–ligand–substrate interactions in metal oxide-supported catalyst systems. The result obtained herein suggests that the activity of nitroxyl radical catalysts can be evaluated from the spectral information on the catalyst structure itself when restricted to the same structural families. Our results demonstrate the importance of using spectroscopic techniques that reflect the electron density of the N atom, either ESR or IR. ESR is useful for evaluating the physical properties of radical species; however, it is not particularly versatile and requires specific skills. By contrast, IR spectroscopy is a universal and simple technique that may be able to qualitatively predict the reactivity of radical-catalyzed oxidation.

Furthermore, the bond order of NO is directly affected by the electron density of the target atoms and orbital hybridization based on structural distortion. A clear correlation was observed between  $\varphi$  and the bond order (Figure 3d). This positive correlation is not surprising, because bond order is an indicator of bond strength. The electron density of the N and O atoms of NO radicals, determined from DFT calculations, also exhibits a moderate correlation (Figure S22). Based on this consideration, the correlation between  $k_{1\text{st}}$  and the bond order of AZADO derivatives and TEMPO is plotted in Figure 4 with  $r = 0.89$ . In addition, one of the most relevant electronic parameters of the NO bond is the bond order, as presented in Table 1. The bond order of the NO bond in the radical species with the unpaired electron on the O atom is formally 1.5; however, DFT calculations predict a bond order of approximately 1.46 for all radicals. This suggests that some of the electrons on the N or O atoms occupy  $\pi$  orbitals, resulting in a decrease in the electron density of the  $\sigma_{\text{NO}}$  bond via  $sp^3$  hybridization. These slight differences in the bond order of NO are reflected in both electronic (*i.e.*, spin density and frequency energy) and steric (*i.e.*, bond distance and steric



**Figure 3.** Relationships between (a)  $k_{1\text{st}}$  of radical-catalyzed *l*-menthol oxidation and  $A_{\text{N}}$ , (b)  $\varphi$  and  $\nu_{\text{NO}}$ , (c)  $k_{1\text{st}}$  and  $\nu_{\text{NO}}$ , and (d)  $\varphi$  and the bond order of NO.

repulsion) factors; therefore, the bond order is considered the optimal parameter to evaluate the catalytic ability of NO radicals in this oxidation.

This study provides a comprehensive analysis of the radical-catalyzed oxidation of *l*-menthol using numerous AZADO derivatives, including TEMPO, based on the correlation between the observed ESR, ATR, and IR spectral parameters, such as  $A_{\text{N}}$  and  $\nu_{\text{NO}}$ , and the structural and electronic parameters calculated by DFT. These results indicate that the  $\varphi$  values of AZADOs and TEMPO, in which the NO radical is the catalytic center, have a strong correlation with the

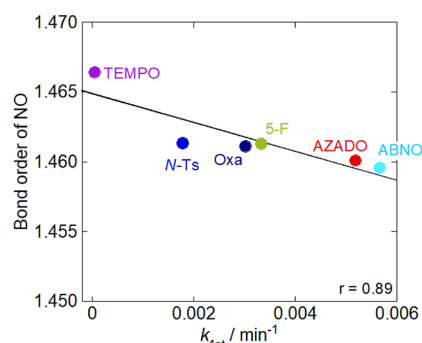


Figure 4. Relationships between  $k_{1st}$  and the bond order of NO.

$A_N$  value. However, only a moderate correlation between  $\varphi$  and  $\nu_{NO}$  was observed. Consequently, a moderate correlation between the  $k_{1st}$  of *l*-menthol oxidation and both the  $A_N$  value and the NO stretching vibration of AZADO derivatives was obtained. This may indicate that the prediction of spectra by DFT is more difficult than the prediction of chemical structures and electron densities.

Furthermore, the bond order of NO, which reflects both structural and electronic effects, exhibits an excellent correlation with  $k_{1st}$  and both the AZADO derivatives and TEMPO. From these findings, the catalytic activity of the radical catalyst can be easily predicted by IR measurements rather than by the trial-and-error approach of earlier studies. Furthermore, the bond order of NO can be estimated using DFT calculations. We believe that this method will facilitate the design of novel catalysts and development of unique reactions.

## EXPERIMENTAL SECTION

**Materials and Instruments.** Nitroxyl radical catalysts were synthesized according to established procedures.<sup>8,15,29–33</sup> Several reagents and solvents were purchased from Wako Chemicals, TCI, and Sigma-Aldrich. The ESR, ATR, and IR spectra of all samples were measured without further purification. ESR and IR spectra were obtained using Bruker E580 and JASCO FT/IR-4200 spectrometers, respectively. ATR spectra were obtained using a JASCO ATR PRO450-S (Ge prism), which was installed as an additional feature on the FT/IR-4200 spectrometer.

**Sample Preparation and Measurements.** ESR samples were prepared in dichloromethane (approximately 300–500  $\mu$ M) and the solutions were analyzed using  $\varphi$  5 mm quartz cells. The steady-state ESR spectra were obtained at room temperature. The spectral analysis was performed using the included analysis software. The integration of spectra was performed with Igor software (version 6.1.1.0) to ensure signal linearity. IR samples were prepared by dissolving a few milligrams of ABNO and Nor in carbon tetrachloride. IR spectra were obtained using the liquid film method with a CaF cell (pass length is approximately 0.05 mm). ATR spectra were acquired using trace samples of AZADOs and TEMPO on the Ge prism window as solid or neat samples.

**Calculation.** The optimization, frequency calculation, and NBO analysis of all compounds were performed by using density functional methods with the unrestricted hybrid density functional B3LYP (UB3-LYP). The basis function used was a Pople-type triple- $\zeta$  basis set with a diffuse function, 6-311+G(d).<sup>26</sup> The solvation effects were modeled by using a

polarizable continuum model (PCM) of  $CCl_4$ . The standard functions implemented in Gaussian 16 and the basis set were used. The bond order was evaluated with the NBO program (version 3.1).<sup>27</sup> The calculation was performed using Gaussian 16 installed on a PC (HP Z2 G5 mini).

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.3c06902>.

ESR and ATR (or IR) spectra, the relationship of electron spin density of NO radical, and optimized geometries, for all AZADO derivatives and TEMPO (PDF)

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### Notes

The authors declare no competing financial interest.

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