

Radical Scavenging Activity of Natural Anthraquinones: a Theoretical Insight

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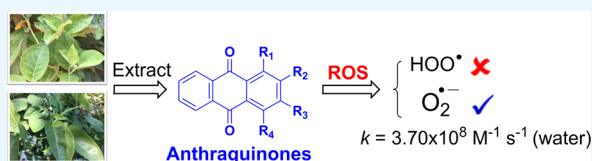


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Supporting Information

ABSTRACT: Anthraquinones (ANQs) isolated from *Paederia* plants are known to have antidiarrheal, antitussive, anthelmintic, analgesic, anti-inflammatory, antihyperlipidemic, antihyperglycaemic, and antimicrobial activities. The antioxidant properties were also noted but not confirmed thus far. In this study, the superoxide and hydroperoxide radical scavenging activities of six ANQs were evaluated using a computational approach. The results suggest that the ANQs exhibit low $\text{HOO}^\bullet$ antiradical activity in all environments, including the gas phase ($k < 10^2 \text{ M}^{-1} \text{ s}^{-1}$). In contrast, the ANQs might exert excellent $\text{O}_2^{\bullet-}$ radical scavenging activity, particularly in aqueous solution. The rate constants of the superoxide anion scavenging in water (at pH = 7.4) range from 3.42×10^6 to $3.70 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$. Compared with typical antioxidants such as ascorbic acid and quercetin, the superoxide anion scavenging activity of ANQs is significantly higher. Thus, the ANQs are promising $\text{O}_2^{\bullet-}$ radical scavengers in polar media.



1. INTRODUCTION

Reactive oxygen species (ROS) play an important role in the normal metabolism of humans. They participate in the bacterial ingestion of phagocytes as well as the regulation of signaling pathways, and thus cellular processes related to, for example, metabolism and proliferation.¹ However, excess ROS production is harmful to the native biochemistry of the human body, indicted as a common pathway to some incurable conditions including cardiovascular disease, cancer, and diabetes.^{2–6} The adverse effects of ROS are kept in check by dietary antioxidant intake; several recent studies showed that the antioxidant constituents from natural plants are vital factors in disease prevention.^{7,8}

Species of Polygonaceae, Leguminosae, Rubiaceae, and some 30 other families contain an abundance of natural antioxidants, including but are not limited to phenolic compounds.^{9,10} Anthraquinones (ANQs) belong to this group but mostly have been used as colorants in food, drugs, and cosmetics.^{11,12} ANQ derivatives with acidic or polar, hydrophilic substitution such as aloe-emodin, emodin, rhein, chrysophanol, and physcion were described with antiangiogenic activities.^{13,14} Experimental antioxidant activity data of ANQs that were collected by the 2,2-diphenyl-1-picrylhydrazyl, total reducing power ability, oxygen radical absorbance capacity, and low-density lipoprotein methods showed that ANQs could exhibit good antioxidant activity.^{11,15–17}

Paederia plants i.e., *P. foetida* and *P. scandens* are distributed widely in temperate and tropical East Asia and tropical South-East Asia.¹⁸ These plants are well known not only as traditional food ingredients in daily meals but also as traditional medicinal plants to treat toothache, tumors, rheumatoid arthritis,

inflammation, diarrhea, and hemorrhoids.^{19,20} *Paederia* extracts showed antidiarrheal, antitussive, anthelmintic, analgesic, anti-inflammatory, antihyperlipidemic, antihyperglycaemic, antimicrobial, and antioxidant activity.^{21–29} From these extracts, a number of ANQs were isolated and characterized including 1,3-dihydroxy-2,4-dimethoxy-9,10-anthraquinone (1), 2-hydroxy-1,4-dimethoxy-9,10-anthraquinone (2), 1-methoxy-2-methoxymethyl-3-hydroxy-9,10-anthraquinone (3), 1-hydroxy-2-hydroxymethyl-9,10-anthraquinone (4), 1-methyl-2,4-dimethoxy-3-hydroxyanthraquinone (5), and 1-methoxy-3-hydroxy-2-ethoxymethylanthraquinone (6) (Figure 1).^{30,31} ANQ derivatives were also described as photosensitizers to create singlet oxygen and superoxide anions in UV environments,^{32–34} whereas some studies indicated that these compounds could exhibit the $\text{O}_2^{\bullet-}$ scavenging activity, particularly in polar environments.^{35,36} Hence, it is desirable to gather further insights into the radical scavenging activity of ANQs.

Previous studies confirmed that the quantum chemical calculation offers a useful and reliable pathway to evaluate the radical scavenging as well as the antioxidant activity of natural products.^{8,37–42} Thus, in this study, the antioxidant activity of six ANQs (Figure 1) was investigated by using thermodynamic and kinetic calculations. The antioxidant properties of the

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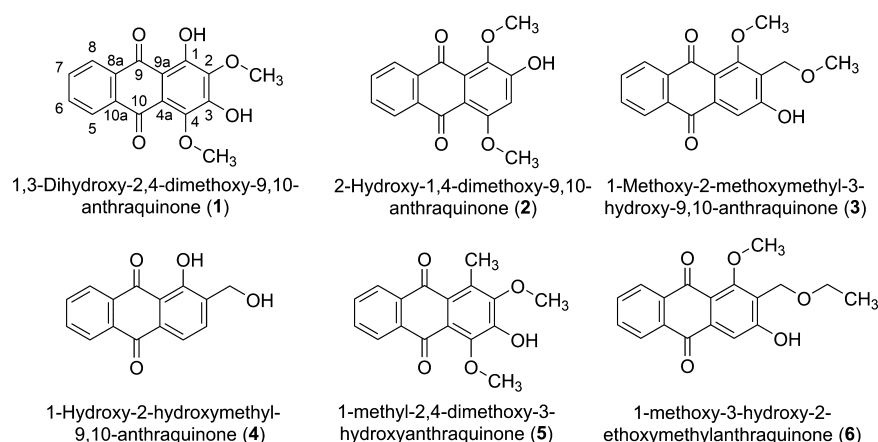


Figure 1. Structures of the six ANQs in this study.

Table 1. Calculated BDEs, PAs, and IEs of Studied Compounds and ΔG° (kcal/mol) for the ANQs + $\text{HOO}^\bullet$ Reaction Following the FHT, SP, and SET Mechanisms in the Gas Phase

comp.	FHT			SP			SET	
	positions	BDE	ΔG	positions	PA	ΔG	IE	ΔG
1	O3	88.7	1.6	O3	335.1	257.0	180.9	234.2
2	O2	90.6	2.1	O2	334.1	255.7	183.3	237.1
3	C2	83.8	−4.0	O3	334.4	255.8	191.7	244.9
4	C2	79.6	−7.1	O1	347.2	268.3	192.7	245.7
5	O2	88.2	1.1	O2	335.7	258.1	185.9	239.9
6	C2	82.7	−4.4	O3	338.6	260.3	189.1	242.8

ANQs were investigated in the $\text{HOO}^\bullet$ and $\text{O}_2^{\bullet-}$ radical scavenging reactions in the gas phase as well as physiological environments.

2. RESULTS AND DISCUSSION

2.1. Thermodynamic Study. Previous studies indicated that conformation plays an important role in the antioxidant activity of molecules that have multiple stable conformers.^{8,37} Thus, the studied ANQs were first screened to find the conformers with low electronic energy.⁴³ The five lowest electronic energy conformers were then analyzed to find the most stable conformers, and these forms were used in further computations. For example, for compounds 3 and 6 that contain both methoxy and ethoxy groups, the five lowest electronic energy conformers were analyzed by the M06-2X/6-311++G(d,p) method (Figure S1, Supporting Information) and the most stable forms (3 and 6, >99%) were achieved by using the Maxwell–Boltzmann distribution to estimate the relative populations of conformers.^{44,45}

In the initial step of the study, the thermodynamic parameters, including bond dissociation energies (BDEs), ionization energies (IEs), and proton affinities (PAs) were evaluated for all the studied compounds following the method reported previously.^{38,40} To save computing time, the BDE and PA values of all possible bonds were first calculated at the M06-2X/3-21G level of theory and the lowest values were then re-computed with a more accurate method (M06-2X/6-311++G(d,p) level of theory). The results are presented in Table 1.

As shown in Table 1, the lowest BDEs (X–H, X = O, C) of the ANQs range from 79.6 to 90.6 kcal/mol. The lowest calculated PAs are observed at (O–H) bonds with PA = 334.1–347.2 kcal/mol, which are significantly higher than the IE values of the ANQs (IE = 180.9–192.7 kcal/mol). Notably,

the thermochemical parameters are generally higher than those of natural hydroanthraquinone derivatives (BDE = 76.2–88.6 kcal/mol; PA = 313.8–331.8 kcal/mol; and IE = 172.7–180.3 kcal/mol).⁴⁶ This result suggests that reducing the carbonyl group (C=O) of the ANQ system to the alcohol group (hydroanthraquinones) may decline the BDE, PA, and IE values and that the antioxidant activity of ANQs may be lower than the activities of the hydroanthraquinones.

The lowest BDE is calculated for the 4–C2–H bond (BDE = 79.6 kcal/mol), while the lowest for PA and IE are observed at compound 2 with PA = 334.1 kcal/mol and 1 with IE = 180.9 kcal/mol. The BDEs of ANQs are higher than those of typical natural antioxidants, such as Trolox, ascorbic acid (BDE < 78 kcal/mol);^{8,47} thus, the radical scavenging activity of these ANQs following the FHT mechanism is expected to be weaker than the reference antioxidants.

As an initial assessment of the $\text{HOO}^\bullet$ radical scavenging ability of the ANQs, Gibbs energies (ΔG°) of the reactions between $\text{HOO}^\bullet$ radicals and the ANQs were calculated for each of the three typical radical scavenging mechanisms: formal hydrogen transfer (FHT),⁴⁸ sequential proton [SP, first step of SP loss electron transfer mechanism (SPLET)],^{49–52} and single electron transfer [SET, first step of SET followed by the proton transfer mechanism (SETPT)];^{7,53} the results are summarized in Table 1. The results showed that the $\text{HOO}^\bullet$ radical scavenging was only spontaneous ($\Delta G^\circ < 0$) for the FHT mechanism and not for the other two mechanisms (SP and SET) in the gas phase. Thus, these mechanisms can be disregarded in the following kinetic modeling.

2.2. Kinetic Study. **2.2.1. $\text{HOO}^\bullet$ Radical Scavenging of ANQs in the Gas Phase.** As shown in the thermodynamic section, the FHT pathway is the favored mechanism for the $\text{HOO}^\bullet$ radical scavenging of ANQs. Thus, in this section, the

kinetic calculations were performed for the H-abstraction of the X–H (X = C, O) bonds with the lowest BDEs (Table 1). The results are shown in Table 2 and Figure 2.

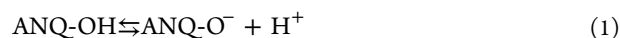
Table 2. Calculated $\Delta G^\ddagger$ (kcal/mol), κ , and k_{Eck} ($\text{M}^{-1} \text{s}^{-1}$) for the $\text{HOO}^\bullet$ Scavenging of the ANQs in the Gas Phase

reaction	ΔH	$\Delta G^\ddagger$	κ	k_{Eck}
1–O3–H + $\text{HOO}^\bullet$	7.7	18.0	39.5	1.63×10^1
2–O2–H + $\text{HOO}^\bullet$	9.1	19.1	48.5	3.13
3–C2–H + $\text{HOO}^\bullet$	8.8	18.2	84.8	2.23×10^1
4–C2–H + $\text{HOO}^\bullet$	8.4	17.9	50.6	2.47×10^1
5–O2–H + $\text{HOO}^\bullet$	7.0	17.4	61.3	6.63×10^1
6–C2–H + $\text{HOO}^\bullet$	7.2	17.1	30.8	5.24×10^1

It is clear from Table 2 that the $\text{HOO}^\bullet$ radical scavenging of ANQs is slow with $k_{\text{Eck}} = 3.13\text{--}66.3 \text{ M}^{-1} \text{s}^{-1}$ and $\Delta G^\ddagger = 17.1\text{--}19.1$ kcal/mol. This is in logical agreement with the high BDE values obtained from the thermodynamic calculations. Previous studies showed that the $\text{HOO}^\bullet$ antiradical activity of most model lipid media (i.e., in pentyl ethanoate solvent) mainly occurred following the FHT pathway, and the rate constant was usually lower than in the gas phase.^{39,40,54} Thus, this suggests that the ANQs are not good antioxidants in the lipid media.

2.2.2. $\text{HOO}^\bullet$ and $\text{O}_2^{\bullet-}$ Scavenging of ANQs in Aqueous Solution. **2.2.2.1. Acid–Base Equilibria.** As a requirement of antioxidant activity evaluation in aqueous solution,^{8,37,48} the molar fractions (f) of the deprotonated state of ANQs were calculated at physiological pH. The alcohol moiety has a dissociation equilibrium as per reaction 1, and the pK_a values are calculated according to eq 2 (Table 3).

The calculated pK_a values (Table 3) range from 6.94 to 10.76; hence, at pH 7.4, the neutral species are present in 25.3–94.8% and the dissociated state makes up the remaining 5.2–74.7%. Among the studied compounds, 1 could also form a dianion with $\text{pK}_{a2} = 10.76$. However, at pH 7.4, this state only populates 0.033% of the total concentration of 1; thus, the dianion species can be omitted in the kinetic calculations.



$$\text{pK}_a^{\text{calc}} = m\Delta G_{\text{BA}}^\circ + C_0 \quad (2)$$

$$\Delta G_{\text{BA}}^\circ = \Delta G_{\text{A}^-}^\circ - \Delta G_{\text{HA}}^\circ \quad (3)$$

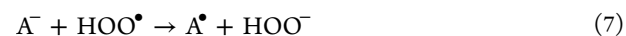
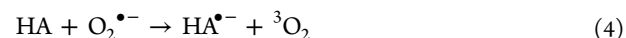
Table 3. Calculated pK_a and f at pH = 7.4

comp.	positions	pK_a	f	
			HA	A^-
1	O3–H	6.94	0.253	0.747
	O1–H	10.76 ^a		
2	O2–H	7.00	0.285	0.715
3	O3–H	7.72	0.676	0.324
4	O1–H	8.66	0.948	0.052
5	O2–H	7.53	0.574	0.426
6	O3–H	7.75	0.691	0.309

^a pK_{a2} .

where $\Delta G_{\text{BA}}^\circ$ was obtained from reaction 2 following eq 4 and m and C_0 are fitted parameters directly obtained from ref 55.⁵⁵

2.2.2.2. Kinetic Study. The study on the $\text{HOO}^\bullet$ radical scavenging of ANQs in the gas phase showed that the rate constants for this process according to the FHT pathway were low. Thus, the study on radical scavenging in the polar environment only focused on the SPLET mechanism (the second step as the SET mechanism) against typical radicals, that is, $\text{HOO}^\bullet$ and $\text{O}_2^{\bullet-}$. It was already established that the SET mechanism is the main pathway for superoxide anion scavenging in polar media to form stable diradical $^3\text{O}_2$.^{56–58} Therefore, the $\text{HOO}^\bullet$ and $\text{O}_2^{\bullet-}$ scavenging of ANQs in aqueous solution could occur via reactions 4–7, and the overall rate constants (k_{overall}) were calculated according to eqs 8 and 9. The results are presented in Table 4.



$$k_{\text{overall}}(\text{HOO}^\bullet) = f(\text{HA}) \cdot k_{\text{app}}(\text{HA-OOH}) + f(\text{A}^-) \cdot k_{\text{app}}(\text{A}^- \text{-OOH}) \quad (8)$$

$$k_{\text{overall}}(\text{O}_2^{\bullet-}) = f(\text{HA}) \cdot k_{\text{app}}(\text{HA-O}_2) + f(\text{A}^-) \cdot k_{\text{app}}(\text{A}^- \text{-O}_2) \quad (9)$$

As shown in Table 4, the neutral states (HA) have virtually no contribution in the $\text{HOO}^\bullet$ radical scavenging of ANQs in aqueous solution ($\Delta G^\ddagger = 33.2\text{--}56.1$ kcal/mol and $k_{\text{app}} = 4.70 \times 10^{-29}$ to $2.90 \times 10^{-12} \text{ M}^{-1} \text{s}^{-1}$). The $\text{HOO}^\bullet$ scavenging

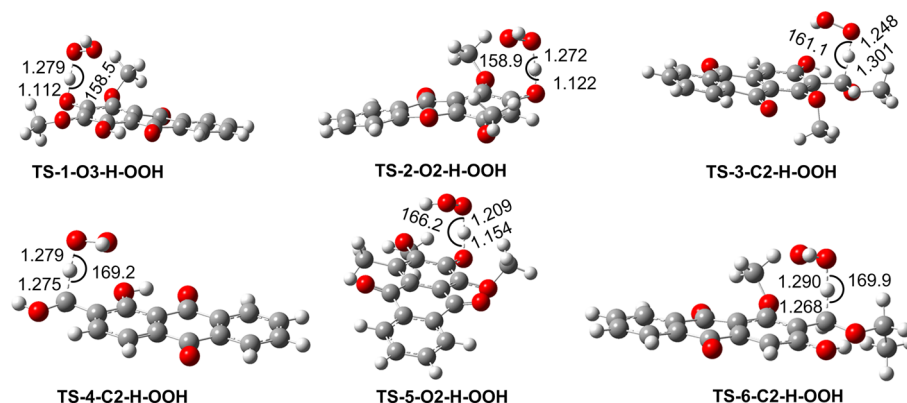


Figure 2. Optimized geometries of TSs between the studied compounds and $\text{HOO}^\bullet$ radical in the gas phase following the FHT mechanism.

Table 4. Calculated $\Delta G^\ddagger$ (in kcal/mol), Nuclear Reorganization Energy (λ), and Rate Constants (k_{app} , k_f , $\text{M}^{-1} \text{s}^{-1}$) of the $\text{HOO}^\bullet$ and $\text{O}_2^{\bullet-}$ Scavenging of the ANQs in Aqueous Solution Following the SPLET Mechanism

comp.		$\text{HOO}^\bullet$					$\text{O}_2^{\bullet-}$				
		$\Delta G^\ddagger$	λ	k_{app}	k_f^a	k_{overall}	$\Delta G^\ddagger$	λ	k_{app}	k_f^a	k_{overall}
1	HA	40.8	22.7	7.90×10^{-18}	2.00×10^{-18}	1.57×10^1	6.0	20.6	2.60×10^8	6.68×10^7	6.59×10^7
	A^-	15.6	19.5	2.10×10^1	1.57×10^1		10.5	20.2	1.30×10^5	9.71×10^4	
2	HA	33.2	30.3	2.90×10^{-12}	8.27×10^{-13}	2.50×10^{-1}	7.8	20.2	1.20×10^7	3.42×10^6	3.42×10^6
	A^-	18.1	15.5	3.50×10^{-1}	2.50×10^{-1}		13.4	19.8	8.60×10^2	6.15×10^2	
3	HA	56.1	18.9	4.70×10^{-29}	3.18×10^{-29}	7.78×10^{-3}	7.1	20.0	4.20×10^7	2.84×10^7	2.84×10^7
	A^-	19.7	14.9	2.40×10^{-2}	7.78×10^{-3}		11.7	19.0	1.70×10^4	5.51×10^3	
4	HA	53.4	17.9	4.50×10^{-27}	4.27×10^{-27}	4.63×10^{-1}	5.7	20.5	3.90×10^8	3.70×10^8	3.70×10^8
	A^-	16.2	15.4	8.90	4.63×10^{-1}		13	18.7	1.90×10^3	9.88×10^1	
5	HA	42.5	22.7	4.00×10^{-19}	2.30×10^{-19}	8.95×10^1	8.3	21.1	5.10×10^6	2.93×10^6	2.93×10^6
	A^-	14.3	16.4	2.10×10^2	8.95×10^1		13.6	20.4	6.50×10^2	2.77×10^2	
6	HA	49.3	20.9	4.30×10^{-24}	2.97×10^{-24}	5.56×10^{-3}	7.1	20.7	3.70×10^7	2.56×10^7	2.56×10^7
	A^-	19.8	14.6	1.80×10^{-2}	5.56×10^{-3}		11.5	19.3	2.30×10^4	7.11×10^3	

^a $k_f = f \cdot k_{\text{app}}$

activity of the anions (A^-) is somewhat higher; however, k_{app} and k_f values range from 1.80×10^{-2} to 2.10×10^2 and 5.56×10^{-3} to $8.95 \times 10^1 \text{ M}^{-1} \text{s}^{-1}$, respectively. The highest overall rate constant for the $\text{HOO}^\bullet$ antiradical activity is $k_{\text{overall}} = 89.1 \text{ M}^{-1} \text{s}^{-1}$ that is much lower than that of typical natural antioxidants, that is, Trolox⁸ and ascorbic acid.³⁷ As anticipated based on the energetic analysis above, ANQs exhibit significantly lower ($\sim 10^5$ to 10^6 times) $\text{HOO}^\bullet$ radical scavenging activity than natural hydroanthraquinone derivatives,⁴⁶ particularly in the polar media, emphasizing the importance of the alcohol moieties. Consistently, the studied ANQs are poor $\text{HOO}^\bullet$ radical scavengers in physiological environments.

However, ANQ compounds exhibit excellent $\text{O}_2^{\bullet-}$ radical scavenging activity, particularly in polar environments. The anion states have moderate $\text{O}_2^{\bullet-}$ antiradical activity with $k_{\text{app}} = 6.50 \times 10^2$ to $1.30 \times 10^5 \text{ M}^{-1} \text{s}^{-1}$, whereas the activities of the HA states fall range from 5.10×10^6 to $3.90 \times 10^8 \text{ M}^{-1} \text{s}^{-1}$. As a result, the k_{overall} range from 3.42×10^6 to $3.70 \times 10^8 \text{ M}^{-1} \text{s}^{-1}$. That is in good agreement with the previous findings in carotenoids.⁵⁹ Compound 4 exhibits the highest $\text{O}_2^{\bullet-}$ radical scavenging activity with $k_{\text{overall}} = 3.70 \times 10^8 \text{ M}^{-1} \text{s}^{-1}$. This is about 100 times higher than that of compound 5 (the lowest $\text{O}_2^{\bullet-}$ radical scavenger). Compared with typical antioxidants such as ascorbic acid and quercetin ($k = 0.1 \times 10^3$ to $3.0 \times 10^3 \text{ M}^{-1} \text{s}^{-1}$),⁶⁰ the superoxide anion scavenging of ANQs is much higher. Thus, ANQs are promising $\text{O}_2^{\bullet-}$ radical scavengers in polar environments.

3. CONCLUSIONS

In this study, the superoxide and $\text{HOO}^\bullet$ radical scavenging activity of six ANQs was evaluated. It was found that the ANQs have very low $\text{HOO}^\bullet$ antiradical activity in both gas phase and physiological environments. The rate constants of the $\text{HOO}^\bullet$ radical scavenging of ANQs are less than $10^2 \text{ M}^{-1} \text{s}^{-1}$, implying that they are not useful $\text{HOO}^\bullet$ radical scavengers. However, ANQs were found to be excellent $\text{O}_2^{\bullet-}$ radical scavengers, particularly in aqueous solution. The rate constants of the superoxide anion scavenging of ANQs range from 3.42×10^6 to $3.70 \times 10^8 \text{ M}^{-1} \text{s}^{-1}$, which is much higher than that of typical antioxidants, such as ascorbic acid and quercetin. Thus, the ANQs are promising $\text{O}_2^{\bullet-}$ radical scavengers in polar environments.

4. COMPUTATIONAL METHODS

Thermochemical properties (BDEs, IEs, and PAs) as well as kinetic parameters, activation energies $\Delta G^\ddagger$ (kcal/mol), tunneling corrections (κ), and rate constants (k) in the studied environments (the gas phase and in physiological environments) were computed using the M06-2X functional.^{48,61–64} M06-2X/6-311++G(d,p) has been well established as a suitable method to compute both thermochemical and kinetic parameters due to its good accuracy compared with the more complex functionals [i.e., G3(MP2)-RAD] and experimental data.^{8,48,61,64} The quantum mechanic-based test for the overall free radical scavenging activity protocol^{8,37,61,65–67} was used to perform the kinetic calculations. The rate constant (k) was calculated by using the conventional transition-state theory and 1M standard state at 298.15 K.^{40,54,62,67–72} The details of the method are shown in Table S3, Supporting Information.⁵⁴ All DFT calculations in this work were carried out using Gaussian 16 package.⁷³

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.1c01448>.

Thermodynamic parameters, Cartesian coordinates, and frequency and energies of all the transition states in the studied environments (PDF)

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Notes

The authors declare no competing financial interest.

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