

In Silico Evaluation of the Radical Scavenging Mechanism of Mactanamide

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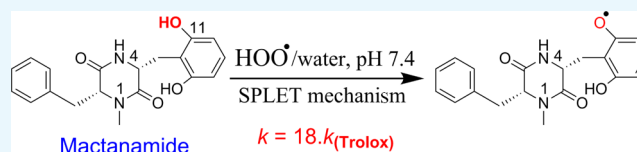


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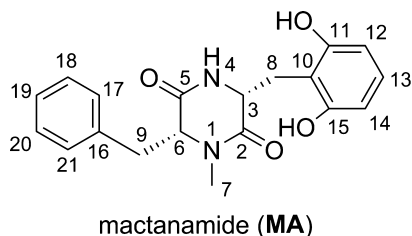
Supporting Information

ABSTRACT: Mactanamide (MA) is a diketopiperazine isolated from marine fungi of the genus *Aspergillus*. This compound is known as a natural antioxidant from experimental studies, yet this activity has not been successfully modeled thus far. In this work, the hydroperoxyl radical scavenging activity of MA was evaluated in the gas phase and physiological environments by thermodynamic and kinetic calculations. The results revealed that the HOO• radical scavenging of MA in the lipid media follows the formal hydrogen transfer mechanism via hydrogen abstraction at the O11–H bond. In the aqueous solution, however, the antioxidant activity follows the sequential proton loss electron transfer mechanism. The rate constant of the HOO• scavenging of MA in the polar environment is about 1045 times ($k_{\text{overall}} = 2.23 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$) higher than that in the lipid medium ($k_{\text{overall}} = 2.20 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$). In polar media, the HOO• radical scavenging activity of MA is therefore 18 times higher than that of Trolox, the reference compound when assessing antioxidant activity. The results presented here align well with the experimental data, validating the mechanistic pathways and thus providing useful insights into the antioxidant activity of MA.



1. INTRODUCTION

Mactanamide (MA, Figure 1) is a diketopiperazine that was isolated from marine fungi of the genus *Aspergillus*.^{1,2} In



mactanamide (MA)

Figure 1. Structure of MA.

experimental studies, MA exhibited good radical scavenging activity in 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABST) assays with IC_{50} values of 138.12 ± 0.34 and $1.72 \pm 0.01 \mu\text{M}$, respectively, which reveals better antioxidant activity than a range of other natural products of marine fungal origin including chraceopone F, aspertetranone D, cyclochinulin, wasabidienone E, and even the reference antioxidant Trolox ($\text{IC}_{50} = 5.52 \pm 0.41 \mu\text{M}$).²

However, computational results reported in the same study suggested that MA is a weaker radical scavenger than the other natural products (the overall rate constants $k_{\text{overall}} = 1.11 \times 10^{-3}$ and $2.39 \times 10^{-1} \text{ M}^{-1} \text{ s}^{-1}$ in pentyl ethanoate and water solvents, respectively, for MA vs $k_{\text{overall}} = 1.16\text{--}2.60 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ for the other compounds).² While the calculations were performed for HOO• scavenging that was not assessed

experimentally, based on the results of DPPH and ABST assays that are good predictors of overall antioxidant activity, it is expected that MA is a better radical scavenger, and therefore, there is a conflict between the reported experimental data and the calculated results.

It is important to note that in the computational study, the contribution of the O11(15)–H bond of MA was ignored in the evaluation of the HOO• radical scavenging activity. However, several previous studies showed that phenolic alcohol groups can also contribute to the antioxidant activity, and hence, the site of hydrogen abstraction has to be established for each compound individually.^{3–7} The phenolic alcohol groups played an important role in the antioxidant activity of phenolic compounds such as flavonoids, stilbenes, lignans, anthocyanins, and phenolic acids.^{8,9} The computational study also omitted the acid–base equilibrium of the phenolic O11–H bond of MA, even though it was shown before that the dissociated form, even if only present in trace amounts, may dominate the antiradical activity of phenolic compounds^{3,5} in aqueous solutions. Hence, there is scope for improving the computational analysis of the radical scavenging activity of MA.

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This study is aimed at accurate computational evaluation of the HOO• radical scavenging activity of MA by using thermodynamic and kinetic calculations including the consideration of all important structural and environmental factors. The obtained results will provide reliable and accurate data on HOO• radical scavenging activity of MA to inform the use of this compound in practice.

2. RESULTS AND DISCUSSION

2.1. Radical Scavenging in the Gas Phase. Study on the MA structure indicated that the aromatic rings can rotate around the single bonds (C6–C9, C3–C8 bonds) to form a range of conformers. Thus, in the initial step, the possible conformers of MA were screened¹⁰ and the six lowest electronic energy conformers were then analyzed at the M06-2X/6-311++G(d,p) level of theory (Figure 2). The

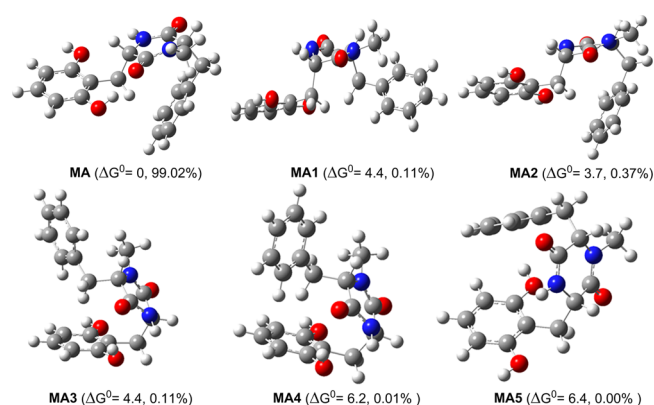


Figure 2. Typical conformers of MA and the relative free energies ΔG° (in kcal/mol) compared with the MA conformer.

hindered internal rotation treatment was also applied to the single bonds to ensure that the obtained conformer has the lowest electronic energy.^{11,12} As shown in Figure 2, MA has the lowest ΔG° value in all of the studied conformers. MA1–MA5 have 3.7–6.4 kcal/mol higher free energy than MA. Using the Maxwell–Boltzmann distribution to estimate the relative populations of tautomers^{13,14} indicated that MA is the dominant conformer (>99%), and therefore, this conformer was used in further studies.

Antioxidant activity is usually evaluated by thermodynamic calculations based on three typical radical scavenging mechanisms: (i) formal hydrogen transfer (FHT), (ii) single electron transfer–proton transfer (SETPT), and (iii) sequential proton-loss electron-transfer (SPLET).¹⁵ Which of these three mechanism is the dominant one depends on both the antioxidant structure and the radical; previous studies showed that the SETPT and SPLET mechanisms do not take place in HOO• radical scavenging in the gas phase.^{3,5} Thus, in this study, the HOO• radical scavenging of MA in the gas phase was only assessed via the FHT mechanism, and hence, bond dissociation energy (BDE) values were calculated for all bonds. The results are presented in Table 1.

It is clear from Table 1 that the BDEs of MA are in the range of 77.2–111.2 kcal/mol. The lowest BDE value is observed at the C3–H bond with BDE = 77.2 kcal/mol. The BDE(O11–H) is the second lowest at 84.8 kcal/mol. The N4–H bond has the highest BDE at 111.2 kcal/mol.

The calculation of ΔG° values of the reactions of MA with HOO• revealed that the H-abstraction was only spontaneous

Table 1. Calculated BDEs and ΔG° Values (in kcal/mol) of the Reactions of MA with HOO• Following the FHT Mechanism in the Gas Phase

position	BDE	ΔG°
C3	77.2	−8.3
C6	86.0	0.6
C7	93.4	7.8
C8	89.3	4.3
C9	101.4	15.7
N4	111.2	25.4
O11	84.8	−0.8

($\Delta G^\circ < 0$) at the C3–H and O11–H bonds, while the reactions at other positions were not spontaneous, and therefore, these positions can be disregarded in the following kinetic modeling.

The results of kinetic calculations for the HOO• radical scavenging of MA are presented in Table 2 and optimized

Table 2. Calculated ΔG^\ddagger (in kcal/mol), Tunneling Corrections (κ), and k_{Eck} ($\text{M}^{-1} \text{s}^{-1}$) for the HOO• Scavenging of the MA in the Gas Phase at 298.15 K

comp.	position	ΔG^\ddagger	κ	k_{Eck}
MA	C3	14.8	444.5	3.73×10^4
	O11	11.4	18.0	1.02×10^6
	k_{overall}			1.06×10^6
Trolox	OH	9.7	36.7	1.87×10^7

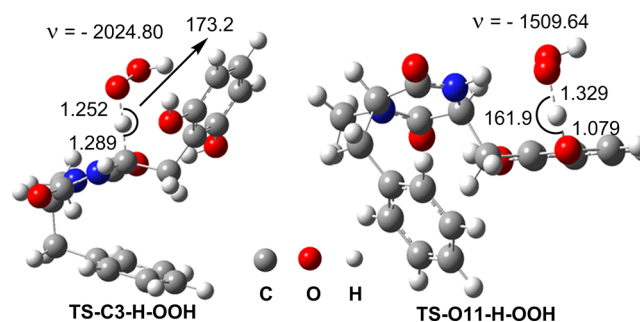
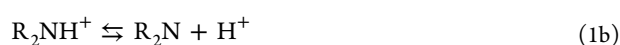


Figure 3. Optimized geometries and imaginary frequencies (ν) of the typical TSs according to the FHT mechanism between the MA and HOO• radicals.

transition state (TS) structures are shown in Figure 3. The higher rate constant was predicted for the H-abstraction of the O11–H bond with $k_{\text{Eck}} = 1.02 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$. The activity at the C3–H bond is 27.3 times lower, even though the BDE value of the C3–H bond (BDE(C3–H) = 77.2 kcal/mol) is lower than that of O11–H bond (BDE(O11–H) = 84.8 kcal/mol) and tunneling correction value of the M–C3–H + HOO• reaction ($\kappa(\text{C3–H}) = 444.5$) is higher than that of the M–O11–H + HOO• reaction ($\kappa(\text{O11–H}) = 18.0$). Thus, the H-abstraction occurs at the O11–H bond and not the C3–H bond, as suggested in the former study.² This may explain that H abstraction at the O11–H occurs via proton coupled electron transfer mechanism, while abstraction at the C3–H bond occurs via hydrogen atom-transfer pathway.¹⁶ The HOO• radical scavenging of MA in the gas phase is lower than that of Trolox ($k_{\text{Eck}} = 1.87 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$).³

2.2. Radical Scavenging in Physiological Environments. To identify the possible radical scavenging pathways, the protonation state of **MA** has to be evaluated at physiological pH. The **MA** structure allows protonation at the N1 and N4 positions following reactions 1a and 1b and deprotonation of the alcohol moiety at O11–H position following reaction 2. The pK_a for the deprotonation of N4 is trivially seen to be too high for consideration. Thus, the pK_a values of **MA** were calculated based on the model reactions 1a, 1b and 2¹⁷ according to eq 2.^{3,18}



$$pK_a^{\text{calc}} = m\Delta G_{\text{BA}}^{\circ} + C_0 \quad (3)$$

$$\Delta G_{\text{BA}}^{\circ} = \Delta G_{\text{A}}^{\circ} - \Delta G_{\text{HA}}^{\circ} \quad (4)$$

where $\Delta G_{\text{BA}}^{\circ}$ was obtained from reactions 1a, 1b, and 2 following eq 3; m and C_0 are fitted parameters directly obtained from ref 17.

The calculated pK_a values for the amines were <1, whereas that for the O11–H bond was 9.34. Therefore, in pH = 7.4 aqueous solution there is a non-negligible population of the monoanionic state (**MA**–O11[−], 1%) (Figure 4). Hence, both

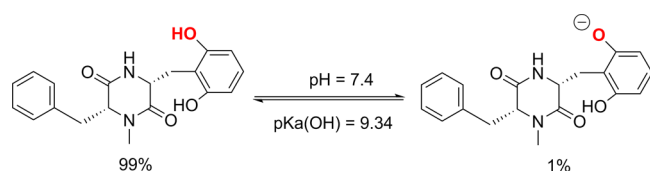
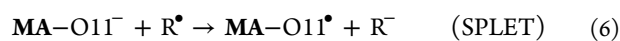


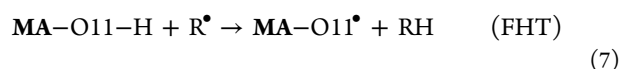
Figure 4. Acid dissociation equilibrium of **MA** at pH = 7.4.

the neutral and anionic states were used in the kinetic evaluation of the HOO^\bullet radical scavenging of **MA** in water at pH = 7.4. The antiradical activity of **MA** against HOO^\bullet radical in water can follow the following mechanisms:^{3,19}

Single electron transfer (SET)



FHT that was introduced above for the gas-phase calculations



where $\text{R}^\bullet = \text{HOO}^\bullet$.

The results of the calculations are presented in Table 3. The H-abstraction of the O11–H bond in the HOO^\bullet radical scavenging of **MA** in lipid media yielded $k_{\text{overall}} = 2.20 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$, while in the aqueous solution, the dominant mechanism was SPLET with $k_{\text{overall}} = 2.23 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$. Thus, the HOO^\bullet antiradical activity of **MA** in the polar environment is about 1045 times higher than that in the lipid medium. The results suggest that the anionic state (**MA**–O11[−]) plays a dominant role in the HOO^\bullet radical scavenging of **MA** in the aqueous solution, despite the fact that this state is only present in 1% under the given conditions. Therefore, omitting this state in the evaluation of the antioxidant activity in polar solvents leads to inaccurate results, explaining the discrepancy between experimental and computational data in the above-described study.² In a comparison with the reference antioxidant Trolox,³ the HOO^\bullet radical scavenging of **MA** is slightly lower in the lipid medium; however, in polar solvent it is about 18 times higher. Thus, **MA** is a promising antioxidant in physiological environments, in particular in aqueous media.

3. CONCLUSIONS

The hydroperoxyl radical scavenging activity of **MA** in the gas phase as well as in physiological environments was investigated by thermodynamic and kinetic calculations. It was found that the H-abstraction at the O11–H bond defined the HOO^\bullet radical scavenging of **MA** in lipid media with $k_{\text{overall}} = 2.20 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$, while in aqueous solution radical scavenging followed the SPLET mechanism with $k_{\text{overall}} = 2.23 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$. Compared with Trolox, the HOO^\bullet radical scavenging activity of **MA** is slightly lower in the lipid medium and 18 times higher in water than that of Trolox. Thus, **MA** is a promising antioxidant in an aqueous environment.

4. COMPUTATIONAL METHODS

In this study, the M06-2X/6-311++G(d,p) level of theory, which is proven to be highly accurate for computing both thermodynamic and kinetic parameters,^{20–24} was used to compute thermochemical properties [proton affinities (PAs), BDEs and ionization energies (IEs)] and kinetic parameters [activation energies ΔG^\ddagger (kcal/mol), tunneling corrections (κ), and rate constants (k)] in the gas phase and in physiological environments (water for the aqueous solution and pentyl ethanoate for the lipid medium).^{21–24} BDE, PA, and IE were calculated as follows^{4,7,8}

$$\text{BDE} = H(\text{MA}^\bullet) + H(\text{H}^\bullet) - H(\text{MA}) \quad (8)$$

$$\text{PA} = H(\text{MA}^-) + H(\text{H}^+) - H(\text{MA}) \quad (9)$$

$$\text{IE} = H(\text{MA}^{\bullet+}) + H(\text{e}^-) - H(\text{MA}) \quad (10)$$

Table 3. Gibbs Free Energies of Activation (ΔG^\ddagger , kcal/mol) and Rate Constants (k_{app} , k_f , $\text{M}^{-1} \text{ s}^{-1}$) at 298.15 K in the **MA** Oxidation by HOO^\bullet Radicals in Water and Pentyl Ethanoate Solvents

mechanism	pentyl ethanoate				water				
	ΔH	ΔG^\ddagger	κ	k_{app}	ΔG^\ddagger	κ	k_{app}	f	k_f^b
SET							~0	0.990	
SPLET					6.1	16.3 ^a	2.20×10^8	0.010	2.23×10^6
FHT	O11	6.0	15.9	74.0	2.20×10^3	17.8	56.4	3.16×10^1	3.13×10^1
k_{overall}					2.20×10^3				2.23×10^6

^aThe nuclear reorganization energy (λ). ^b $k_f = f \cdot k_{\text{app}}$.

where $H(\text{MA})$, $H(\text{MA}^{\bullet})$, $H(\text{H}^{\bullet})$, $H(\text{MA}^{\bullet+})$, $H(\text{e}^{-})$, and $H(\text{H}^{+})$ are enthalpies of the neutral molecule, radical, radical cation, electron, and proton, respectively.

The kinetic calculations were performed following the quantum mechanics-based test for overall free-radical scavenging activity (QM-ORSA) protocol with the solvation model density method that is widely used for evaluating the radical scavenging activity of antioxidants with low errors compared to experimental data ($k_{\text{calc}}/k_{\text{exp}}$ ratio = 1–2.9).^{18,20,25,26}

The rate constant (k) was calculated by using the conventional TS theory and IM standard state at 298.15 K according to eq 10^{20,27–33}

$$k = \sigma \kappa \frac{k_{\text{B}} T}{h} e^{-(\Delta G^{\ddagger})/RT} \quad (11)$$

where σ is the reaction symmetry number,^{34,35} κ stands for tunneling corrections which were calculated using the Eckart barrier,³⁶ k_{B} is the Boltzmann constant, h is the Planck constant, and ΔG^{\ddagger} is Gibbs free energy of activation. The details of the method are shown in Table S1.³³ The calculations were performed with the Gaussian 16 suite of programs.³⁷ The conformers were screened by the Spartan software.¹⁰

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.0c03646>.

Cartesian coordinates, frequency and energies of all of the precomplexes, TSs, and postcomplexes in the studied environments (PDF)

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Notes

The authors declare no competing financial interest.

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