An In-Depth Computational Study of Alkene Cyclopropanation Catalyzed by Fe(porphyrin)(OCH₃) Complexes. The Environmental Effects on the Energy Barriers

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**ABSTRACT:** Iron porphyrin methoxy complexes, of the general formula [Fe(porphyrin)(OCH₃)], are able to catalyze the reaction of diazo compounds with alkenes to give cyclopropane products with very high efficiency and selectivity. The overall mechanism of these reactions was thoroughly investigated with the aid of a computational approach based on density functional theory calculations. The energy profile for the processes catalyzed by the oxidized [Fe(III)(Por)(OCH₃)] (Por = porphine) as well as the reduced [Fe(II)(Por)(OCH₃)]⁻ forms of the iron porphyrin was determined. The main reaction step is the same in both of the cases, that is, the one leading to the terminal-carbene intermediate [Fe(Por)(OCH₃)(CHCO₂Et)] with simultaneous dinitrogen loss; however, the reduced species performs much better than the oxidized one. Contrarily to the iron(III) profile in which the carbene intermediate is directly obtained from the starting reactant complex, the favored iron(II) process is more intricate. The initially formed reactant adduct between [Fe(II)(Por)(OCH₃)]⁻ and ethyl diazoacetate (EDA) is converted into a closer reactant adduct, which is in turn converted into the terminal iron porphyrin carbene [Fe(Por)(OCH₃)(CHCO₂Et)]⁻. The two corresponding transition states are almost isoenergetic, thus raising the question of whether the rate-determining step corresponds to dinitrogen loss or to the previous structural and electronic rearrangement. The ethylene addition to the terminal carbene is a downhill process, which, on the open-shell singlet surface, presents a defined but probably short-living diradicaloid intermediate, though other spin-state surfaces do not show this intermediate allowing a direct access to the cyclopropane product. For the crucial stationary points, the more complex catalyst [Fe(II)(Por)(OCH₃)]⁻, in which a sterically hindered chiral bulk is mounted onto the porphyrin, was investigated. The corresponding computational data disclose the very significant effect of the porphyrin skeleton on the reaction energy profile. Though the geometrical features around the reactive core of the system remain unchanged, the energy barriers become much lower, thus revealing the profound effects that can be exerted by the three-dimensional organic scaffold surrounding the reaction site.

**INTRODUCTION**

Iron porphyrins are recognized as having a fundamental importance in chemistry and biology; among others, they play a key role for their function as a heme in the case of cytochromes. Enzymes of the cytochrome P450 family are able to catalyze numerous oxidative processes with very high selectivity, for example, by inserting oxygen atoms into C−H and C≡C bonds through the action of an iron oxene intermediate. It is well-known that these enzymes have been engineered to become able to catalyze carbene transfer reactions through the intermediacy, in this case, of an iron carbene intermediate. Moreover, bioinspired iron porphyrin systems have been described that are able to transfer a carbene moiety in processes involving the formation of similar iron carbene intermediates, which show the carbene functionality on one of the two axial positions in the coordination sphere of iron, the other one being considered empty or, more often, occupied by neutral ligands such as imidazole derivatives or anionic ligands such as chloride, methoxy, or methylthiolate. A lot of investigations have been performed to disclose the mechanism of carbene formation as well as of the subsequent carbene transfer reaction to C≡C and C−H bonds with the fundamental contribution of theoretical calculations. To describe satisfactorily the electronic features of these systems, very simple computational models of the porphyrin complexes have been usually used, for example, simple porphine, thus neglecting the contribution of the overall environment in

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which the catalytic active metal is operating, whether it is a protein or the ligand skeleton of a bioinspired system.

Among the reactions performed via iron porphyrin catalysis, cyclopropanation reactions make use of a diazo compound as the carbene source to be added to a suitable alkene. When chiral moieties are mounted onto the tetrapyrrolic core of the catalyst, stereoselective reactions can be achieved, which mimic the selectivity of the corresponding engineered metalloenzyme-catalyzed reactions. One of the most-used diazo compounds is ethyl diazoacetate (EDA), which, thanks to its considerable chemical stability, can be safely handled in a laboratory and, by addition to a substituted ethylene such as α-methylstyrene, can furnish cyclopropane products that sometimes show a considerable diastere and enantioselectivity. In this context, we recently described the use of the iron(III) porphyrin methoxy complex [Fe(1)(OCH₃)] (FP) (Por = porphine), bearing suitable chiral C₂ symmetrical moieties onto the porphyrin core, as catalysts for cyclopropanation reactions showing high turnover number (TON) and turnover frequency (TOF) values, as well as high diastereo and enantioselectivity. The stereochemical outcome of these reactions was rationalized through theoretical calculations mainly focused on the tridimensional arrangement of the ligand framework of the catalyst. However, an in-depth investigation on the various steps of the catalytic cycle is still missing. So, we decided to study the mechanism of the reaction between EDA and ethylene, first using the model catalyst containing simple porphine [Fe(Por)(OCH₃)] (FP) (Por = porphine), then extending the study, for the main mechanistic step, to the more complex mono-strapped catalyst [Fe(2)(OCH₃)] (FP-2), in which one chiral organic moiety is mounted onto the porphyrin tetrapyrrolic core (Chart 1).

Because it has been often reported that EDA is able to reduce iron from the Fe(III) to the Fe(II) oxidation state, both electronic states should be taken into account in the mechanistic investigation. Thus, the reaction pathway involving [Fe(III)(Por)(OCH₃)] (FP) and that involving the reduced methoxy porphyrin [Fe(II)(Por)(OCH₃)]− (FP⁻) complex were determined during the theoretical investigation of the reasonable reaction mechanisms. Scheme 1 reports a generic overall picture of the reaction mechanism from the starting reactants to the cyclopropane product (CP), which shows that the initial attack of EDA on FP and the concomitant loss of dinitrogen give rise to the carbene intermediate [Fe(Por)(OCH₃)(CHCO₂Et)], which

Scheme 1. General Scheme of the Cyclopropane Formation Catalyzed by [FeIII(Por)(OCH₃)] (FP)

Chart 1. Molecular Structures of Iron Porphyrin Complexes Discussed in the Text
can exist in the two different modes, namely, terminal-carbene TC and bridging-carbene BC, though usually the former is considered to lay along the reaction pathway, whereas the latter is in equilibrium with it. Reaction of ethylene with the intermediate affords the cyclopropane adduct CP and restores the catalyst FP in its initial state.

**RESULT AND DISCUSSION**

**Reaction Catalyzed by [Fe\textsuperscript{II}(Por)(OCH\textsubscript{3})]\textsuperscript{3+}** (FP\textsuperscript{−}).

*Carbene Intermediates Formation.* All the reactants, intermediates, and transition states along the reaction pathway were optimized in toluene using the unrestricted UB3LYP functional at the 6-31G(d) level\textsuperscript{15} for all the atoms, except for iron, for which the effective core potential LanL2DZ was used. With the optimized geometries, single-point energy calculations in toluene were performed using the all-electron Def2-TZVP basis set for all atoms. Dispersion corrections were computed with the Grimme D3 method. For the open-shell structures the stability of the wave function was always checked, optimizing it when found unstable. For all the species containing iron, the closed-shell singlet, open-shell singlet, triplet, and quintet spin states were investigated.

First, EDA and FP\textsuperscript{−} were separately optimized, and the iron ground state in FP\textsuperscript{−} was determined to be the high-spin quintet state, 5FP\textsuperscript{−}, preferred by 9.2 kcal/mol over the triplet state 3FP\textsuperscript{−} and by almost 14 kcal/mol over the closed-shell singlet 1FP\textsuperscript{−}. When EDA approaches FP\textsuperscript{−}, an FP-EDA loose complex initially forms with a distance between iron and the EDA C2 atom (d\textsubscript{C2-Fe}) longer than 3.5 Å. The singlet states remained the less stable ones, and the energy gap with respect to the quintet state 5FP-EDA even increases (Figure 1 and Table S1). This 5FP-EDA local energy minimum geometry is 9.7 kcal/mol more stable than the isolated EDA and 3FP\textsuperscript{−} reactants in terms of energy, but, due to the entropy penalty, it is slightly less stable than the reactants in terms of Gibbs free energy.

The energy profile that leads to the loss of dinitrogen and the formation of the terminal carbene species TC\textsuperscript{−} was then determined, and, as shown in Figure 1, it resulted more intricate than in Scheme 1. Three of the four FP-EDA complexes, in particular, the radical or diradicaloid species, are not directly connected to the transition states corresponding to the dinitrogen loss but give rise, in the first reaction step, to three intermediate structures, 1FP\textsuperscript{−}INT1, 1FP\textsuperscript{−}INT1\textsuperscript{−}, and 1FP\textsuperscript{−}INT1\textsuperscript{−}, in which the distance between the EDA C2 and N\textsubscript{α} (d\textsubscript{C2-N\textalpha}) atoms is still a bond distance (∼1.45 Å). In these structures the interaction between EDA and iron is already significant (d\textsubscript{C2-Fe} has shortened to a bond distance, 2.22–2.25 Å), and the stability order of the various spin states is reversed, the broken-symmetry solution of the singlet 1FP\textsuperscript{−}INT1\textsuperscript{−} and the triplet 3FP\textsuperscript{−}INT1\textsuperscript{−} being the most stable ones and 5FP\textsuperscript{−}INT1\textsuperscript{−} being the least stable. A significant charge transfer is simultaneously observed, as the neutral EDA moiety of 1FP-EDA, with an entire charge hosted by FP\textsuperscript{−}, gains an overall charge of −0.490 with only −0.510 left on the iron porphyrin moiety. An inspection of the structures of the FP-EDA and INT1\textsuperscript{−} species showed that they differ mainly in two geometrical features, namely, the already mentioned distance between iron and the C2 carbon atom of EDA and the geometry of the first nitrogen atom (N\textalpha) of EDA, linear in the complexes FP-EDA and trigonal planar in the intermediates INT1\textsuperscript{−}, suggesting a change of its hybridization. We were able to locate the transition state, 1TS\textsuperscript{−}, corresponding to their interconversion characterized by a very strong negative frequency and correctly connectable, through intrinsic reaction coordinate (IRC) calculations, to FP-EDA and INT1\textsuperscript{−}. Energy barriers of 12–13 kcal/mol with respect to isolated EDA and 5FP\textsuperscript{−} were found for 1TPS\textsuperscript{−} and 3TS\textsuperscript{−}, while 5TS\textsuperscript{−} is less stable by 10–11 kcal/mol.

Then, further shortening of d\textsubscript{C2-Fe} leads to the three open-shell transition states 1TS\textsuperscript{−}, 2TS\textsuperscript{−}, and 3TS\textsuperscript{−}. The most stable one is 1TS\textsuperscript{−}, followed by the triplet and the quintet transition states. The closed-shell transition state 1TS\textsuperscript{−}, directly accessible from the reactant complex 1FP-EDA, is
The preferred transition state $^1\text{TS}^2$ is characterized by $d_{C2-Fe} = 2.06 \text{ Å}$ and $d_{C2-N0} = 1.81 \text{ Å}$ and by a partial charge return toward the iron porphyrin moiety (the overall charge on EDA is $-0.351$). In $^1\text{TS}^2$ the electronic energy barrier is 13 kcal/mol with respect to isolated EDA and $^5\text{FP}^-$ and is much higher if the Gibbs free energy is considered, 29.5 kcal/mol, a value that seems too high for a viable reaction pathway. This barrier might be overestimated due to overestabilization of the higher spin-state precursors by the B3LYP hybrid functional. However, it should be also considered that these investigations on the reaction mechanism are referred to a very simplified reaction model, whereas the real reaction is experimentally performed with $[\text{Fe}(\text{Por})(\text{OCH}_3)]$ catalyst, which shows a C$_2$-symmetrical steric chiral bulk surrounding the tetrapyrrolic core (Figure 1). In agreement with previous experimental and computational data, the singlet state was preferred by this broken-symmetry solution of the singlet state overestimates the entropy involved. In fact, the computed free energy barrier from the reactant complex $^5\text{FP}^-$ EDA shows an even lower value (21.5 kcal/mol), compatible with the fast reaction catalyzed by the $[\text{Fe}(1)(\text{OCH}_3)]$ complex, able to catalyze cyclopropanation reactions even below room temperature. It is presumably to envisage that the energy barrier of the reaction mediated by the bis-strapped $[\text{Fe}(1)(\text{OCH}_3)]$ complex should be approximately the same or even lower than that calculated in the presence of the mono-strapped $[\text{Fe}(2)(\text{OCH}_3)]$ (FP-2), the second strap not being directly involved in the carbene formation.

Going back to the simple porphine model, the IRC calculations performed on the four transition states TS2, the barrier from the reactant complex to the transition state is lowered by the enzyme environment, due to the large organic moiety that surrounds the reaction site, might act in a similar way. To confirm this hypothesis, transition states including the entire bis-strapped porphine 1, instead of the simple porphine present in $^1\text{TS}^2$, should be located, but this is beyond our current computational possibilities. In a previous paper we showed that the behavior of the $[\text{Fe}(1)(\text{OCH}_3)]$ complex can be safely reproduced in calculations by the corresponding single-stranded porphine model complex $[\text{Fe}(2)(\text{OCH}_3)]$ (FP-2) (Figure 1). So, we tried to locate the corresponding transition state $^1\text{TS}^2-2^-$, and, after a considerable computational effort, the goal was reached. While the geometrical data of EDA inside the reaction site found for $^1\text{TS}^2-2^-$ are very similar to those of $^1\text{TS}^2$, the electronic energy barrier is significantly lower, 5 kcal/mol for the former (Table S2) and 13 kcal/mol for the latter (Table S1). The decrease is significant also in terms of relative free energy, as the barrier approaches the value of 24 kcal/mol, 5.5 kcal/mol lower than in the simplified model, thus evidencing the large effect of the three-dimensional organic scaffold surrounding the reaction site on the energy barriers. Moreover, it should be remarked that the barrier from the isolated reactants overestimates the entropy involved. In fact, the computed free energy barrier from the reactant complex $^5\text{FP}^-$ EDA shows an even lower value (21.5 kcal/mol), compatible with the fast reaction catalyzed by the $[\text{Fe}(1)(\text{OCH}_3)]$ complex, able to catalyze cyclopropanation reactions even below room temperature. It is presumably to envisage that the energy barrier of the reaction mediated by the bis-strapped $[\text{Fe}(1)(\text{OCH}_3)]$ complex should be approximately the same or even lower than that calculated in the presence of the mono-strapped $[\text{Fe}(2)(\text{OCH}_3)]$ (FP-2), the second strap not being directly involved in the carbene formation.

Going back to the simple porphine model, the IRC calculations performed on the four transition states TS2-2$^-$ allowed to connect them, on the forward side, to the terminal carbene intermediate species $[\text{Fe}(\text{Por})(\text{OCH}_3)(\text{CHCO}_{3\text{Et}})]^-$ (TC$^-$) and dinitrogen as byproduct. The stability order of these terminal carbenes reflects that of the transition state leading to them, the broken-symmetry solution of the singlet $^1\text{TC}^-$ being the most stable one, with energy comparable, even lower, than that of the starting reactants (Table S1 and Figure 1). In agreement with previous experimental and computational data, the singlet state was preferred by this carbene species.

The spin density in $^1\text{TC}^-$ terminal carbene resides on iron and the carbon atom linked to it, evidencing an antiferromagnetic coupling between the carbon-centered radical and the unpaired electron on iron as already found in the corresponding terminal carbene bearing a methylthiolate...
instead of the methoxy group as the other axial ligand on iron. The diradicaloid structure of 1OSBC terminal carbene resembles that of the cobalt carbene radical species. A positive natural population analysis (NPA) charge was found on iron (qFe = +0.159), while the two atoms linked to it are negatively charged (qC1 = −0.119 and qO = −0.628). The overall charge on the carbene moiety (−0.195) highlights the further charge shift toward the iron porphyrin moiety.

It is worth mentioning that the distance between iron and the methoxy oxygen atom remains almost unchanged during the reaction (from 1.901 Å in 3FP− to 1.853 Å in 1OSINT1 and 1.905 Å in 1OSFC−; see Table S1). The experimental evidence indicated that, regardless of the nature of the active carbene intermediate, the methoxy ligand of the catalyst is not lost during cyclopropanation.

Starting from the terminal carbenes [Fe(Por)(OCH3)(CHCO2Et)]− (TC−) we then looked for the corresponding bridging structures BC− and the transition states connecting them, TS3. The lowest-energy transition state, 11OSTS3−, occurs on the singlet open-shell surface with a barrier of 15 kcal/mol with respect to 11OSBC− and gives a bridging structure 11OSBC− almost isoenergetic to 11OSFC− (Table S1 and Figure 2). However, the most stable bridging carbene is the high-spin quintet 5BC+, 9.4 kcal/mol more stable than 11OSBC−.

In the above results the broken-symmetry solutions of the singlet species could have been corrected for spin contamination using the Yamaguchi corrections of energy. If used, the corrections generally further stabilize this solution (Table S7), for example, making also 11OSTS1− more stable than 3TS1−, but do not significantly modify the energy profiles. So, they were not added to the energy data in the figures and tables.

**Reaction of the Carbene Intermediates with Ethylene.**

Then focus was placed on the right side of the cyclopropanation reaction (Scheme 1) by looking for the transition states deriving from the attack of ethylene to the porphyrin carbene intermediates [Fe(Por)(OCH3)(CHCO2Et)]− (TC−). The most stable TS was found to be 11OSTS4− (Table S3 and Figure 3), which lies on the open-shell singlet surface and is characterized by a very low energy barrier (4.8 kcal/mol from 11OSBC−), much smaller than that of the corresponding terminal-bridging interconversion.

Once again, 11OSTS4− is preferred over 3TS4− and largely preferred over 11OSTS4− and 5TS4−. The IRC path from 11OSTS4− leads in the forward direction to an intermediate with a diradicaloid character, 11INT2−. In this intermediate one new C−C bond is already formed (1.55 Å), and the other one is far from being formed (2.52 Å), suggesting that it is a reaction intermediate with a radical nature. However, the IRC path from 5TS4− gives access to a structure, 11INT2−, separated by the final products by a very low energy barrier, which disappears in terms of free energy. Moreover, both the closed-shell 11OSTS4− and the highest-spin 5TS4− transition states are directly connected to the final products. Thus, it cannot be excluded that the pathways cross after the 11OSTS4− transition state to generate the cyclopropane product without passing the 11INT2− intermediate. Anyway, the process ends in a deep valley, ~50 kcal/mol below the starting reactants, both in terms of electronic energy and free energy (Table S3) with formation of cyclopropane CP plus the catalyst, which, after crossing to the most stable quintet ground state, is ready for a new reaction cycle.
Reaction Catalyzed by [Fe\textsuperscript{III}(Por)(OCH\textsubscript{3})]\ (FP). Carbene Intermediates Formation. The computational approach was the same as above-described. In this case, the doublet, quartet, and sextet spin states were investigated for all the species containing iron. When the oxidized iron porphyrin [Fe\textsuperscript{III}(Por)-(OCH\textsubscript{3})] (FP) was optimized, the preferred ground state was found to be the high-spin sextet state, \textsuperscript{6}FP, preferred by 3.2 and 8.5 kcal/mol over the quartet and doublet states \textsuperscript{4}FP and \textsuperscript{2}FP, respectively (Figure 4 and Table S4). The most stable reactant complex \textsuperscript{6}FP-EDA is 8.4 kcal/mol more stable than the isolated EDA and \textsuperscript{6}FP in terms of energy but less stable in terms of Gibbs free energy, as observed for [Fe\textsuperscript{II}(Por)-(OCH\textsubscript{3})]\ (FP\textsuperscript{−}). Moving from the reactant complexes at decreasing d\textsubscript{C2−Fe} distances, once more the lowest spin state becomes preferred. In this case, no intermediate structure was observed, and the transition state for dinitrogen loss, \textsuperscript{2}TS\textsubscript{2}, is directly reached. The electronic energy barrier with respect to isolated EDA and \textsuperscript{6}FP is higher than with the reduced catalyst (22.6 kcal/mol) and becomes extremely high if the Gibbs free energy is considered (37 kcal/mol). The free energy barrier computed from the reactant complex \textsuperscript{6}FP-EDA shows a lower but still high value (33.3 kcal/mol). With the model single-stranded porphyrin complex [Fe\textsuperscript{III}(2)(OCH\textsubscript{3})] (FP-2), a significant decrease of ~6 kcal/mol of the electronic energy barrier was observed (Table S5). The decrease is significant also in terms of the relative free energy (~4 kcal/mol), and the barrier approaches the value of 30 kcal/mol as the computed free energy barrier from the reactant complex \textsuperscript{6}FP-2-EDA.

An IRC analysis from \textsuperscript{2}TS\textsubscript{2} allowed connecting it, in the forward direction, to the terminal carbene \textsuperscript{2}TC and dinitrogen. The transition states for the N\textsubscript{2} loss on the quartet and sextet surfaces \textsuperscript{4}TS\textsubscript{2} and \textsuperscript{6}TS\textsubscript{2} were found to be much less stable than \textsuperscript{2}TS\textsubscript{2} (Figure 4 and Table S4).

Contrarily to \textsuperscript{2}TS\textsubscript{2}, the IRC calculations from these higher spin transition states gave direct access to the bridging carbenes \textsuperscript{4}BC and \textsuperscript{6}BC, the former being the most stable carbene species, more than 25 kcal/mol more stable than \textsuperscript{2}TC. The carbene species \textsuperscript{2}BC, not directly obtained through the IRC calculations, was also located and optimized as well as the transition state for the terminal-bridging interconversion, \textsuperscript{2}TS\textsubscript{3}, which is very terminal-like in its geometry and shows a very low energy barrier from the terminal carbene \textsuperscript{2}TC (3.3 kcal/mol).

Reaction of the Carbene Intermediates with Ethylene. The most stable transition state was found to be \textsuperscript{2}TS\textsubscript{4} (Table S6 and Figure 4), characterized by a very small energy barrier (0.8 kcal/mol) from the \textsuperscript{2}TC carbene intermediate, even lower than that of the terminal-bridging interconversion. Once again,
**CONCLUSION**

In this paper the overall mechanism of cyclopropanation reaction catalyzed by an iron porphyrin methoxy complex was investigated with the aid of a computational approach. In the catalyst experimentally used to perform such reactions, \([\text{Fe}^{II}(\text{Por})(\text{OCH}_3)]\), iron is in the +3 oxidation state and is recovered as such at the end of the reaction to be used again with virtually unmodified catalytic performances. However, a significant amount of literature on comparable systems suggests consideration of its reduced form, \([\text{Fe}^{III}(\text{Por})(\text{OCH}_3)]^{-}\), as the catalytically active form, obtained from the resting iron(III) species by action of ethyl diazoacetate, which can promote its in situ reduction. During the recovery, the iron(III) species by action of ethyl diazoacetate, which can promote its in situ reduction. The reaction rate is almost unaFFECTED by the change from the linear to the trigonal planar geometry of its first nitrogen atom and by a significant shortening of the Fe–C2 distance. Actually, the barrier of the two steps has comparable heights so that, whatever the highest barrier, the reaction rate is almost unaffected.

The ethylene addition to the terminal carbene is a downhill process, which, on the broken-symmetry solution of the singlet surface, presents a defined but elusive intermediate. This intermediate is badly defined on the triplet surface and does not exist on the closed-shell singlet and quintet surfaces.

Finally, the computational data obtained with the single-stranded porphyrin catalyst \([\text{Fe}^{III}(\text{Por})(\text{OCH}_3)]^{-}\) made clear the very significant effects of the three-dimensional scaffold surrounding the reaction site on the reaction profile and underline the strong influence of the entire catalyst on its performance. Though the geometrical features around the reactive core of the system remain unchanged, the energy barrier becomes much lower (a Gibbs free energy value of 21.5 kcal/mol with respect to the reactant complex), making feasible an apparently unfeasible reaction.

This paper further advances the understanding of the mechanism of action of the metal porphyrin complexes in the particular case of the iron porphyrin methoxy complexes. It compares the predictable energy profiles determined for both the oxidized and reduced forms of the catalyst on all the reasonable spin states of the metal center and describes all the mechanistic detail of the carbene intermediate formation. Further studies will determine the extensibility of these results to other iron porphyrin complexes.

**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/10.1021/acs.inorgchem.0c00912.

Computational details, electronic energy, and Cartesian coordinates of all computed structures (PDF)

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Author Contributions

The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.
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