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ACS Catal., Just Accepted Manuscript • DOI: 10.1021/acscatal.8b04175 • Publication Date (Web): 11 Jan 2019

Downloaded from http://pubs.acs.org on January 12, 2019

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Mechanism of Coupling of Alcohols and Amines to Generate Aldimines and H₂ by a Pincer Manganese Catalyst.

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ABSTRACT: Acceptorless dehydrogenative coupling (ADC) of alcohols and amines using a manganese-based catalyst is able to produce aldimes, which have a wide reactivity, without underestimating the generation of a clean fuel, since as a result of this coupling, molecular hydrogen is also obtained. Therefore, the aldime synthesis represents an interesting reaction from chemical and clean energy points of view. In this work, the computational study, via Density Functional Theory (DFT) calculations, of a manganese-based catalyst for the acceptorless dehydrogenative coupling of alcohols and amines reaction, together with the elucidation of its catalytic cycle using benzene as a solvent, is carried out. Calculations provided insight not only into the catalytic pathway, but also on the non-catalyzed organic transformation to reach the desired aldime, based on the aldehyde generated in the catalytic cycle. The importance of the alternative isomers of the Mn-pincer complex, previously characterized experimentally, as well as the assisting role of alcohol or water, are also described.

KEYWORDS: aldime, manganese, water assisted, catalysis, pincer ligand, green chemistry

INTRODUCTION

Aldimes are imines with the general formula R-CH=N-R'. Aldime structure is analogous to an aldehyde, substituting the oxygen of the carbonyl group for a nitrogen, which enables a particular reactivity and, consequently, a wide range of applications; mainly as synthesis intermediates used for the production of pharmaceutical derivatives, colorants and agrochemical products between many others.¹

In a general recipe for the synthesis of imines, a mixture of an aldehyde or ketone with an amine in presence of an acid catalyst is required. Recent routes to aldimes involve acceptorless dehydrogenative coupling (ADC) of alcohols and amines,²³ depicted in Scheme 1.

Scheme 1. Acceptorless dehydrogenative coupling (ADC) of alcohols and amines using a metal-based catalyst.

Interestingly, in this type of reaction, the involved hydrogen atoms do not hydrogenate the C=N double bond; instead, molecular hydrogen is generated as the only co-product, resulting in an environmentally benign reaction.³ Moreover, H₂ is a possible energy source that may be the main fuel in the future, as the only by-product from its combustion. Since no carbon based products are released from the combustion of H₂, the procedure becomes promising for green chemistry.³⁴⁻⁵ Furthermore, the possibility of using an alcohol as reactant increases the interest for this sustainable reaction, since alcohols can be obtained in high amounts at the industrial level, even from renewable resources such as lignocellulose biomass.⁶⁻⁷ In the first synthesis of imines by ADC of alcohols and amines, a Ru-based complex was used as catalyst.²¹ Since 2011, other transition metal complexes, mostly based on precious metals, have been used as catalysts for this reaction.²² Currently, there is a strong interest in replacing these catalysts for complexes of cheaper and earth-abundant transition metals, which is taking ground.²³⁻²⁴ Apart from iron⁶ and cobalt,²⁴ there is interest in utilizing manganese as transition metal for the development of new catalysts due to being the third most abundant transition metal on earth.²⁵⁻²⁶ In 2016, Milstein and co-workers described a Mn-pincer complex (Figure 1) which catalyzes the ADC of alcohols with amines.²⁷ Pincer complexes generally adopt meridional geometry,²⁸⁻²⁹ although the facial shape may be preferred in some cases.³⁰ The chelating nature and rigidity of pincer ligands generally confers high thermal stability of the resulting complexes, without hindering reactivity. Concurrently Kirchner and coworkers showed that with Co¹¹ catalysts featuring a PCP ligand holding a 1,3-diaminobenzene scaffold the alkylation of aromatic amines with primary alcohols did not lead to imines but amines.¹¹ Thus, there is a general trend: iron and cobalt based transition metal catalysts tend to lead to amines, whereas manganese and cobalt ones to imines.¹²
In this work, we report a computational study starting from the mechanism proposed by Milstein et al.\textsuperscript{15} using the Mn\textsuperscript{2+} catalyst displayed in Figure 1; bearing a trigonal bipyramid geometry, constrained by its PNP pincer ligand.\textsuperscript{21,22} The aldime generation using benzene as solvent went up to conversions and yields of over 99% with substituted benzyl alcohols and/or amines, and to 92% with non-substituted reactants after 60 h at 135 °C. Structural and electronic properties have also been explored by Density Functional Theory (DFT) calculations to unveil further mechanistic insights.

## RESULTS AND DISCUSSION

First of all, we optimized complex 1 for the different possible spin states in order to check the multiplicity with the lowest energy, locating the triplet state 6.7 kcal/mol above in energy than the singlet, followed by all the remaining species. Thus, we determined that in all cases the singlet is the ground state.

In Figure 2, we depicted the full reaction mechanism, trying to link all the structures experimentally characterized by Milstein and coworkers,\textsuperscript{15} mimicking past work of hydrogenation of nitriles and ketones by Beller and coworkers.\textsuperscript{23}

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**Figure 1.** Manganese catalyst (1) used for the ADC of benzyl alcohols with benzyl amines ((a) Lewis structure and (b) 3D view; selected bond distances in Å).

**Figure 2.** Full reaction mechanism for the ADC of benzyl alcohols with benzyl amines (in blue the steps assisted by water and in green by the alcohol; \( R_1 = \text{CH}_2\text{-Ph} \); in black (minima) and in orange (transition states) Gibbs free energies in solvent in kcal/mol and referred to catalyst 1, whereas to the aldehyde 5 in the metal free reaction pathway included in the box).
Starting from $\mathbf{1}$, we can observe three main steps: $1 \rightarrow 1'$, $1 \rightarrow 2$ and $1 \rightarrow 4$. To form in a single step the required aldehyde $\mathbf{5}$ we must overcome an energy barrier of 31.9 kcal/mol, reaching the hydride Mn complex $\mathbf{2}$ through TS $\mathbf{1} \rightarrow \mathbf{2}$. The complexity of this step is due to the protonation of a sp$^3$ carbon of the pincer ligand together with the geometrical rearrangement around the metal, going from a trigonal bipyramid to an octahedral geometry (see Figure 3a). This mechanism had already been described by Boncella et al. for an aliphatic PNP-pincer complex using a water molecule instead of an alcohol. The incorporation of the alkoxy moiety to the metal center on $\mathbf{1}$, combined with the protonation of the methine moiety of the pincer ligand, is a competing reaction that leads to species $\mathbf{1}'$ (see Figure 3b). This alternative step requires almost half the energy of the aldehyde formation path $\mathbf{1} \rightarrow \mathbf{2}$, being kinetically preferred. Thermodynamically, $\mathbf{1}'$ is 1.0 kcal/mol above $\mathbf{1}$, whereas $\mathbf{2}$ is 1.2 kcal/mol below in energy, being $\mathbf{2}$ the thermodynamically favoured isomer. However, from $\mathbf{1}'$ it is possible to reach the same intermediate $\mathbf{2}$, overcoming an energy barrier of 32.4 kcal/mol. The assistance of an external water or alcohol molecule lowers this second energy barrier by 2.5 and 3.2 kcal/mol (see Figures 3c and d), respectively. According to this, at the initial step we might lose part of our active catalyst in such equilibria but, in the long term, the reaction will evolve through $\mathbf{1}'$, specially with the additional formation of water as a byproduct (see Scheme 1).

From intermediate $\mathbf{2}$, the formation of molecular hydrogen and the regeneration of catalyst $\mathbf{1}$ is straightforward; holding both hydrogen atoms in syn conformation, $\mathbf{H}_2$ is formed but still attached to the metal center, with an energy cost of 31.9 kcal/mol (see Figure 3e), and leading to $\mathbf{3}$. Finally, in the step that closes the catalytic cycle, the hydrogen molecule previously formed is released, via a transition state with an associated energy barrier of 30.8 kcal/mol (see Figure 3f). Kinetically, the formation of $\mathbf{H}_2$ on Mn becomes the rate determining step (rds), although still in competition with the previous step, isoenergetic, or only 1-2 kcal/mol less energetically demanding if assisted by an external water or alcohol molecule. Furthermore, previous work by Kirchner et al.\textsuperscript{20} led also to nearly identical energy values for both latter transition states. Thus, both transition states must be taken into account.\textsuperscript{21} On the other hand, the $\mathbf{H}_2$ release from benzyl alcohol, prone to be undertaken without the presence of a metal catalyst, was reconsidered but with a huge energy barrier of 82.1 kcal/mol, almost 50 kcal/mol above the corresponding catalytic barrier, \textit{i.e.} for step $\mathbf{1} \rightarrow \mathbf{2}$. This unveils the fundamental role of the transition metal complex in the kinetics. Moreover, the thermodynamics were also favoured by the catalyst with an exergonic balance of 1.2 kcal/mol, whereas a destabilization of 4.9 kcal/mol without a metal catalyst was found, deeming once more the non-catalysed reaction unviable.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3}
\caption{Transition states (a) $\mathbf{1} \rightarrow \mathbf{2}$; (b) $\mathbf{1} \rightarrow \mathbf{1}'$; (c) $\mathbf{1} \rightarrow \mathbf{2}$ (assisted by alcohol); (d) $\mathbf{1}' \rightarrow \mathbf{2}$ (assisted by water); (e) $\mathbf{2} \rightarrow \mathbf{3}$; and (f) $\mathbf{3} \rightarrow \mathbf{1}$; selected distances given in Å.}
\end{figure}
Once the aldehyde 5 is formed, the mechanism might evolve through two possible ways. The non-catalyzed step 5 → 7, where 5 reacts with the benzyl amine (6), requires more energy than the interaction of the aldehyde with the catalyst in 1 → 4, even when this step is assisted by water or benzyl alcohol molecules. Kinetically, the formation of 7 is still 2.7 kcal/mol more expensive than the formation of 4. Actually, this shows a preference towards the interaction of the aldehyde with the catalyst 1 instead of the direct reaction between amine and aldehyde, even both are possible at our given conditions. The explanation for the stabilization achieved while assisted by the water molecule is related with the constrained 4-member ring that involves the four main atoms involved in such a step without water, two from the aldehyde and two from the amine. With water, the concerted transition state is more relaxed, presenting a nearly symmetrical 6-member ring (see Figure 4a). From the organic intermediate 7, the generation of the desired aldimine 8 consists of a proton transfer and a C-O bond cleavage (see Figure 4b), releasing a water molecule as a byproduct. It requires to overcome an important energy barrier of 54.2 kcal/mol, which decreases sharply to 39.5 or 34.1 kcal/mol when assisted by two water or benzyl alcohol molecules, respectively. The latter transition state describes the rate determining step (rds), and its associated energy barrier is completely reasonable bearing the experimental temperature (150°C), but only taking into account the aid of the alcohol reagent or the water as a cocatalyst, without which the barrier could not be overcome. As the reaction itself generates water as a by-product, even though at the first stages the alcohol will take the assisting role, the water will participate actively afterwards. Thus, only a sort of preactivation would be necessary before facing the regular catalytic cycle assisted by water molecules from the same reaction. Moreover, the use of no thoroughly dried solvent is a hint that the traces of water are enough to activate the catalysis at the beginning. Furthermore, even though the most reasonable path to get intermediate 7 is directly from the aldehyde 5, in agreement with the proposed mechanism by Milstein et al., the metal assisted step was also attempted. We found that the hemiaminal intermediate homologous to 7 was placed 14.9 kcal/mol above it.

Figure 4. Transition states (a) 5→6→7 and (b) 7→8 assisted by one and two alcohol molecules, respectively (phenyl groups simplified for clarity as green balls; selected distances given in Å).

Complex 4 can progress through the intramolecular C-C bond formation between the former aldehyde and the close carbine moiety (4→4'). Even though kinetically it is rather facile, with a low energy barrier of 6.8 kcal/mol, and that 4' is 3.4 kcal/mol more stable than 4, the process is thermodynamically not favored by 9.9 kcal/mol with respect to 1. Consequently, this indicates that we use part of our catalyst in this equilibrium, slowing down the reaction, as it occurs in the equilibria involved in the transformation of the initial 1 that leads to intermediate 2.

Once we detailed the mechanism, we wanted to identify the influence of the amine in terms of electronics. According to Milstein et al. an aryl imine with a methoxy group (OMe) in para position leads to a 97% conversion with a 99% yield, while the same amine, but now with a fluoride ligand (F) instead of the methoxy group, has a poor 52% conversion with a 55% yield. To explain the experimental results we undertook DFT calculations for the steps 5→6→7 and 7→8, as shown in Scheme 2. In general, larger upper barriers were found for the fluoride-substituted amine, whereas for the methoxy-substituted the energy barriers were unveiled nearly unmodified. However, the energy differences are extremely low (<1 kcal/mol) which do not allow us to extract robust conclusions as we are within the DFT error. Thus, the latter low energy differences forced characterization calculations in order to better understand the role of the substituents in para of the benzylamine. We extracted from the Natural Population Analysis (NPA) and compiled in Table 1 the natural charges of the nitrogen atoms from the different species. We do not observe a remarkable change in the charge of the hydrogen, independently of the electron-donating (OMe) or electron-withdrawing (F) character of the functional group located in the para position of the aryl ring, in comparison with the H-substituted. Therefore, we must conclude that the charge is not affected.

Scheme 2. Metal free reaction pathway between the aldehyde and the benzylamine, with H, OMe or F substituents in para position (step 5+6→7 and 7→8 are assisted by either two water (R2 = H) or benzyl alcohol (R2 = CH3-Ph) molecules; energies in kcal/mol).
Table 1. Natural charge for the N atom according to different substituents.

<table>
<thead>
<tr>
<th>Substituent</th>
<th>H-</th>
<th>F- (para)</th>
<th>MeO- (para)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>-0.873</td>
<td>-0.874</td>
<td>-0.872</td>
</tr>
<tr>
<td>5+6 → 7</td>
<td>-0.707</td>
<td>-0.707</td>
<td>-0.706</td>
</tr>
<tr>
<td>7</td>
<td>-0.720</td>
<td>-0.721</td>
<td>-0.719</td>
</tr>
<tr>
<td>7 → 8</td>
<td>-0.610</td>
<td>-0.609</td>
<td>-0.607</td>
</tr>
<tr>
<td>8</td>
<td>-0.453</td>
<td>-0.455</td>
<td>-0.453</td>
</tr>
</tbody>
</table>

Continuing with the electronic analysis of the benzylamines, we checked the aromaticity of the aryl group through the calculation of the Nuclear Independent Chemical Shift (NICS), defined by Schleyer et al. This magnetic aromaticity index is defined as the negative value of the absolute shielding computed at the central point of a ring, even it can be computed at any point of the system. The more negative the value, the higher the aromaticity. In our case, we performed the calculation on the center of the aryl ring (NICS(o)) and 1 Å above and below it (NICS(t), and NICS(t), respectively). To properly interpret the results obtained, which are compiled in Table 2, the computation of a reference value is required. In our case, we used benzene as reference for checking whether electron-donating or electron-withdrawing groups induce an increase or decrease on the intrinsic aromaticity of the ring. We observe that the aromaticity increases for the fluoride-substituent arene, which combined with the higher energy barrier compared to the methoxy-substituted one, explains better the lower yields and conversion. To confirm the data, we performed the HOMA index calculation. As a geometrical index, closer to 1 the value obtained, more similar our structure is to the reference one (benzene, again, with equal C-C bond distances of 1.388 Å) and, thus, more aromatic the molecule. The index provided a value of 0.889 and 0.920 for the OMe and F substituted aryl, respectively, while 0.907 (in between both data) for the non-substituted one. Taking into account that as more aromaticity the aryl ring, less reactivity will present, the geometrical index HOMA, together with the electronic index NICS(t), confirmed that the OMe and the F substituted aryls will be the more and less reactive species, respectively.

Table 2. NICS analysis for the para substituted amine.

<table>
<thead>
<tr>
<th>Substituent</th>
<th>H-</th>
<th>F- (para)</th>
<th>MeO- (para)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICS(o)</td>
<td>-7.647</td>
<td>-9.310</td>
<td>-8.431</td>
</tr>
<tr>
<td>NICS(t)</td>
<td>-10.134</td>
<td>-9.944</td>
<td>-9.587</td>
</tr>
<tr>
<td>NICS(t)_out</td>
<td>-9.394</td>
<td>-9.657</td>
<td>-9.301</td>
</tr>
</tbody>
</table>

Last but not least, we performed conceptual DFT analyses to evaluate the overall electronics of the benzylamine molecule, as it has allowed the study of the reactivity and regioselectivity of chemical reactions. We used the Highest Occupied Molecular Orbital (HOMO) and the Last Occupied Molecular Orbital (LUMO), which corresponds to the frontier molecular orbitals, to calculate the chemical hardness and the electrophilicity within the Koopmans theorem. The results obtained were compiled in Table 3. For both concepts the differences obtained are quantitatively small, but qualitatively the electrophilicity values unveil that the F based amine becomes the less nucleophilic, whereas the nucleophilicity with a methoxy group is maximum with respect to the non-substituted amine: in perfect agreement with Scheme 2, despite the low energy differences due to the para substituents.

Table 3. Chemical hardness (η) and electrophilicity (ε) for the non-substituted amine and the para substituted amine.

<table>
<thead>
<tr>
<th>Substituent</th>
<th>H-</th>
<th>F- (para)</th>
<th>MeO- (para)</th>
</tr>
</thead>
<tbody>
<tr>
<td>η</td>
<td>0.160</td>
<td>0.153</td>
<td>0.149</td>
</tr>
<tr>
<td>ε</td>
<td>0.043</td>
<td>0.049</td>
<td>0.040</td>
</tr>
</tbody>
</table>

Finally, to emphasize the role of stabilization between aromatic rings, we plot the Non-Covalent Interactions (NCI), calculated using the NCIplot program developed by Contreras, on the transition state 7 → 8 for the differently substituted aryl rings (see Figure 5).

Figure 5. NCIplots of 7 → 8, substituted with (a) H, (b) F and (c) OMe and assisted by two benzyl alcohol molecules. Isosurface represented of value 0.4 with color scale for the reduced density gradient from -0.05 (red) to 0.05 (blue).
The NCI plots allow to observe and qualitatively evaluate and depict, in the tridimensional space, the strength of the noncovalent interactions between the different regions of the molecular system. In our case, between the several aryl rings in this particular condensation step. In Figure 5, we represented the results obtained for the three differently substituted amines studied, plotting the isocontour obtained with a value of 0.4 of the reduced density gradient. For the correct interpretation of the results, we selected, for the color scale, the interval from -0.05 (red and repulsive) to 0.05 (blue and attractive) of the second density Hessian eigenvalue. Qualitatively, and taking into consideration the interaction between aryl rings, we distinguish a trend that unveils more attractive regions for the OMe substituent rather than with F. This is in perfect agreement with experimental findings.

**CONCLUSIONS**

We determined the full mechanism of the aldimine formation reaction, undertaking calculations using a manganese-based catalyst. The catalyst is necessary in the generation of aldimines starting from amines and alcohols, as the formation of the aldehyde from the alcohol requires mandatorily its assistance. Still, the presence of the reagent benzyl alcohol is necessary to undertake the step that leads to the intermediate between the aldehyde and the desired aldimine, when there are no traces of water. The last step that leads to the aldimine must be again assisted by water or alcohol. The cocatalyst role of those protic agents is due to the formation of at least six-member rings more stable than the four-member rings in both transition states (5+6 → 7, and 7 → 8). As the reaction evolves, water is generated as a by-product and the alcohol is not necessary anymore for the last two pure organic steps, because the formation of this intermediate is easily water-assisted with a lower energy barrier. Overall, the effect of water/alcohol was demonstrated for both the Mn-catalyzed and the metal-free sides of the reaction. In the former part (Figure 2), the major effect applies to lower the energy barrier corresponding to the step 1' → 2. Nevertheless, this was not the case for the rest of the catalytic cycle, i.e. the energies associated with the other steps are not solvent-dependent.

Furthermore, other forms of the catalyst can be formed (as 1' and 4'), since they are kinetically facile, but they are less stable thermodynamically than 1, thus the formation of the product 8 is always favored. Nonetheless, those equilibria are considered as a possible drawback of the reaction because they may reduce the quantity of available catalyst, and force the increase of the catalyst loading.

On the other hand, to show the importance of the nature of the amine reagent, we added a substituent in para position to the aryl group of the amine, with consequent changes in the energy barrier of the formation of 7 and 8. Actually, when the substituent is a fluoride, the energy barrier increases with respect to the amine without substituents, and it is similar when the substituent is a methoxide group. However, the step 5+6 → 7 is kinetically easier to overcome with the latter electron donor methoxy substituent. For this reason, yields are higher when there is a methoxide in para position of the aryl group of the amine, based on the higher nucleophilicity.

### COMPUTATIONAL DETAILS

DFT static calculations were performed with the Gaussian09 set of programs, using the BP86 functional of Becke and Perdew, together with the Grimme D3BJ correction term to the electronic energy. The electronic configuration of the molecular systems was described with the double-ζ basis set with polarization of Ahlrichs for main-group atoms (SVP keyword in Gaussian). The geometry optimizations were performed without symmetry constraints, and analytical frequency calculations performed the characterization of the located stationary points. These frequencies were used to calculate unscaled zero-point energies (ZPEs) as well as thermal corrections and entropy effects at 298 K. Energies were obtained by single-point calculations on the optimized geometries with the Mo6 functional and the cc-pVTZ basis set, and estimating solvent effects with the universal solvation model SMD of Cramer and Truhlar, using benzene as solvent. The reported free energies in this work include energies obtained at the Mo6/cc-pVTZ-sdd level of theory corrected with zero-point energies, thermal corrections and entropy effects evaluated at 153°C, achieved at the BP86-D3BJ/SVP-sdd level. Further, the approach of Martin et al was used to exclude the potential overestimation of the entropy contribution (further details in the Supporting Information).

Frontier molecular orbitals (HOMO and LUMO) have been used in the framework of conceptual DFT, thanks to the Koopmans approximation, such as chemical harness and electrophilicity, which describe the stability of the system and the affinity to interact with a nucleophile. Electrophilicity is calculated by Eq. 1, using the chemical potential (Eq. 2) and the chemical hardness values (Eq. 3).

$$\omega = \frac{\mu^2}{2\eta}$$

$$\mu = \frac{1}{2}(\epsilon_L + \epsilon_H)$$

$$\eta = \frac{1}{2}(\epsilon_L - \epsilon_H)$$

In addition, the changes in local aromaticity have been quantified using two probes of local aromaticity, based on the structure and the magnetic properties, respectively. As a measure for the aromaticity structure, the harmonic oscillator model of the aromaticity index (HOMA), defined by Kruzewski and Krygowski in Eq. 4,

$$\text{HOMA} = 1 - \frac{\sum_{i=1}^{n} (R_{opt} - R_i)^2}{R_{opt}^2}$$

where \(n\) is the number of bonds considered, and \(\alpha\) is an empirical constant (for C-C bonds \(\alpha = 257.7\)) fixed to give \(\text{HOMA} = 0\) for a model non-aromatic system, and \(\text{HOMA} = 1\) for a system with all bonds equal to an optimal value \(R_{opt}\), which is 1.388 Å for C-C bonds, assumed to be achieved for fully aromatic systems. \(R\) stands for a running bond length. As a magnetic aromaticity index, NICS (nucleus-independent chemical shift) calculations have been undertaken, using the GIAO (Gauge-including atomic orbital method) model, calculated at the level BP86-D3BJ/6-31+G(d,p)//BP86-D3BJ/SVP.
ASSOCIATED CONTENT

Supporting Information

XYZ coordinates, with the energies in a .xyz file of all computed species, and a file with the benchmark with the tested computational methods. This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

J.A.L.U. thanks Universitat de Girona for a IFUdG2017 PhD fellowship. M.G. thanks Generalitat de Catalunya for a IFUdG2017 PhD fellowship. A.P. thanks the European Research Council (ERC AdG 692775). D. M. holds the Israel Science Foundation. D.M. thanks the European Research Council (project number 2017SGR39, Xarxa de Referència en Química Teòrica i Computacional). D.M. thanks the European Research Council (ERC AdG 692775). D. M. holds the Israel Matz Professorial Chair. We thank referees for helpful comments.

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