COMMUNICATION

A Predictive Journey Towards *trans*-Thioamides/Amides

Michele Tomasini,[a,b] Jin Zhang,[c] Hui Zhao,[c] Emili Besalú,[a] Laura Falivene,[b] Lucia Caporaso,[b] Michal Szostak *[d] and Albert Poater *[a]

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

The *cis-trans* isomerization of (thio)amides was studied by DFT calculations to get the model for the higher preference for the *cis* conformation by guided predictive analyses, suggesting how to select the alkyl/aryl substituents on the C/N atoms that lead to the *trans* isomer. Multilinear analyses, together with cross-validation analyses, helped to select the best fitting parameters to achieve the energy barriers of the *cis* to *trans* interconversion, as well as the relative stability between both isomers. Double experimental check led to the synthesis of the best *trans* candidate with sterically demanding *t*-butyl substituents, confirming the utility of predictive chemistry, bridging organic and computational chemistry.

Considering the rich scope of applications of amides, in particular in medicinal chemistry and biochemistry, their synthesis has been one of the gold rushes of the last decades. The isolation of *cis* and *trans* conformations of the amide bond has become an utmost target. In addition, the continuing interest to switch from amides to thioamides is even higher,[1] as sulphur is largely present in drugs.[2] Even though for acyclic amides the *trans* conformation predominates around the N–C(O) bond,[3] the picture changes radically with *N*-methylbenzanilides. Thus, in the nineties Itai and coworkers demonstrated the *cis*-preference of the amide bond in *N*-methylbenzanilides.[4] Nevertheless, still retaining substantial double bond character of the amide bond through $n_N \rightarrow \pi^*_{C=O}$ conjugation,[5,6] this class of *N*-alkylated amides may undergo a conformational switch arising from avoidance of unfavourable steric interactions.[7] This led to switch from *trans* to *cis* conformation by changing the substituents next to the amide.[8] Among the possibilities of this *cis-trans* equilibrium, oxygen was also exchanged by sulphur, thus paving the way for thioamides, hence to amide bond isoesters.[9] On one hand, structurally, the radius of sulphur is 0.45 Å longer, and this length increase is identical to the C-S bond elongation. On the other, electronically, the electronegativity of sulphur (2.58) is much lower than of oxygen (3.44),[10] but interestingly this leads to a major stabilization of proteins/natural products owing to a thioamide functional group[11] by a stronger $n \rightarrow \pi^*$ interaction.[12]

The recent work by Szostak and coworkers on the increased contribution of *cis* thioamides in *N*-thioacyl-*N*-methylanilines with respect to homologous oxygen in amide structures emphasized the challenge of achieving *trans* isomer even more, and highlighted the point of conformational change in amides,[13] even more challenging in thioamides. In the current work, we study with Density Functional Theory (DFT) calculations the mechanism of the *cis-trans* isomerization of thioamides or amides (see Figure 1). The study establishes the origin of the higher preference for the *cis* conformation, and expands to lead to *trans* amides/thioamides.[13,14]

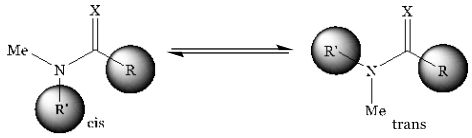

Figure 1. *Cis-trans* equilibrium of N-methylbenzanilides.

Machine learning has a long history of applications in computational chemistry,[15,16] used for the prediction of various chemical and biological properties. However, currently this approach still is in an exciting state of transition, where the integration of machine learning and big data science tools may revolutionize the discipline.[17] ~~The minimization of the error relative to reference data allows machine learning algorithms to deliver predictive models, mapping a set of descriptors into one or more properties of interest.~~ One aim is the generation of models that ~~can handle robustly sets of data that can be very large and complex and, once compiled, they a~~llow to make accurate predictions in a fraction of a second.[18,]~~The fast execution of machine learning predictions allows the exploration of the large chemical space with different approaches,[19] including the~~

[a] *Institut de Química Computacional i Catàlisi and Departament de Química, Universitat de Girona, C/ Maria Aurèlia Capmany 69, 17003 Girona, Catalonia, Spain.*
[b] *Dipartimento di Chimica e Biologia, Università di Salerno, Via Ponte don Melillo, 84084, Fisciano, Italy.*
[c] *College of Chemistry and Chemical Engineering, Key Laboratory of Chemical Additives for China National Light Industry, Shaanxi University of Science and Technology, 6 Xuefu Road, Xi'an 710021, China.*
[d] *Department of Chemistry, Rutgers University, 73 Warren Street, Newark, NJ 07102, United States.*

Electronic Supplementary Information (ESI) available: Computational details and all XYZ coordinates, absolute energies of all computed species. See DOI: 10.1039/x0xx00000x

~~multi-objective optimization,[20] and inverse design.[21]~~ However, how to link machine learning to *trans* amides? The use of predictive chemistry becomes a golden nugget.[19] Thus, in the strong preference of the *cis* conformation in thioamides/amides in *N*-thioacyl-*N*-methylanilines, the equilibrium must reach steric and/or electronic point where it is inverted. Predictive chemistry can overcome this hurdle from which there is the turning point by means of DFT calculations that can be experimentally tested in the most accentuated systems with *trans* preference. The proposed solution of predictive chemistry is a strategy towards machine learning,[20] and it leads to precise results. In addition, predictive chemistry and by extension predictive catalysis may seem like substitutes for machine learning, but it has a great comparative advantage since this approach compensates for the lack of the indispensable database that artificial intelligence needs. A small demand for limited calculations, that is, it is a question of making a minimal database from the great reliability that it has already achieved today through the DFT.

The sets of data **1**-**6** for thioamides and **7**-**12** for amides were recalculated with other combinations,[14] up to 46, using *t*-Bu to increase the steric hindrance, and electron-withdrawing groups like NO_2 and fluorinated ligands, as well as electron-donating groups like methoxy and NR_2 (R = H, Me, Ph). Table 1 collects the relative stability of the *trans* isomer and the energy barrier to get it from the *cis* isomer. The increase of steric hindrance of complexes **17** and **22,** by exchanging Ph by *t*-Bu group leads to the desired major stability for the *trans* isomer by 6.2 kcal/mol for the thioamide and 8.3 kcal/mol for the amide. On the other hand, the electronic point of view was also tested, and only the electron-donating capacity of the methoxy ligand is able to favour the *trans* isomer by 0.4 kcal/mol for the amide, whereas still it is not favoured by 0.9 kcal/mol for the thioamide. Furthermore, when mixing steric and electronic factors at the same time as with inputs **24** and **28** with the *t*-Bu groups and the fluorinated *t*-Bu, it is clear that both factors are important since there is still a stable trend towards the preference for the *trans* isomer, but still not enough and the *cis* isomer remains slightly more stable because of the electron-withdrawing character of the fluorine atoms compensating, and thus destabilizing the *trans* isomer. After the thermodynamics, comments are in order for the kinetics. Despite the existence of differences, the experimental temperature, 110ºC allows for any isomerization process, and thus thermodynamics is fundamental. It can be pointed out that the increase of steric hindrance between both R substituents, and the increase of the electron-withdrawing character of R increases the energy barrier.

Going to the detailed analysis of the steric effect of the two substituents, R and R', we proceeded to make an analysis using the steric index $\%V_{Bur}$ developed by Cavallo and collaborators.[21] Table S1 lists these values, as well as Table S2 with dihedral C-N-C-C angle (C-N-C-O for methoxy or C-N-C-N for NO_2 and NR_2 substituents). The analysis of the $\%V_{Bur}$ values allows to get a trend where the higher the steric hindrance in the plane that crosses the C-N bond in the *cis* isomer, the lower the energy barrier. Steric maps in Figure 2 allow to explain the instability of the *cis* isomer in **22**, to be compared with the null collision between R and R' substituents in **12**.[22] However, the agreement with respect to the energy barrier of the transition state is $R^2 = 0.349$. This leads to conclude that the steric effects that collide when going from *trans* to the *cis* conformation alone are not enough to explain such an isomerization.

Table 1. Relative Gibbs energies of (thio)amides with respect to the cis isomer (energies in kcal/mol; a = methyl on N is substituted by ethyl, in green the favourable trans structures).

		Thioamides			Amides		
R	R'	Entry	ΔG‡	$\Delta G_{cis\text{-}trans}$	Entry	ΔG‡	$\Delta G_{cis\text{-}trans}$
Ph	Ph	**1**	14.7	1.8	**7**	12.1	2.6
$C(Me)=CH_2$	Ph	**2**	13.8	1.7	**8**	11.4	2.3
cyclopropyl	Ph	**3**	17.7	3.7	**9**	15.3	3.8
iPr	Ph	**4**	19.9	3.9	**10**	15.2	2.1
t-Bu	Ph	**5**	11.5	1.5	**11**	10.3	0.7
Me	Ph	**6**	19.7	3.0	**12**	17.4	4.7
H	Ph	**13**	23.9	1.5	**18**	17.0	0.3
NO_2	Ph	**14**	20.4	1.2	**19**	17.6	0.5
NMe_2	Ph	**15**	4.2	3.2	**20**	4.0	2.7
OMe	Ph	**16**	14.9	0.9	**21**	11.0	**-0.4**
t-Bu	*t*-Bu	**17**	0.7	**-6.2**	**22**	0.8	**-8.3**
CF_3	Ph	**23**	18.0	0.7	**27**	18.8	2.7
$C(CF_3)_3$	Ph	**24**	6.6	0.4	**28**	10.7	0.7
NPh_2	Ph	**25**	8.4	2.7	**29**	8.2	3.4
NH_2	Ph	**26**	13.3	3.3	**30**	10.0	3.4
t-Bu	1-adamantyl	**31**	0.7	**-5.5**	**35**	0.1	**-8.1**
t-Bu	2-adamantyl	**32**	9.0	**-2.8**	**36**	8.3	**-3.1**
iPr	1-adamantyl	**33**	12.2	5.2	**37**	11.6	1.5
iPr	2-adamantyl	**34**	17.4	4.8	**38**	16.0	1.7
t-Bu	1-adamantyl	**39**[a]	2.7	0.1	**43**[a]	0.8	**-5.4**
t-Bu	2-adamantyl	**40**[a]	9.8	**-1.1**	**44**[a]	9.6	3.1
iPr	1-adamantyl	**41**[a]	14.5	4.2	**45**[a]	13.8	1.4
iPr	2-adamantyl	**42**[a]	20.6	**-0.6**	**46**[a]	17.1	0.2

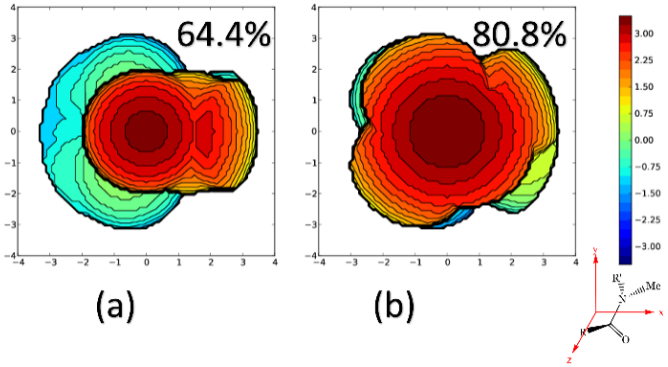

Figure 2. Topographic steric maps (plane xy) and $\%V_{Bur}$ of the *cis*-amide structure in *N*-thioacyl-*N*-methylanilines that lead to the aldehyde/ketone to generate (a) **12** and (b) **22**; with a radius of 3.5 Å. $\%V_{Bur}$ is the percent of buried volume. The midpoint between the two substituents (R and R'), R and R' at the Z axis, whereas the midpoint of the C-N bond defines the xz plane (with a radius of 3.5 Å, the isocontour curves of the steric maps are given in Å).

Apart from reaching the perfect (thio)amide in *trans* conformation, also in the opposite direction this study allows us to achieve with clear certainty how to have only the *cis* isomer. The premises oblige us to avoid the collision of two bulky groups, such as *t*-Bu and adamantyl derived logically, sterically, but less intuitively, using phenyl as a reference R' substituent on the N, electron-donating R groups must be avoided, because they help not only the thermodynamics of the trans conformation, but also drastically

lower the cis to trans interconversion barrier. In quantitative detail, to put the data in order, a series of failed correlations could first be outlined, with no clear linear correlation between the kinetics and thermodynamics (R^2 = 0.373). Interestingly, structurally the correlation between the energy barrier for the *cis*→*trans* step with the C-N bond distance in the *cis* conformation is high (0.723), with the $\%\tau_{cis}$ component of the Winkler analysis,[23] decreasing up to 0.551, while electronically the NBO charge on the nitrogen of the *cis* isomer goes up to a R^2 value of 0.701. Then, we applied a systematic statistics study to refer to several variables, but also to a broader range of variables, while searching for right correlations from linear regressions and multilinear analysis.[24] The best combination was found with 6 variables with a coefficient agreement of 0.906 with the energy barrier, and slightly worse, 0.843, for the thermodynamics equilibrium *cis-trans*. The latter is more interesting since the thermodynamics computationally can be more rapidly checked than kinetics. In addition, since some of the variables are strictly not independent of each other, the best multilinear regression agreement with statistical significance of all variables was achieved for the energy barrier with the bond length for the *cis* conformation ($d(C\text{-}N)_{cis}$), $\%\tau_{cis}$ and $\%\chi C_{cis}$ from the dihedral angle analysis, $\%V_{Bur}$, and the NBO charge on selected atoms. In Figure 3, we plot the best results employing 4 significative variables, and in Eqs. 1-3 we present the corresponding formula and associated errors for 2, 3 and 4 variables, respectively:

$$\Delta G^{\ddagger} = -0.183776 \cdot \%\tau_{cis} + 103.136 \cdot q(N)_{trans} + 67.3267, \text{ with } R^2 = 0.834 \quad (1)$$

$$\Delta G^{\ddagger} = -284.477 \cdot d(C\text{-}N)_{cis} - 27.8078 \cdot q(S)_{cis} - 17.3217\, q(C)_{trans} + 397.715, \text{ with } R^2 = 0.864 \quad (2)$$

$$\Delta G^{\ddagger} = -0.236961 \cdot \%\chi C_{cis} - 254.332 \cdot d(C\text{-}N)_{cis} - 27.7536 \cdot q(S)_{trans} - 17.5024 \cdot q(C)_{trans} + 357.741, \text{ with } R^2 = 0.887 \quad (3)$$

We point out that the selected equations were not obtained by combining the independent variables in order to reach a maximum fitting R^2 value, but by searching for the maximal leave-one-out cross-validation coefficient (R^2_{cv} values equal to 0.805, 0.830 and 0.849, respectively). This cross-validation procedure predicts the $\Delta G^{\ddagger}$ value for each molecule at a time from an equation fitted with the data of the remaining molecules. Once a set of variables is selected, in Figure 3 the global fitting equation is found.

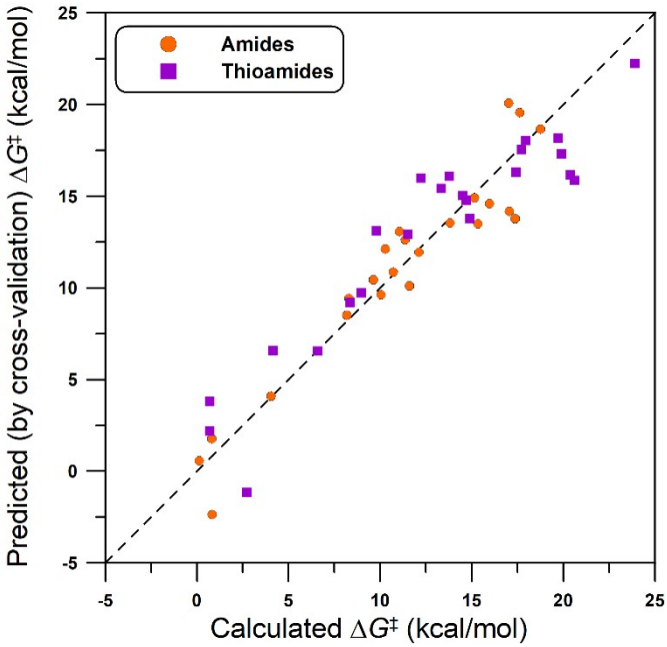

Figure 3. Computed theoretical Gibbs energies ($\Delta G^{\ddagger}$) in kcal/mol in front of the modeled ones according to the multilinear adjustment with 4 variables ($\%c_{cis}$; $d(C\text{-}N)_{cis}$; $q(S)_{trans}$; $q(C)_{trans}$).

Experimentally, next the synthesis and characterization by x-ray crystallography was attempted for the best candidate, *trans*-amide **22**, and after many attempts succeeded by slow evaporation from CH_2Cl_2/hexane at -18 °C as shown in Figure 4. The amide features the predicted trans geometry with the Winkler-Dunitz distortion parameters of t = 7.8°, cN = 14.0° and cC = 1.7°. The additive Winkler-Dunitz distortion parameter $\Sigma(\tau+\chi N)$ = 21.8°,[25] indicating that steric repulsion between *t*-Bu/C=O and *t*-Bu/Me substituents does not significantly affect amide bond twist and pyramidalization, thus representing a good model for isomerization with a substantial nN→π*C=O conjugation within the amide bond.

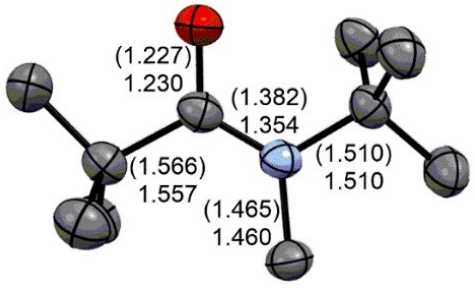

Figure 4. X-ray structure (CCDC 2166745) of the *trans* predicted amide **4** including relevant bond lengths in Å (computed values between parentheses).

In conclusion, the *cis-trans* isomerization of amide/thioamides bond has been studied through computational methodologies. Steric and electronic effects were tested and they play a key role in determining *cis-trans* preference. Beyond doubt, the steric element predominates when two large groups collide in *cis* conformation. Although it may seem utopia to arrive at an experimentally validated structure from computational

prediction, here the predictive chemistry worked well, and the best predicted *trans* amide structure was confirmed with a *trans* conformation in the experimental study. Maybe it is a golden nugget, but it is certainly a step forward on the road to machine learning in amide bond conformational analysis. It should be noted that DFT calculations are not randomized, but use human intelligence on the existing experimental results to create a correlation between different parameters. A posteriori, simple experiments completely validate this prediction. The increase of steric hindrance (R=*t*-Bu, R'=*t*-Bu) leads to the desired major stability for the *trans* isomer. The electronic effects were also tested and only the electro-donating capacity of the methoxy ligand (R=OMe, R'=Ph) is able to favour the *trans* isomer in the amide, whereas still not favour in the thioamide counterpart. Mixing steric and electronic factors at the same time ($R=C(CF_3)_3$ and R' = Ph) shows that both effects are important. The *cis* conformer remains only slightly more stable because of the electron-withdrawing character of substituents including fluorine atoms that destabilize the *trans* isomer.

Acknowledgments: A.P. is a Serra Húnter and thanks the Ministerio de Economía y Competitividad (MINECO) of Spain (Grant PID2021-127423NB-I00) and ICREA Academia prize 2019. M.S. thanks Rutgers University and the NSF (CHE-1650766).

References

[1] B. Khatri, P. Majumder, J. Nagesh, A. Penmatsa and J. Chatterjee, *Chem. Sci.*, 2020, **11**, 9480−9487; H. Verma, B. Khatri, S. Chakraborti and J. Chatterjee, *Chem. Sci.*, 2018, **9**, 2443−2451; M. Saito, S. Murakami, T. Nanjo, Y. Kobayashi and Y. Takemoto, *J. Am. Chem. Soc.*, 2020, **142**, 8130−8135; S. Fukagawa, Y. Kato, R. Tanaka, M. Kojima, T. Yoshino and S. Matsunaga, *Angew. Chem., Int. Ed.*, 2019, **58**, 1153−1157; J. Zhang, H. Zhao, G. Li, X. Zhu, L. Shang, Y. He, X. Liu, Y. Ma and M. Szostak, *Org. Biomol. Chem.*, 2022, DOI:10.1039/D2OB00412G

[2] B. R. Beno, K. S. Yeung, M. D. Bartberger, L. D. Pennington and N. A. Meanwell, *J. Med. Chem.*, 2015, **58**, 4383−4438; K. A. Scott and J. T. Njardarson, *Top Curr. Chem.*, 2019, **376**, 1−34.

[3] L. Pauling, The Nature of the Chemical Bond; Oxford University Press: London, 1940.

[4] A. Itai, Y. Toriumi, S. Saito, H. Kagechika and K. Shudo, *J. Am. Chem. Soc.*, 1992, **114**, 10649−10650.

[5] C. R. Kemnitz and M. J. Loewen, *J. Am. Chem. Soc.* 2007, **129**, 2521−2528; J. I. Mujika, J. M. Mercero and X. López, *J. Am. Chem. Soc.*, 2005, **127**, 4445−4453; S. A. Glover and A. A. Rosser, *J. Org. Chem.*, 2012, **77**, 5492−5502; J. Morgan, A. Greenberg and J. F. Liebman, *Struct. Chem.*, 2012, **23**, 197−199; J. P. Morgan, H. M. Weaver-Guevara, R. W. Fitzgerald, A. Dunlap-Smith and A. Greenberg, *Struct. Chem.*, 2017, **28**, 327−331; H. E. Elashal and M. Raj, *Chem. Commun.*, 2016, **52**, 6304−6307; H. E. Elashal, R. D. Cohen, H. E. Elashal and M. Raj, *Org. Lett.*, 2018, **20**, 2374−2377; S. Mahesh, K. C. Tang and M. Raj, *Molecules*, 2018, **23**, 2615.

[6] T. Nanda, P. Biswal, B. V. Pati, S. K. Banjare and P. C. Ravikumar, *J. Org. Chem.*, 2021, **86**, 2682–2695.

[7] W. J. Wedemeyer, E. Welker and H. A. Scheraga, *Biochemistry*, 2002, **41**, 14637–14644; C. Dugave and L. Demange, *Chem. Rev.*, 2003, **103**, 2475–2532; K. Nguyen, M. Iskandar and D. L. Rabenstein, *J. Phys. Chem. B*, 2010, **114**, 3387–3392; K. Tani and B. M. Stoltz, *Nature*, 2006, **441**, 731–734; I. V. Komarov, S. Yanik, A. Y. Ishchenko, J. E. Davies, J. M. Goodman and A. J. Kirby, *J. Am. Chem. Soc.*, 2015, **137,** 926–930; Y. Otani, X. Liu, H. Ohno, S. Wang, L. Zhai, A. Su, M. Kawahata, K. Yamaguchi and T. Ohwada, *Nat. Commun.*, 2019, **10**, 461; H. Takezawa, T. Shitozawa and M. Fujita, *Nat. Chem.*, 2020, **12**, 574–578.

[8] R. Yamasaki, A. Tanatani, I. Azumaya, S. Saito, K. Yamaguchi and H. Kagechika, *Org. Lett.*, 2003, **5**, 1265–1267; P. C. Knipe, S. Thompson and A. D. Hamilton, *Chem. Sci.*, 2015, **6**, 1630−1639.

[9] N. Mahanta, D. M. Szantai-Kis, E. J. Petersson and D. A. Mitchell, *ACS Chem. Biol.*, 2019, **14**, 142–163.

[10] A. Choudhary and R. T. Raines, *ChemBioChem*, 2011, **12**, 1801–1807.

[11] L. Kjaerulff, A. Sikandar, N. Zaburannyi, S. Adam, J. Herrmann, J. Koehnke and R. Müller, *ACS Chem. Biol.*, 2017, **12**, 2837–2841.

[12] R. W. Newberry, B. Van Veller, I. A. Guzei and R. T. Raines, *J. Am. Chem. Soc.*, 2013, **135**, 7843–7846.

[13] G. Meng, S. Shi, R. Lalancette, R. Szostak and M. Szostak, *J. Am. Chem. Soc.*, 2018, **140**, 727–734; R. Szostak and M. Szostak, *Org. Lett.*, 2018, **20**, 1342–1345; C. Liu, G. Li, S. Shi, G. Meng, R. Lalancette, R. Szostak and M. Szostak, *ACS Catal.*, 2018, **8**, 9131–9139; C. Liu, S. Shi, Y. Liu, R. Liu, R. Lalancette, R. Szostak and M. Szostak, *Org. Lett.*, 2018, **20**, 7771–7774.

[14] J. Zhang, Z. Liu, Z. Yin, X. Yang, Y. Ma, R. Szostak and M. Szostak, *Org. Lett*., 2020, **22**, 9500–9505.

[15] A. Tkatchenko, *Nat. Commun.*, 2020, **11**, 4125.

[16] K. T. Butler, D. W. Davies, H. Cartwright, O. Isayev and A. Walsh, *Nature*, 2018, **559**, 547–555.

[17] D. Balcells and B. B. Skjelstad, *J. Chem. Inf. Model.*, 2020, **60**, 6135–6146; M. Anand, B. Rohr, M. J. Statt and J. K. Nørskov, *J. Phys. Chem. Lett.*, 2020, **11**, 8518–8526.

[18] R. Gómez-Bombarelli, J. N. Wei, D. Duvenaud, J. M. Hernández-Lobato, B. Sánchez-Lengeling, D. Sheberla, J. Aguilera-Iparraguirre, T. D. Hirzel, R. P. Adams and A. Aspuru-Guzik, *ACS Cent. Sci.*, 2018, **4**, 268–276.

~~[19] J.-L. Reymond, *Acc. Chem. Res.*, 2015, **48**, 722−730.~~

~~[20] J. P. Janet, S. Ramesh, C. Duan and H. J. Kulik, *ACS Cent. Sci.*, 2020, **6**, 513−524.~~

~~[21] B. Sanchez-Lengeling and A. Aspuru-Guzik, *Science*, 2018, **361**, 360−365; J. G. Freeze, H. R. Kelly and V. S. Batista, *Chem. Rev.*, 2019, **119**, 6595−6612.~~

~~[19][22] V. D'Elia, H. Dong, A. Rossini, C. Widdifield, S. V. C. Vummaleti, Y. Minenkov, A. Poater, E. Abou-Hamad, J. D. A. Pelletier, L. Cavallo, L. Emsley and J. M. Basset, *J. Am. Chem. Soc.*, 2015, **137**, 7728-7739~~ M. Mehdizadeh, S. Sadjadi, A. Poater, A. Mansouri and N. Bahri-Laleh, ~~Molecular modelling aided catalyst design for PAO oils hydrofinishing,~~ *J. Mol. Liq*., 2022, **352**, 118675; M. Tomasini, J. Duran, S. Simon, L. M. Azofra and A. Poater, *Mol. Catal.*, 2021, **510**, 111692; S. Sadjadi, F. Koohestani, G. Pareras, M. Nekoomanesh-Haghighi, N. Bahri-Laleh and A. Poater, *J. Mol. Liq.*, 2021, **331**, 115740; A. Vidal-López, S. Posada-Pérez, M. Solà, V. D' Elia and A. Poater, *Green Chem. Eng.*, 2022, **3**, 180–187; M. C. D'Alterio, È. Casals-Cruañas, N. V. Tzouras, G. Talarico, S. P. Nolan and A. Poater, *Eur. J.*, 2021, **27**, 13481-13493; M. Gimferrer, N. Joly, S. Escayola, E. Viñas, S. Gaillard, M. Solà, J.-L. Renaud, P. Salvador and A. Poater, *Organometallics*, 2022, **41**, 1204–1215; W. Natongchai, J. A. Luque-Urrutia, Ch. Phungpanya, M. Solà, V. D'Elia, A. Poater and H. Zipse, *Org. Chem. Front*., 2021, **8**, 613-627.

[20] P. Friederich, G. Dos Passos Gomes, R. De Bin, A. Aspuru-Guzik and D. Balcells, *Chem. Sci.*, 2020, **11**, 4584–4601.

[21] A. Poater, B. Cosenza, A. Correa, S. Giudice, F. Ragone, V. Scarano and L. Cavallo, *Eur. J. Inorg. Chem.*, 2009, **2009**, 1759–1766.
[22] L. Falivene, Z. Cao, A. Petta, L. Serra, A. Poater, R. Oliva, V. Scarano and L. Cavallo, *Nat. Chem.*, 2019, **11**, 872–879; L. Falivene, R. Credendino, A. Poater, A. Petta, L. Serra, R. Oliva, V. Scarano and L. Cavallo, *Organometallics*, 2016, **35**, 2286–2293.
[23] F. K. Winkler and J. D. Dunitz, *J. Mol. Biol.*, 1971, **59**, 169–182; M. Szostak, J. Aubé, *Chem. Rev.*, 2013, **113**, 5701–5765; R. Szostak, J. Aubé and M. Szostak, *Chem. Commun.*, 2015, **51**, 6395–6398.
[24] J. De Jesus Silva, M. A. B. Ferreira, A. Fedorov and M. S. Sigman, C. Copéret, *Chem. Sci.*, 2020, **11**, 6717–6723; J. J. Dotson, E. V. Anslyn and M. S. Sigman, *J. Am. Chem. Soc.*, 2021, **143**, 19187–19191.