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Unexpected triaxial preferences in some all-*syn* 1,3,5-trifluorocyclohexanes†

Cihang Yu,[a] Bruno A. Piscelli,[b] Nawaf Al Maharik,[c] David B. Cordes,[a] Alexandra M. Z. Slawin,[a] Rodrigo A. Cormanich *[b] and David O'Hagan *[a]

Theory and solution NMR indicate that all-*syn* 1,3,5-trifluorocyclohexane 5 adopts the expected tri-equatorial conformation, however in the solid state the more polar triaxial conformation is observed. This and the favoured conformations of substituted (Me, OMe, NH(CO)Me, NHBoc) derivatives of 5 are investigated to explore triaxial C–F preferences.

It is a fundamental feature of substituted cyclohexane rings that the lower energy conformer tends to have the maximum number of equatorial substituents[1] due to unfavourable steric clashes associated with 1,3 diaxial interactions. Here we consider all-*syn*-1,3,5-trifluorocyclohexanes where electrostatic repulsion between tri-axial fluorines is anticipated to further favour the tri-equatorial conformers. Previously we prepared all *syn*-1,2,3,4,5,6-hexafluorocyclohexane **1** and found it to be a particularly polar aliphatic with a molecular dipole moment of μ = 6.2 D, the largest recorded for an aliphatic.[2] The polarity in **1** arises almost exclusively from the net dipole of the co-aligned tri-axial C–F bonds. Ring interconversion generates an isoenergetic conformer. Removing fluorines from **1** leads to non-equivalent interconverting conformers and it was anticipated that the conformer with more equatorial fluorines will be favoured. Polar organic motifs can offer advantageous properties to materials[3] and therefore in order to maximise polarity in such systems, the challenge is to maintain tri-axial C–F bonds. We recently reported the synthesis and properties of all-*syn* 1,3,5-trifluoro-2,4,6-trialkyl cyclohexanes such as **2**, and showed that they favour tri-axial C–F bonds as steric interactions between the Me groups are higher in energy than repulsion between the fluorines.[4] These trialkyl systems have potential utility as the favoured conformers are also the most polar. For this study we wished to explore systems with less functionality and confined to unsubstituted all-*syn*-trifluorocyclohexane **5**, and mono substituted derivatives (R = Me **6**, OMe **7**, NHAc **9**, NHBoc **10**) to explore their tendencies, or not, to adopt triaxial fluorine conformations. At the outset we re-calculated[5] the conformational energy differences for all-*syn* pentafluoro- **3**, tetrafluoro- **4** and trifluoro- **5** cyclohexanes at the PBE0-D3/def2-TZVP//B3LYP-D3/def2-TZVP level of theory, sequentially removing a fluorine from the rings as illustrated in Fig. 1. The B3LYP-D3/def2-TZVP level was chosen for the optimisation and frequency calculations since it reproduces accurately the experimental X-ray geometries of the compounds studied herein (Fig. S1 in the ESI†) and the PBE0-D3/def2-TZVP was chosen

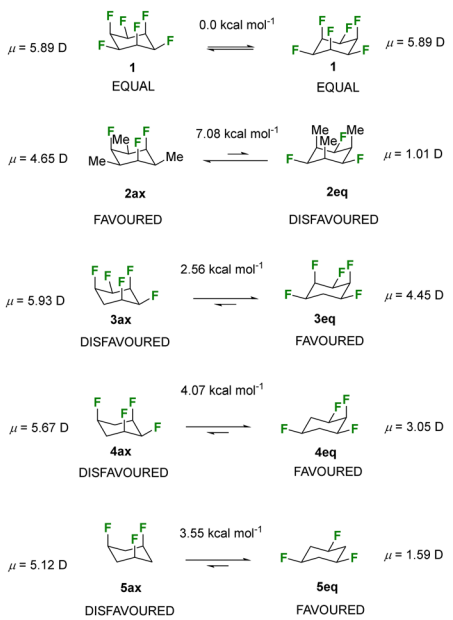

Fig. 1 Comparative properties for cyclohexanes **1–5** calculated at the PBE0-D3/def2-TZVP//B3LYP-D3/def2-TZVP level of theory.

[a] University of St Andrews, School of Chemistry, North Haugh, St Andrews, Fife, KY16 9ST, UK. E-mail: do1@st-andrews.ac.uk; Fax: +44 01334 463800; Tel: +44 01334 467171

[b] University of Campinas, Chemistry Institute, Monteiro Lobato Street, Campinas, Sao Paulo, 13083-862, Brazil. E-mail: cormanich@unicamp.br

[c] Department of Chemistry, Faculty of Science, An Najah National University, Nablus, Palestine

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for single point energy calculations because it showed the lowest mean absolute error (MAE) with respect to DLPNO-CCSD(T) for similar molecular systems.[4] The outcomes were similar to previous calculations[5] where the gas phase structures favour the tri-equatorial conformers in each case, and most significantly so in the case of all-*syn* 1,3,5-trifluorocyclohexane **5**, where the triaxial conformers $\mathbf{5_{ax}}$ is 3.55 kcal mol^{-1} higher in energy than $\mathbf{5_{eq}}$. Essentially in the gas phase the less polar conformers are favoured, however as we report here, the outcome can change in the condensed state and more polar conformers are often favoured.

Trifluoro cyclohexane **5** could be readily prepared by a direct aryl hydrogenation of 1,3,5-trifluorobenzene as previously described by the Glorius lab.[6] It is a solid (mp = 90 °C) and a suitable crystal of **5** proved amenable to X-ray diffraction analysis. The striking feature of the solid-state structure shown in Fig. 2a is the triaxial arrangement $\mathbf{5_{ax}}$ of the C–F bonds. This was unexpected given that the relative gas phase energies favour $\mathbf{5_{eq}}$ by 3.55 kcal mol^{-1} and that $\mathbf{5_{ax}}$ is a significantly more polar conformer ($\mathbf{5_{ax}}$ μ = 5.12 D *versus* μ = 1.59 D for $\mathbf{5_{eq}}$). In order to rationalise this observation, the energy gained in condensing three molecules of **5** together was calculated in the gas phase, when they adopt either the $\mathbf{5_{ax}}$ or the $\mathbf{5_{eq}}$ conformations. The outcome summarised in Fig. 2a is quite striking. If three triaxial $\mathbf{5_{ax}}$ conformers are stacked one on top of another,

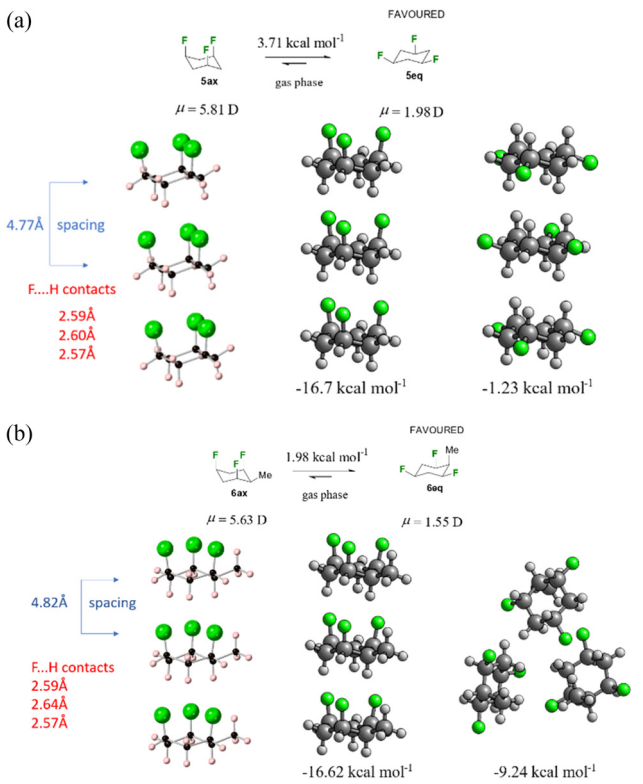

Fig. 2 Equilibrium energies, X-ray structures (left hand side images – showing three molecules) and computational analysis indicating the energy gained from condensation of tri-axial and tri-equatorial conformers of **5** and **6** in the gas phase. (a) The condensation energy is greater for $\mathbf{5_{ax}}$ than $\mathbf{5_{eq}}$ and in (b) is greater for $\mathbf{6_{ax}}$ than $\mathbf{6_{eq}}$.

approximating the arrangement in the X-ray structure, then the interaction energy gained is −16.7 kcal mol^{-1}. Calculations were conducted using the London Dispersion-corrected Hartree–Fock method (HFLD)[7] and the aug-cc-pVTZ basis set as implemented in ORCA 5.0.3[8] due to its high accuracy – between that of DLPNO-CCSD and DLPNO-CCSD(T) schemes – and fast basis set convergence. However, if three tri-equatorial $\mathbf{5_{eq}}$ conformers are similarly stacked, then the interaction energy is significantly lower at −1.23 kcal mol^{-1}. The stabilisation observed in condensing $\mathbf{5_{ax}}$ comes from the inherent polarity and consequent electrostatic attraction accorded by intermolecular packing, where the electronegative fluorine faces contact the electropositive hydrogen faces of adjacent rings. The tri-equatorial conformer $\mathbf{5_{eq}}$ is significantly less polar and the energy gained during condensation is far less significant (1.23 kcal mol^{-1} *versus* 16.7 kcal mol^{-1}).

^{1}H-NMR data in chloroform ($CDCl_3$) indicate a predominant tri-equatorial $\mathbf{5_{eq}}$ conformation in solution for **5**. There are no large $^3J_{HF}$ coupling constants indicative of *anti*-periplanar HC–CF relationships. *anti*-Periplanar HC–CF relationship will normally have $^3J_{HF}$ values in the range 20–35 Hz. The vicinal coupling constants are significantly smaller and measured at $^3J_{HF}$ =11.5 Hz and $^3J_{HF}$ = 4.5 Hz only, indicative of predominant *gauche* relationships in $\mathbf{5_{eq}}$.[9,10] It is interesting also to observe the change in the $^1J_{CF}$ coupling constants in the ^{13}C-NMR spectra of **5** in solvents of varying polarity. The axial and equatorial conformers are not resolved due to rapid ring interconversion, thus the $^1J_{CF}$ coupling constant is an average of the triaxial **5** and tri-equatorial **5** populations.

The value of $^1J_{CF}$ = 179.4 Hz in cyclohexane, the least polar solvent, reduces to $^1J_{CF}$ = 173.5 Hz in acetone, the most polar solvent, and can be rationalised in terms of the Perlin effect.[11] The Perlin effect describes the phenomenon that the $^1J_{CF}$ coupling constants in NMR for an axial C–F bond has a lesser value than that for an equatorial C–F bond. This has been attributed to hyperconjugation from *anti*-periplanar C–H bonds donating electron density to the σ^*_{CF} antibonding orbital and weakening (lengthening) the C–F bond, an effect that only occurs for axial C–F bonds. The observed reduction in the $^1J_{CF}$ coupling constant with increasing dielectric constants (e), progressing from cyclohexane, through toluene and chloroform to acetone as illustrated in Fig. 3 is consistent with more polar solvents increasingly accommodating the more polar $\mathbf{5_{ax}}$ conformer, and computational outcomes suggest a $\mathbf{5_{ax}}$ = $\mathbf{5_{eq}}$ population at parity in acetone, which is significantly the most polar solvent explored (ε = 20.7). Such solvent effects have been observed for *cis*-fluorinated piperidines where the more polar conformers are stabilised by more polar solvents.[12] A similar situation is found for the methyl substituted trifluorocyclohexane **6** also prepared by aryl hydrogenation as illustrated in Fig. 2b. In the gas phase $\mathbf{6_{eq}}$ is less polar and the lower energy conformer is favoured by 1.98 kcal mol^{-1}, however X-ray diffraction reveals that in the solid state $\mathbf{6_{ax}}$ is the only conformer. A similar analysis to that carried out for **5**, condensing three molecules of **6** in the gas phase and approximating the solid-state packing, resulted in significant intermolecular

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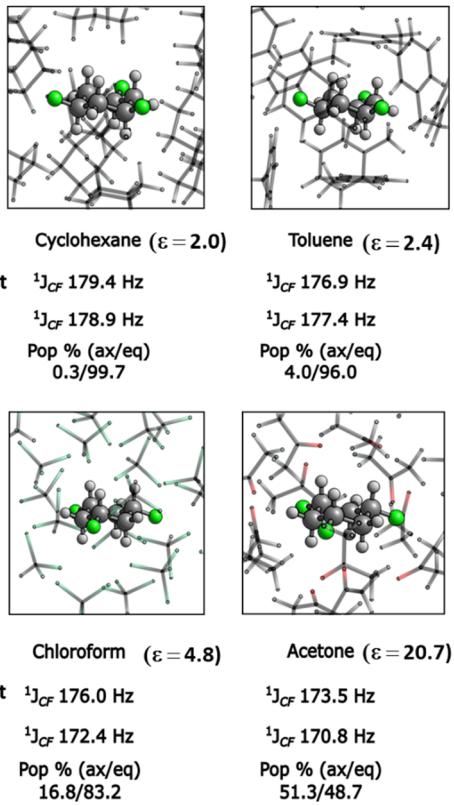

Fig. 3 Experiment and theory (M06L/pcJ-1//M06L/pc-1)[8] derived $^1J_{CF}$ NMR-coupling constants for **5** tend to lower values with increasing polarity (ε = dielectric constant) consistent with an increasing ratio of $\mathbf{5_{ax}}$ in solution.

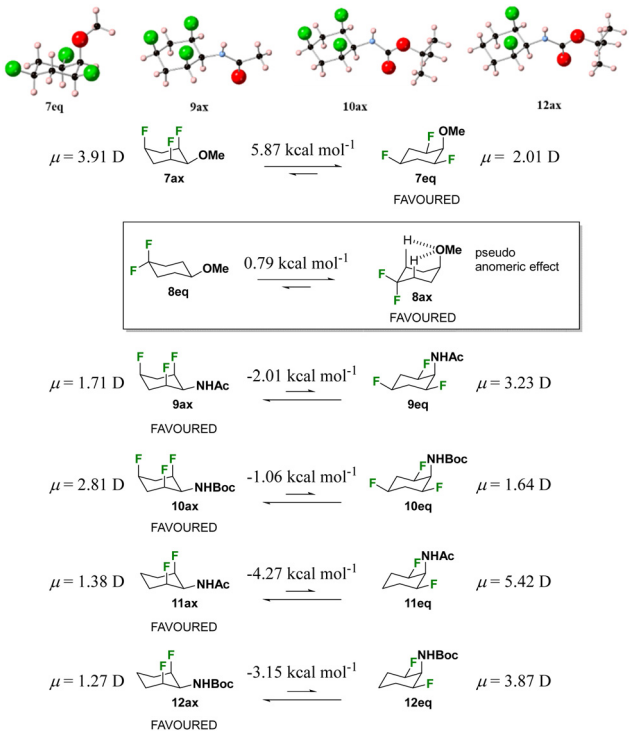

Fig. 4 X-Ray structures of $\mathbf{7_{eq}}$, $\mathbf{9_{ax}}$, $\mathbf{10_{ax}}$ and $\mathbf{12_{ax}}$ and equilibrium energies (PBE0-D3/def2-TZVP) of **7–12**. The favoured conformers are the same in the gas and solid state phases. The preference for **8** (inset) was previously reported.[15]

stabilisation after condensations of $\mathbf{6_{ax}}$ (−16.62 kcal mol^{-1}), and much less so after condensations of $\mathbf{6_{eq}}$ (−9.24 kcal mol^{-1}) (see Table S4, ESI†). Again, intermolecular interactions between the more polar conformers result in supramolecular stabilisation and this leads to the adoption of the triaxial conformer in the condensed phase. It was noted that stacking $\mathbf{6_{eq}}$ one molecule on top of another did not result in a local minimum, and direct geometry optimization always led to a less organized trimeric arrangement. This is probably a result of the steric influence of the axial methyl group, evidencing that neither intermolecular interaction energy nor spatial organization favours the crystalline assembly of $\mathbf{6_{eq}}$. Therefore, Grimme's iterative-static metadynamics (iMTD-sMTD) protocol implemented in CREST software[13] and GFN2-xTB method[14] was used to explore the conformational space of the $\mathbf{6_{eq}}$ trimer, and the global minimum was re-optimized in DFT and used for further calculations. The same procedure was carried out for $\mathbf{7_{ax}}$, $\mathbf{9_{ax}}$, $\mathbf{10_{ax}}$ and $\mathbf{12_{ax}}$ trimers, and in each case the global minimum was in good agreement with the experimental structures, evincing the reliability of the methodology (See ESI† for details).

When a methoxy group is placed *syn* at C-2 of 1,3,5-trifluorocyclohexane **5**, as in **7**, the all-equatorial conformer $\mathbf{7_{eq}}$ is favoured in the gas phase as might be expected. This compound was also prepared by aryl hydrogenation,[6] in this case from the tri-fluoroanisole precursor and an X-ray structure (Fig. 4) also revealed the tri-equatorial structure $\mathbf{7_{eq}}$ in the solid state, with the OMe group adopting an axial orientation. We have recently reported that unexpectedly, 4,4-difluoromethoxycyclohexane **8** prefers a conformation with the OMe axial, displaying a pseudo anomeric effect.[15] This was attributed in part to the accommodation of electrostatic non-conventional hydrogen bonds (NCHB) between the methoxy oxygen and 1,3 diaxial hydrogens in conformer $\mathbf{8_{ax}}$ (see inset Fig. 4). Such NCHB interactions may also influence the preferred conformation of $\mathbf{7_{eq}}$. Although this might have been anticipated, it is against the trend so far in this series, where the more polar conformers emerge in the solid-state structures. It should be noted however that the polarity difference, as measured by the molecular dipole moment, is not so large between $\mathbf{7_{ax}}$ (3.9 D) and $\mathbf{7_{eq}}$ (2.0 D).

Introduction of an amide (acetamide) and also a carbamate (NHBoc) substituent was also explored. Amide **9** and carbamate **10** were also prepared by aryl hydrogenation of their aromatic precursors.[6] In both cases solid state structures were determined by X-ray structure analysis, and the outcomes are illustrated in Fig. 4. The structures $\mathbf{9_{ax}}$ and $\mathbf{10_{ax}}$ respectively each have their C–F bonds triaxial and the amide/carbamate equatorial. Unlike tri-fluorocyclohexane **5**, the triaxial C–F conformers are unexpectedly found to be lower in energy and clearly the substituents are influencing the conformational preference in these molecules. This was not the case for –Me and –OMe in **6** and **7** respectively and clearly there are factors associated with

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the amide or carbamate groups in $\mathbf{9_{ax}}$ and $\mathbf{10_{ax}}$ over-riding electrostatic repulsion between the fluorines in the gas phase. This is consistent with the previously observed preference of an amide substituent to lie *gauche* to a vicinal fluorine.[16c] Probably the most celebrated stereoelectronic associated with fluorine recognises unexpectedly, that 1,2-difluoroethane **13** has a lower energy *gauche* over *anti* conformer by about ~0.8 kcal mol^{-1} in the gas phase (see Fig. S5, ESI†).[16] This contrasts with 1,2-dichloro-, 1,2-dibromo- and 1,2-iodo-ethanes which have lower energy *anti* conformers. The origin of the *gauche* effect is generally attributed to $\sigma_{CH} \rightarrow \sigma^*_{CF}$ donation between *anti*-periplanar σ_{C-H} orbitals and lower energy σ^*_{CF} antibonding orbitals, interactions not found in the *anti* conformer of **13**. There are also competing electrostatic explanations for the *gauche* effect.[17] Larger *gauche* preferences are found[18] when one fluorine in 1,2-difluoroethane is replaced by other substituents such as the amide in **14**. For **14** the preference has been reported[16c,18] to be 1.78 kcal mol^{-1}, twice that of the classical *gauche* effect and is attributed to several factors beyond hyperconjugation. For the lowest energy conformers in **14** the C–F and amide dipoles oppose each other, and there is an electrostatic attraction between the fluorine and the amide hydrogen, thus electrostatic factors reinforce the basic stereoelectronic origin of the *gauche* effect here. In order to explore this further, rotational energy profiles, rotating around the C–NAc $\mathbf{9_{ax}}$ or C–NBoc $\mathbf{10_{ax}}$ bonds, were conducted for each of the triaxial (and tri-equatorial see ESI†) conformers (see Fig. S4, ESI†). Both the *cis*-amide/carbamate (blue traces) and *trans*-amide/carbamate (black traces) geometries were explored, and in each case the *trans*-amides/carbamate gave the lowest energy conformer as expected. In both case there is a steep energy well of ~14–15 kcal mol^{-1} indicating a clearly preferred conformation. The lower energy conformers have the N–H bond aligned parallel to the three axial C–F bonds, and with the carbonyl group facing *anti* to the C–F bonds. This arrangement minimises the overall molecular dipole. It also introduces an electrostatic attraction between the proximal fluorines and the NH hydrogen, as previously discussed in the fluorine-amide *gauche* effect,[16c] thus the system benefits from a combination of stereoelectronic and electrostatic effects. The influence of removing the distal fluorine was explored for **11** and **12**, to reduce electrostatic repulsion between the axial fluorines (see Fig. 4). This significantly increased the equilibrium energy (−4.27 kcal mol^{-1}) in favour of $\mathbf{11_{ax}}$, relative to **9** (−2.01 kcal mol^{-1}) and also the equilibrium energy in favour of $\mathbf{12_{ax}}$ (−3.15 kcal mol^{-1}) compared to **10** (−1.06 kcal mol^{-1}). Interestingly, $\mathbf{9_{eq}}$ and $\mathbf{10_{eq}}$ have smaller molecular dipoles than $\mathbf{11_{eq}}$ and $\mathbf{12_{eq}}$, indicating that the distal C–F bond plays an important role in decreasing the overall polarity. Indeed, Natural Bond Orbital (NBO) analysis indicates that while hyperconjugative interactions rule the equilibria for **9** and **10**, electrostatics are more important for **11** and **12**. See ESI† for an expanded discussion.

This study demonstrates that the more polar triaxial conformer $\mathbf{5_{ax}}$ is adopted in the solid state, although $\mathbf{5_{eq}}$ is favoured in the gas phase and similarly for **6**. For methoxy derivative **7**, $\mathbf{7_{eq}}$ with OMe axial is strongly favoured (5.87 kcal mol^{-1}) in the gas phase and not overturned in the solid state. For amide and carbamate derivatives **9–12** the fluoro diaxial and triaxial conformers are actually lower in energy than their equatorial counterparts, consistent with the fluorine-amide *gauche* effect.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) O. Hassel and B. Ottar, *Acta Chem. Scand.*, 1947, **1**, 929; (*b*) D. H. R. Barton, *J. Chem. Soc.*, 1953, 1027.
2 N. S. Keddie, A. M. Z. Slawin, T. Lebl, D. Philp and D. O'Hagan, *Nat. Chem.*, 2015, **7**, 483.
3 (*a*) O. Shyshov, S. V. Haridas, L. Pesce, H. Qi, A. Gardin, D. Bochicchio, U. Kaiser, G. M. Pavan and M. von Delius, *Nat. Commun.*, 2021, **12**, 3134; (*b*) R. Mondal, M. Agbaria and Z. Nairoukh, *Chem. – Eur. J.*, 2021, 7193; (*c*) O. Shyshov, K. A. Siewerth and M. von Delius, *Chem. Commun.*, 2018, **54**, 4353; (*d*) P. Kirsch, *Modern fluoroorganic chemistry-Synthesis, reactivity and applications*, Wiley-VCH & Co, Weinheim, 2004.
4 T. J. Poskin, B. A. Piscelli, K. Yoshida, D. B. Cordes, A. M. Z. Slawin, R. A. Cormanich, S. Yamada and D. O'Hagan, *Chem. Commun.*, 2022, **58**, 7968.
5 Q. Luo, K. R. Randall and H. F. Schaefer, *RSC Adv.*, 2013, **3**, 6572.
6 (*a*) Z. Nairoukh, M. Wollenburg, C. Schlepphorst, K. Bergander and F. Glorius, *Nat. Chem.*, 2019, **11**, 264; (*b*) M. P. Wiesenfeldt, Z. Nairoukh, W. Li and F. Glorius, *Science*, 2017, **357**, 908.
7 A. Altun, F. Neese and G. Bistoni, *J. Chem. Theory Comput.*, 2019, **15**, 5894.
8 F. Neese, F. Wennmohs, U. Becker and C. Riplinger, *J. Chem. Phys.*, 2020, **152**, 224108.
9 (*a*) A. Lawer and L. Hunter, *Eur. J. Org. Chem.*, 2021, 1184; (*b*) Y. Lizarme-Salas, A. D. Ariawan, R. Ratnayake, H. Luesch, A. Finch and L. Hunter, *Beilstein J. Org. Chem.*, 2020, **16**, 2663; (*c*) L. Hunter, P. Kirsch, A. M. Z. Slawin and D. O'Hagan, *Angew. Chem.*, 2009, **48**, 5457.
10 M. Giovanetti, L. F. F. Bitencourt, R. A. Cormanich and S. P. A. Sauer, *J. Chem. Theory Comput.*, 2021, **17**, 7712.
11 (*a*) A. C. Tsipis, *New J. Chem.*, 2022, **46**, 13940; (*b*) J. M. Silla, M. P. Freitas, R. A. Cormanich and R. Rittner, *J. Org. Chem.*, 2014, **79**, 6384; (*c*) S. Wolfe, B. M. Pinto, V. Varma and R. Y. N. Leung, *Can. J. Chem.*, 1969, **68**, 1051.
12 Z. Nairoukh, F. Strieth-Kalthoff, K. Bergander and F. Glorius, *Chem. – Eur. J.*, 2020, **26**, 6141.
13 P. Pracht, F. Bohle and S. Grimme, *Phys. Chem. Chem. Phys.*, 2020, **22**, 7169.
14 C. Bannwarth, S. Ehlert and S. Grimme, *J. Chem. Theory Comput.*, 2019, **15**, 1652.
15 B. A. Piscelli, D. O'Hagan and R. A. Cormanich, *Phys. Chem. Chem. Phys.*, 2021, **23**, 5845.
16 (*a*) M. Aufiero and R. Gilmour, *Acc. Chem. Res.*, 2018, **51**, 1701; (*b*) C. Thiehoff, Y. P. Rey and R. Gilmour, *Isr. J. Chem.*, 2017, **57**, 92; (*c*) D. O'Hagan, C. Bilton, J. A. K. Howard, L. Knight and D. J. Tozer, *J. Chem. Soc., Perkin Trans. 2*, 2000, 605.
17 J. C. R. Thacker and P. L. A. Popelier, *J. Phys. Chem. A*, 2018, **122**, 1439.
18 (*a*) D. Y. Buissonneaud, T. van Mourik and D. O'Hagan, *Tetrahedron*, 2010, **66**, 2196; (*b*) N. E. J. Gooseman, D. O'Hagan, M. J. G. Peach, A. M. Z. Slawin, D. J. Tozer and R. J. Young, *Angew. Chem.*, 2007, **119**, 6008.

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