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# A qualitative failure of B3LYP for textbook organic reactions.<sup>†</sup>

Nicolas Chéron,<sup>a</sup> Denis Jacquemin,<sup>b</sup> and Paul Fleurat-Lessard<sup>\*a</sup>

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Depending on the selected DFT functional, two different mechanisms are found for two organic reactions (an intramolecular nucleophilic aromatic substitution and a nucleophilic addition on a carbonyl moiety). Indeed, B3LYP predicts a concerted mechanism whereas M06-2X foresees a multistep one. Calculations at the MP4(SDQ) level proved the mechanisms to be step-wise. We studied these reactions with a large panel of exchange-correlation functionals and demonstrated that the amount of exact exchange is of first importance. For some borderline cases, the form of the functional has also an impact, e.g. the Meisenheimer  $\sigma$ -adduct of the intramolecular nucleophilic aromatic substitution can be located with B3PW91 but not with B3LYP. These results stress the need to use recently proposed functionals to investigate chemical reactivity.

## 1 Introduction

Amongst all available computational methods, density functional theory (DFT) is probably the most popular in organic chemistry. All DFT approximations are concentrated in the so-called exchange-correlation functional (XCF), and a wide panel of XCFs are available. Selecting an adequate XCF for a given problem remains challenging despite the considerable benchmarking achievements of the last decade. Since the original  $X\alpha$ , several improvements of the XCF have been performed: the development of generalized gradient approximation (GGA) functionals in the late 80's, and more importantly the emergence of hybrid functionals that include a fraction of *exact* exchange (also called Hartree-Fock exchange, denoted by HFE) which have been originally introduced by Becke in 1993.<sup>1</sup> The most famous global hybrid (i.e. with an amount of HFE independent of the electronic separation) certainly remains B3LYP,<sup>2–6</sup> which has been widely used in different domains of chemistry. However, this functional has shown some significant failures, notably in non-linear optics<sup>7,8</sup> and in charge transfer systems,<sup>9</sup> but also in the evaluations of formation enthalpies,<sup>10,11</sup> bond dissociation enthalpies,<sup>12</sup> or reaction energies of hydrocarbons.<sup>13</sup> Moreover, surprising results have been observed in studying reactivity of electrocyclic<sup>14,15</sup>

as well as Diels-Alder reactions.<sup>16</sup> In the present contribution, we want to highlight an unexpected failure of B3LYP, which strengthens the need to use the most recent functionals for simulating organic reactions.

## 2 Computational details

All calculations have been done with the Gaussian09 software.<sup>17</sup> Unless otherwise mentioned, calculations are always done with the 6-31+G(d,p) atomic basis set in methanol for the Smiles rearrangement or in toluene for the Nef reaction. The solute-solvent interactions are described by the well-known polarizable continuum model (PCM) using integral equation formalism variant (IEFPCM) with UFF radii.<sup>18–20</sup> These PCM energies might be slightly tuned if other solvent effects models were used, such as the SMD approach of Cramer and Truhlar that is optimal for computing the solvation effects.<sup>21</sup> However, it is unlikely that using a different continuum model would significantly modify the relative responses of the different functionals.

Basis set influence is reported in Supporting Information. Unless otherwise mentioned, total electronic energies are reported. All structures were fully optimised and frequency calculations were performed to ensure the absence of any imaginary frequencies on local minima, and the presence of only one imaginary frequency on transition states (TS). Intrinsic Reaction Coordinate (IRC) calculations were carried out to ascertain that no reaction intermediate has been missed.

## 3 The Smiles rearrangement

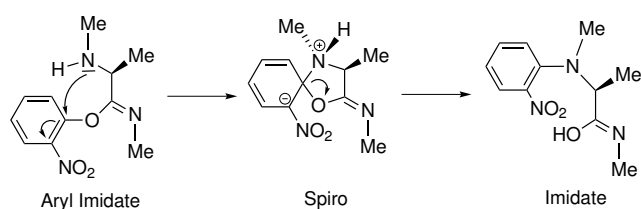
As part of the investigation of the complex Ugi reactions,<sup>22</sup> we recently described the mechanism of an intramolecular nucle-

<sup>†</sup> Electronic Supplementary Information (ESI) available: Basis set influence. Mechanism of the Ugi-Smiles reaction. Influence of the exact exchange in the spiro stabilisation. Cartesian coordinates and total energies of the structures optimised at the M06-2X and MP4(SDQ) levels. See DOI: 10.1039/b000000x/

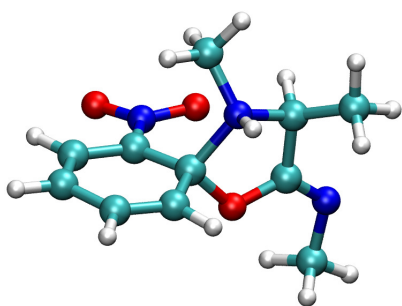
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ophilic aromatic substitution ( $S_NAr$ ) coined as the Smiles rearrangement.<sup>23,24</sup> This reaction involves the nitrogen attack of an aryl imidate onto the aromatic core and leads to a spiro[6,5] which is the Meisenheimer  $\sigma$ -complex<sup>25</sup> (see Figure 1, a full scheme of the reaction is available in ESI). This structure can then undergo a ring-opening and lead to another imidate which, after a final prototropy, gives the final product of the reaction (not shown here). Depending on the relative orientations of the  $NO_2$  and  $NH$  moieties, four spiro structures can be involved: two characterised by an intramolecular hydrogen bond, and two free of such interaction.<sup>24</sup> Here, we focus on the system depicted in Figure 2 that does not contain this interaction: in this case, the  $\sigma$ -adduct formation is more difficult to describe because the constrained 5-member ring is not stabilised by the hydrogen-bond.



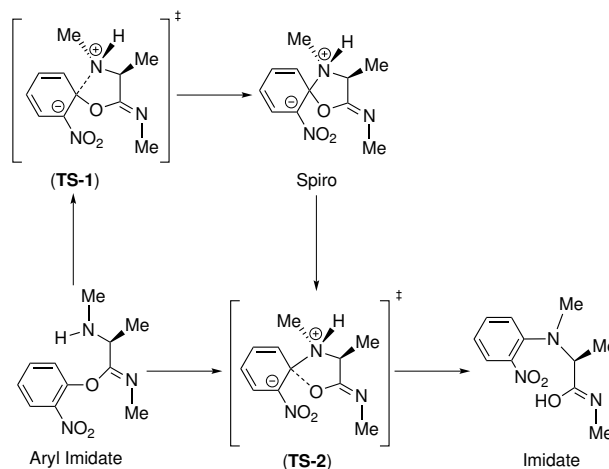
**Fig. 1** The Smiles rearrangement



**Fig. 2** Spiro structure considered in this study

Depending on the methodology, two different mechanisms are crystal-balled by DFT (cf Figure 3): in one case (for example with M06-2X), the spiro is a reaction intermediate (RI) which is the so-called Meisenheimer  $\sigma$ -complex, and therefore two TS are found. In the other case (for example with B3LYP), the spiro does not exist and only one TS is foreseen – which is similar to the second TS found in the multistep mechanism. In the present Article, we want to investigate this discrepancy and unravel the key parameters governing the topology predicted by DFT for this mechanism.

In order to have a reference energetic profile, free of adjusted parameters, we have modeled the rearrangement at both the MP2/6-31+G(d,p) and MP4(SDQ)/6-31+G(d,p) levels of



**Fig. 3** The two mechanisms which are crystal-balled by DFT calculations

calculations. In both cases, the spiro compound was a stable intermediate. Single point calculations at the CCSD(T)/6-31+G(d,p) level on the MP4(SDQ) geometries were performed as well, and these energies were selected to benchmark DFT approaches. We then studied the energy profile according to the XCF used (see Computational details). Results are gathered in Table 1.

Hartree-Fock (HF) calculations strongly overshoot the energies of the transition states, but the spiro intermediate can nevertheless be identified. When GGA functionals are selected, neither (TS-1) nor the spiro exist and a concerted mechanism is foreseen. This can be understood by considering the expected underestimation of the activation energies and the overestimation of the reaction energies with GGA.<sup>26,27</sup> Compared to post-HF calculations, the (TS-1) energy is lowered and the spiro energy increased: as the energy difference between these structures is tiny (best estimate:  $0.9 \text{ kcal.mol}^{-1}$ ), the (TS-1) energy becomes smaller than the spiro one with GGA, the latter losing its stationary features. Obviously *meta*-GGA functionals (TPSS and M06-L) cannot revise sufficiently this incorrect prediction.

Most global hybrid functionals predict a multistep mechanism, the spiro structure being a RI. This is consistent with the improved accuracy of hybrid functionals with activation barriers. Nevertheless, it should be pointed out that, with most global hybrid-GGA functionals, the relative energies of (TS-1) and spiro are very close (less than  $0.2 \text{ kcal.mol}^{-1}$  of difference for five of them): at finite temperature, the spiro would consequently be barely populated, and its presence in Table 1 has no physical signification. More important is the result obtained with TPSSh, O3LYP and B3LYP: neither the spiro nor the (TS-1) exist in these cases. B3LYP, which remains the most popular global hybrid XCF in computational organic

**Table 1** Existence of the spiro structure of the Smiles rearrangement according to the methodology. We also report the associated energy profile (in kcal.mol<sup>-1</sup>, with the 6-31+G(d,p) basis set in methanol) with respect to the aryl imidate energy. For RSH functionals, the attenuation parameter  $\mu$  is given in parenthesis after the HFE range. The last column shows the energy difference between **(TS-1)** and the spiro structure

|                   | % HFE ( $\mu$ )  | Spiro existence | (TS-1) | Spiro | (TS-2) | Prod. | (TS-1)–Spiro |
|-------------------|------------------|-----------------|--------|-------|--------|-------|--------------|
| CCSD(T)//MP4(SDQ) | –                | –               | 12.6   | 11.7  | 19.3   | -8.1  | 0.9          |
| HF                | –                | Yes             | 22.6   | 18.9  | 34.6   | -4.6  | 3.7          |
| BLYP              | 0                | No              |        |       | 15.6   | -4.1  |              |
| OLYP              | 0                | No              |        |       | 18.0   | -4.3  |              |
| BP86              | 0                | No              |        |       | 12.3   | -6.2  |              |
| PBE               | 0                | No              |        |       | 12.0   | -6.5  |              |
| PW91              | 0                | No              |        |       | 11.9   | -6.4  |              |
| TPSS              | 0                | No              |        |       | 13.3   | -4.7  |              |
| M06-L             | 0                | No              |        |       | 18.8   | -6.3  |              |
| TPSSh             | 10               | No              |        |       | 15.2   | -4.9  |              |
| O3LYP             | 11.61            | No              |        |       | 19.1   | -5.1  |              |
| $\tau$ HCTHhyb    | 15               | Yes             | 9.0    | 9.0   | 16.2   | -5.7  | 0.0          |
| B3LYP             | 20               | No              |        |       | 19.0   | -5.0  |              |
| B3P86             | 20               | Yes             | 8.4    | 8.0   | 16.1   | -6.6  | 0.4          |
| B3PW91            | 20               | Yes             | 9.4    | 9.2   | 17.1   | -6.1  | 0.2          |
| X3LYP             | 21.80            | Yes             | 11.8   | 11.8  | 18.9   | -5.2  | 0.0          |
| B98               | 21.98            | Yes             | 10.3   | 10.2  | 18.2   | -5.6  | 0.1          |
| B1LYP             | 25               | Yes             | 13.1   | 13.0  | 20.3   | -4.9  | 0.1          |
| PBE0              | 25               | Yes             | 8.5    | 7.7   | 16.7   | -6.8  | 0.8          |
| M06               | 27               | Yes             | 10.8   | 10.1  | 20.5   | -6.4  | 0.7          |
| BHandHLYP         | 50               | Yes             | 14.6   | 13.1  | 24.0   | -5.4  | 1.5          |
| M06-2X            | 54               | Yes             | 10.5   | 9.1   | 20.6   | -7.0  | 1.4          |
| LC-BLYP           | 0-100 (0.47)     | Yes             | 11.6   | 7.0   | 21.0   | -6.9  | 4.6          |
| LC- $\omega$ PBE  | 0-100 (0.47)     | Yes             | 11.3   | 8.0   | 20.2   | -7.2  | 3.4          |
| $\omega$ B97X     | 15.77-100 (0.30) | Yes             | 13.1   | 11.0  | 20.8   | -6.5  | 2.1          |
| CAM-B3LYP         | 19-65 (0.33)     | Yes             | 12.0   | 10.9  | 20.2   | -5.9  | 1.1          |
| HSE06             | 25-0 (0.11)      | Yes             | 8.7    | 8.0   | 16.6   | -6.7  | 0.7          |
| B2PLYP            | 53               | Yes             | 11.6   | 11.5  | 17.6   | -6.7  | 0.1          |
| MP2               | –                | Yes             | 12.0   | 11.6  | 17.1   | -9.9  | 0.4          |
| MP4(SDQ)          | –                | Yes             | 14.3   | 11.9  | 21.5   | -7.6  | 2.4          |

chemistry, gives a topologically wrong result and an incorrect answer for the mechanism elucidation. It must be pointed out that this outcome is not related to a numerical problem or the selection of a too compact atomic basis set, but is intrinsic to the selected functional. Indeed, the qualitative results (absence of spiro form on the total energy profile) does not change when applying much more extended basis sets (*aug-cc-pVTZ* or *cc-pVQZ*), using a tighter integration grid, changing software (Gamess) or even when starting the B3LYP minimizations from B3PW91 spiro structural parameters. The selection of B3PW91, B3P86, B1LYP or BHandHLYP (which share with B3LYP the B88 exchange functional) yield the correct result. Similarly, X3LYP, B1LYP or BHandHLYP (which share with B3LYP the correlation functional LYP) validate the spiro existence. In fact, the HFE ratio seems to primarily guide the

response as all functionals with more than one fifth of Hartree-Fock percentage provide a qualitatively correct description. Around 15–20%, the form of the X and C functionals are predominant: the *meta*-GGA  $\tau$ HCTHhyb (15%) is successful, but B3LYP isn't. This result is consistent with previously reported data from the literature which proved that either B88 or LYP can lead to peculiar behaviours.<sup>28–31</sup> In Table 1, we also report the stabilisation of the spiro structure with respect to **(TS-1)** (i.e. the **(TS-1)**–spiro energy difference). M06 and PBE0 provide the results closest to the CCSD(T)//MP4(SDQ) reference. M06-2X and BHandHLYP also behave satisfactorily, whereas all other XCF yield poor results. The good performances of the Minnesota functionals (M06 and M06-2X) is surely due to the fact that they are *meta*-GGA, self interaction free –contrary to PBE or BP86– and respect the uniform electron gas limit –

contrary to BLYP and B3LYP.<sup>32</sup> However, it is worth noting that it may also come from their large number of parameters (39 and 38 parameters respectively) that give them more flexibility with respect to B3LYP for example, that incorporates much less parameters.

When looking at the (TS-1)–spiro energy difference for global hybrid functionals, it appears that the more HFE the more stabilised is the spiro (but for B1LYP). The amount of HFE seems therefore to have an influence on the topology of the reaction: with GGAs, TPSSh, O3LYP and B3LYP the spiro is not stable, whereas with all others global hybrid functionals the spiro is stable. Starting from the B3LYP functional and changing progressively the amount of exact exchange, it is found that 22–23% is the border ratio to reach the existence of the spiro form (see ESI). Concerning TPSSh, the limit lies at 11% since with 10% or less the spiro undergoes a ring-opening while with 11% or more of exact exchange the spiro is a RI. The BHandHLYP functional involves 50% of exact exchange and is the one with the largest stabilisation of the spiro with respect to (TS-1). This effect is of only 0.7 kcal.mol<sup>-1</sup> with M06, but increases to 1.4 kcal.mol<sup>-1</sup> with functionals optimised for investigating reactivity (M06-2X). It is however still not clear why B3LYP gives such a contrasted result while for example  $\tau$ HCTHhyb or B3PW91 validate the spiro existence.

Concerning the existence of the spiro structure, range-separated hybrids provide an improvement over global hybrid functionals since it is systematically found. However, both LC-BLYP and LC- $\omega$ PBE overestimate the (TS-1)–spiro difference. This originates in the amount of HFE ranges from 0 to 100. In the spiro compound, all bonds are covalent, leading to an effective amount of HFE smaller than in the TS that have long CN or CO bonds. As a consequence, the energy of the spiro is underestimated, similarly to what is found for many global hybrid with small amount of HFE. Having finite HFE at short distance, CAM-B3LYP,  $\omega$ B97X and the screened-Coulomb range-separated hybrid functional HSE06 lead to good estimates for the (TS-1)–spiro difference.  $\omega$ B97X slightly overestimates the activation energies because it includes large amount of HFE at long distances and thus its behaviour comes closer to the HF one. The best results are obtained with the CAM-B3LYP functional: both the reverse barrier and the energy profile are in agreement with CCSD(T) calculations. This is due to the smallest range of the HFE variation: as shown above, a sufficiently high amount of HFE is needed, and this functional starts at an higher amount than  $\omega$ B97X (19% vs 15.77%). Moreover, we have also shown that HF strongly overshoots the energies: at long distances, CAM-B3LYP has an HFE of 65% whereas  $\omega$ B97X has 100%. On the contrary, the HSE06 functional HFE goes to 0% at long distances, leading to a large underestimate of the full profile. Finally, and as expected, double hybrids provide accurate estimates.

**Table 2** Comparison of energy profiles of the Smiles rearrangement (in kcal.mol<sup>-1</sup>, with the 6-31+G(d,p) basis set in methanol) with different methods. Energies are single points calculations on MP4(SDQ) geometries

| Method    | (TS-1) | Spiro | (TS-2) | Prod. | (TS-1)–Spiro |
|-----------|--------|-------|--------|-------|--------------|
| CCSD(T)   | 12.6   | 11.7  | 19.3   | -8.1  | 0.9          |
| BLYP      | 10.0   | 13.1  | 16.0   | -4.3  | -3.1         |
| OLYP      | 10.5   | 13.5  | 17.7   | -4.4  | -3.0         |
| PW91LYP   | 8.6    | 11.4  | 14.6   | -4.7  | -2.8         |
| BPW91     | 7.1    | 9.2   | 13.4   | -5.5  | -2.1         |
| BP86      | 6.4    | 8.2   | 12.5   | -5.7  | -1.8         |
| B3LYP     | 11.3   | 12.4  | 18.8   | -5.1  | -1.1         |
| O3LYP     | 11.0   | 12.9  | 19.0   | -4.9  | -1.9         |
| X3LYP     | 11.1   | 11.9  | 18.7   | -5.2  | -0.9         |
| BHandHLYP | 14.0   | 12.4  | 23.4   | -5.6  | 1.6          |
| B3PW91    | 8.9    | 9.2   | 16.7   | -6.1  | -0.3         |
| B3P86     | 8.0    | 8.0   | 15.7   | -6.4  | 0.0          |
| M06-2X    | 10.0   | 8.9   | 19.8   | -7.1  | 1.1          |

From the last column of Table 1, it appears that using the LYP correlation functional induces a (TS-1)–spiro reverse barrier lower than with other correlation functionals. In order to get a more detailed view on the influence of the functional, we performed simple points calculations with several functionals on MP4(SDQ) geometries; results are gathered in Table 2. The underestimation of activation energies and the overestimation of spiro energy with BLYP appears more clearly. It is worth noting that with BLYP, OLYP or PW91LYP, the (TS-1)–spiro reverse barrier is almost constant (about -3 kcal.mol<sup>-1</sup>). Going to global hybrid functionals, the difference of spiro stabilization due to exact exchange effect is the same between BLYP and B3LYP, between BPW91 and B3PW91, and between BP86 and B3P86 (about -2 kcal.mol<sup>-1</sup>). However, this trend is not large enough to counterbalance the poor results obtained with BLYP, and thus B3LYP slightly corrects the BLYP results but to a too small extend. These unsatisfying results might originate in the lack of uniform electron gas fitting for LYP.<sup>28</sup>

**Table 3** Spiro structure existence and associated energy profile of the Smiles rearrangement (in kcal.mol<sup>-1</sup>, with the 6-31+G(d,p) basis set in methanol) with several dispersion corrected functional. For RSH functionals, the attenuation parameter  $\mu$  is given in parenthesis after the HFE range.

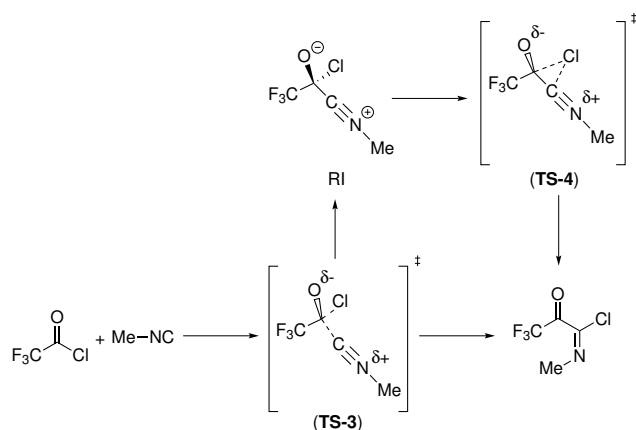
|                       | % HFE ( $\mu$ ) | (TS-1) | Spiro | (TS-2) | Prod. |
|-----------------------|-----------------|--------|-------|--------|-------|
| B97-D                 | 0               |        |       | 13.8   | -7.3  |
| B3LYP-D               | 20              | 11.5   | 11.5  | 18.3   | -5.3  |
| $\omega$ B97X-D       | 22.2-100 (0.20) | 10.8   | 9.3   | 19.2   | -6.8  |
| $\omega$ B97X-D w/o D | 22.2-100 (0.20) | 10.7   | 9.3   | 19.1   | -6.9  |
| B2PLYP-D              | 53              | 10.1   | 9.9   | 16.3   | -7.9  |

It is also of interest to test the impact of an empirical cor-

reaction for dispersion effects<sup>33</sup> and the results are collated in Table 3. With the pure XCF, namely B97-D, the spiro remains unseen. With B3LYP-D, the spiro structure has become a stationary point in the potential energy surface. However an unexpected outcome appeared: the spiro energy is higher of 0.07 kcal.mol<sup>-1</sup> than the (TS-1) energy which is a non-physical result. Energy profiles are only slightly modified when adding dispersion to B2PLYP. The energy profiles for  $\omega$ B97X-D with and without the dispersion term are reported in Table 3. Indeed, the  $\omega$ B97X-D functional is not equivalent to  $\omega$ B97X functional plus a dispersion term since the parameters (and in particular the HFE parameters, including the attenuation speed of these RSH) have been re-optimised for the  $\omega$ B97X-D functional. Comparing  $\omega$ B97X-D and  $\omega$ B97X-D without dispersion, it appears that the variations are trifling: the differences between  $\omega$ B97X and  $\omega$ B97X-D are therefore related to HFE: the dispersion corrections does not significantly impact the energy profile.

## 4 The Nef reaction

These results prompted us to study other specific cases. Due to our ongoing study on isocyanide-based reactions, we focused on the Nef reaction which consists on the insertion of an isocyanide into an acyl chloride to form an imidoyl chloride (see Figure 4).<sup>34</sup> The mechanism of this reaction starts as an S<sub>N</sub>2 reaction on the carbonyl moiety,<sup>35–37</sup> but when the tetrahedral structure is formed the released chloride (strongly nucleophilic) is trapped by the strongly electrophilic nitrilium which leads to an insertion of the isocyanide in the C–Cl bond.<sup>38</sup> Previous studies have shown that this reaction is usually concerted. However when the acyl chloride is substituted by a strong withdrawing group –such as trifluoromethyl– the reaction could proceed step-wisely or in a concerted way.



**Fig. 4** The Nef reaction between methylisocyanide and trifluoroacetyl chloride

The energy profile of this reaction was studied with different XCF. Results are gathered in Table 4 and are similar to those obtained in the previous Section: (i) the tetrahedral structure is a stable intermediate at the MP4(SDQ) and at *ab initio* levels; (ii) with GGAs or *meta*-GGAs the mechanism is found to be concerted; (iii) with global hybrid functionals including a small fraction of HFE (TPSSh, O3LYP,  $\tau$ HCTHhyb, B3LYP, B3P6, B3PW91, X3LYP, B98, B1LYP) the mechanism is concerted; (iv) PBE0, M06, BHandHLYP, M06-2X,  $\omega$ B97X and B2PLYP are able to locate a stable tetrahedral intermediate (stepwise reaction predicted).

However, it must be noted that both B3LYP and B3PW91 fail to describe properly the mechanism of the Nef reaction. Noteworthy is the difference found between B1LYP and PBE0: both have 25% of HFE, but the functional with the LYP correlation form behaves incorrectly (such as the difference between B3LYP and B3PW91 in the Smiles rearrangement). We would like here to point out that M06-2X,  $\omega$ B97X or CAM-B3LYP provide energetic values which are not in very good quantitative agreement with the CCSD(T)//MP4(SDQ) reference; only B2PLYP provides satisfactory results.

## 5 Conclusions

The B3LYP functional has been extensively used from its creation until today, especially in organic chemistry, often in combinations with the 6-31G(d) basis set. Recently new functionals (global hybrid *meta*-GGA, range-separated hybrids and double hybrids) have been developed. In the present contribution, we have shown an unexpected failure of the B3LYP approach, and of the LYP correlation functional: these functionals provide incorrect insights regarding the mechanism of two reactions – an intramolecular nucleophilic aromatic substitution (the Smiles rearrangement) and a nucleophilic addition on a carbonyl moiety (the Nef reaction) – and are unable to locate the reaction intermediates (and their associated transition states). The results provided by B3LYP for these reactions are therefore qualitatively wrong. This adds to the quantitative failures demonstrated by previous benchmarks.<sup>8–13</sup> A special care should thus be taken while using B3LYP, and recently proposed functionals (such as M06-2X<sup>27,32,39</sup> or  $\omega$ B97X<sup>40</sup>) should be preferred while investigating the reactivity in organic chemistry. At least, B3LYP results should be evaluated and cannot be trusted blindly.

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**Table 4** Existence of the tetrahedral structure of the Nef reaction according to the methodology. We also report the associated energy profile (in kcal.mol<sup>-1</sup>, with the 6-31+G(d,p) basis set in toluene) with respect to the reactants energy. For RSH functionals, the attenuation parameter  $\mu$  is given in parenthesis after the HFE range. The last column shows the energy difference between (TS-1) and the tetrahedral structure

|                   | % HFE ( $\mu$ )  | RI<br>existence | (TS-3) | RI   | (TS-4) | Prod. | (TS-1)-RI |
|-------------------|------------------|-----------------|--------|------|--------|-------|-----------|
| CCSD(T)//MP4(SDQ) | –                | –               | 17.1   | 16.5 | 18.3   | -9.5  | 0.6       |
| HF                | –                | Yes             | 25.0   | 24.5 | 24.5   | -1.8  | 0.6       |
| BLYP              | 0                | No              | 8.9    |      |        | -14.2 |           |
| TPSS              | 0                | No              | 7.2    |      |        | -17.9 |           |
| M06-L             | 0                | No              | 10.1   |      |        | -14.7 |           |
| TPSSh             | 10               | No              | 8.4    |      |        | -14.2 |           |
| O3LYP             | 11.61            | No              | 12.5   |      |        | -14.4 |           |
| $\tau$ HCTHhyb    | 15               | No              | 8.6    |      |        | -18.0 |           |
| B3LYP             | 20               | No              | 10.9   |      |        | -12.0 |           |
| B3P86             | 20               | No              | 7.7    |      |        | -17.0 |           |
| B3PW91            | 20               | No              | 8.9    |      |        | -19.5 |           |
| X3LYP             | 21.80            | No              | 10.8   |      |        | -12.4 |           |
| B98               | 21.98            | No              | 10.1   |      |        | -16.5 |           |
| B1LYP             | 25               | No              | 12.1   |      |        | -11.1 |           |
| PBE0              | 25               | Yes             | 8.2    | 5.8  | -2.4   | -17.5 | 2.5       |
| M06               | 27               | Yes             | 9.4    | 8.2  | 8.8    | -12.7 | 1.1       |
| BHandHLYP         | 50               | Yes             | 14.4   | 12.8 | -1.6   | -11.6 | 1.7       |
| M06-2X            | 54               | Yes             | 11.7   | 11.5 | 12.6   | -11.7 | 0.2       |
| $\omega$ B97X     | 15.77-100 (0.30) | Yes             | 12.9   | 11.9 | 13.1   | -14.3 | 1.0       |
| CAM-B3LYP         | 19-65 (0.33)     | Yes             | 11.9   | 10.3 | 10.5   | -13.0 | 1.5       |
| B2PLYP            | 53               | Yes             | 16.9   | 15.5 | 15.6   | -8.9  | 1.4       |
| MP2               | –                | Yes             | 11.6   | 10.3 | 11.4   | -10.8 | 1.4       |
| MP4(SDQ)          | –                | Yes             | 15.7   | 15.3 | 17.3   | -9.0  | 0.4       |

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## References

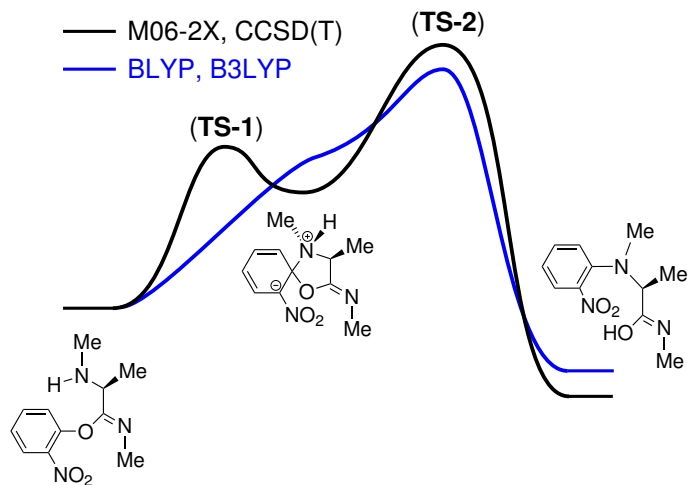
- 1 A. Becke, *J. Chem. Phys.*, 1993, **98**, 1372–1377.
- 2 A. Becke, *Phys. Rev. A*, 1988, **38**, 3098–3100.
- 3 C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B*, 1988, **37**, 785–789.
- 4 A. Becke, *J. Chem. Phys.*, 1993, **98**, 5648–5652.
- 5 P. J. Stephens, F. J. Devlin, C. F. Chabalowski and M. J. Frisch, *J. Phys. Chem.*, 1994, **98**, 11623–11627.
- 6 Y. Zhao and D. G. Truhlar, *Org. Lett.*, 2006, **8**, 5753–5755.
- 7 H. Iikura, T. Tsuneda, T. Yanai and K. Hirao, *J. Chem. Phys.*, 2001, **115**, 3540–3544.
- 8 D. Jacquemin, E. A. Perpète, M. Medved', G. Scalmani, M. J. Frisch, R. Kobayashi and C. Adamo, *J. Chem. Phys.*, 2007, **126**, 191108–1/191108–4.
- 9 M. J. G. Peach, P. Benfield, T. Helgaker and D. J. Tozer, *J. Chem. Phys.*, 2008, **128**, 044118–1/044118–8.
- 10 P. C. Redfern, P. Zapol, L. A. Curtiss and K. Raghavachari, *J. Phys. Chem. A*, 2000, **104**, 5850–5854.
- 11 L. A. Curtiss, K. Raghavachari, P. C. Redfern and J. A. Pople, *J. Chem. Phys.*, 2000, **112**, 7374–7383.
- 12 X.-Q. Yao, X.-J. Hou, H. Jiao, H.-W. Xiang and Y.-W. Li, *J. Phys. Chem. A*, 2003, **107**, 9991–9996.
- 13 C. E. Check and T. M. Gilbert, *J. Org. Chem.*, 2005, **70**, 9828–9834.
- 14 A. G. Leach, E. Goldstein and K. N. Houk, *J. Am. Chem. Soc.*, 2003, **125**, 8330–8339.
- 15 S. M. Bachrach and J. C. Gilbert, *J. Org. Chem.*, 2004, **26**, 6357–6364.
- 16 S. N. Pieniazek and K. N. Houk, *Angew. Chem. Int. Ed.*, 2006, **45**, 1442–1445.
- 17 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, *Gaussian 09, Revision A.02*, Gaussian Inc., Wallingford, CT, 2009.
- 18 S. Miértus, E. Scrocco and J. Tomasi, *Chem. Phys.*, 1981, **55**, 117–129.

- 
- 19 M. Cossi, B. Mennucci and J. Tomasi, *Chem. Phys. Lett.*, 1994, **228**, 165–170.
  - 20 B. Mennucci, E. Cancès and J. Tomasi, *J. Phys. Chem. B*, 1997, **101**, 10506–10517.
  - 21 C. J. Cramer and D. G. Truhlar, *Acc. Chem. Res.*, 2008, **41**, 760–768.
  - 22 N. Chéron, R. Ramozzi, L. El Kaïm, L. Grimaud and P. Fleurat-Lessard, *J. Org. Chem.*, 2012, **77**, 1361–1366.
  - 23 A. A. Levy, H. C. Rains and S. Smiles, *J. Chem. Soc.*, 1931, 3264–3269.
  - 24 N. Chéron, L. El Kaïm, L. Grimaud and P. Fleurat-Lessard, *Chem. Eur. J.*, 2011, **17**, 14929–14934.
  - 25 J. Meisenheimer, *Justus Liebigs Ann. Chem.*, 1902, **323**, 205–246.
  - 26 A. P. Bento, M. Sola and F. M. Bickelhaupt, *J. Chem. Theory Comput.*, 2008, **4**, 929–940.
  - 27 Y. Zhao and D. G. Truhlar, *Acc. Chem. Res.*, 2008, **41**, 157–167.
  - 28 K. Burke, J. P. Perdew and M. Ernzerhof, *Int. J. Quant. Chem.*, 1997, **61**, 287–293.
  - 29 D. R. B. Brittain, C. Y. Lin, A. T. B. Gilbert, E. I. Izgorodina, P. M. W. Gill and M. L. Coote, *Phys. Chem. Chem. Phys.*, 2009, **11**, 1138–1142.
  - 30 G. A. Shamov, G. Schreckenbach and P. H. M. Budzelaar, *J. Chem. Theory Comput.*, 2010, **6**, 3442–3455.
  - 31 J. C. Sancho-Garca, *J. Chem. Theory Comput.*, 2011, **7**, 2761–2765.
  - 32 Y. Zhao and D. G. Truhlar, *Theor. Chem. Account*, 2008, **120**, 215–241.
  - 33 S. Grimme, *J. Comp. Chem.*, 2004, **25**, 1463–1473.
  - 34 J. U. Nef, *Justus Liebigs Ann. Chem.*, 1892, **270**, 267–335.
  - 35 R. A. McClelland, *J. Am. Chem. Soc.*, 1984, **106**, 7579–7583.
  - 36 T. W. Bentley, G. Llewellyn and J. A. McAlister, *J. Org. Chem.*, 1996, **61**, 7927–7932.
  - 37 J. M. Fox, O. Dmitrenko, L. an Liao and R. D. Bach, *J. Org. Chem.*, 2004, **69**, 7317–7328.
  - 38 N. Chéron, L. El Kaïm, L. Grimaud and P. Fleurat-Lessard, *J. Phys. Chem. A*, 2011, **115**, 10106–10112.
  - 39 Y. Zhao and D. G. Truhlar, *Theor. Chem. Account*, 2008, **119**, 525–525.
  - 40 J.-D. Chai and M. Head-Gordon, *J. Chem. Phys.*, 2008, **128**, 084106–1/084106–15.



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