



Spin-flip time dependent density functional theory for singlet–triplet splittings in σ,σ -biradicals

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ABSTRACT

A spin-flip time dependent density functional theory approach with hybrid non-collinear exchange–correlation kernels has been applied to investigate the energy gap between the lowest singlet and triplet states of σ,σ -biradicals. The obtained results indicate that spin-flip time dependent density functional theory is capable to predict the correct ordering of singlet and triplet states among all investigated biradicals and that it gives estimates of singlet–triplet splittings in good agreement with high level correlated *ab initio* calculations. The theory provides a superior accuracy compared to the conventional broken-symmetry unrestricted density functional theory methods.

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1. Introduction

Aromatic σ,σ -biradicals are important intermediates in DNA cleavage reactions initiated by enediyne anti-tumor drugs as well as other biochemically active compounds which interact with DNA by forming reactive biradicals via Bergman cyclization [1–3]. The reactivity and DNA damage potential of such biradicals are interconnected with the singlet–triplet (S–T) splitting of the lowest states in these species [4]. From the rational drug design perspective the knowledge of S–T energy gaps of various aromatic biradicals would be very desirable in the search of the potential new candidates as anti-tumor antibiotics. Despite the importance of this quantity, experimental S–T splittings in aromatic σ,σ -biradicals have, to the best of our knowledge, only been determined for o-, m- and p-benzynes [5], from which only p-bzyne can serve as a model of biradicals encountered in enediyne drugs. One obvious way to overcome the problem of lack of experimental data is to employ quantum chemistry methods for prediction of S–T splittings in targeted biradicals. Despite the appeal of this solution only sophisticated multi-reference *ab initio* methods can in practice describe the S–T splittings in biradicals due to the nature of these species [6–8]. Consequently, only small biradicals, with little relevance to the ones encountered in enediyne antibiotics, have been investigated. Fortunately, recent development of novel density functional theory (DFT) methods, like restricted-ensemble Kohn–Sham (REKS) [9] and spin-flip time dependent density functional theory (TD-DFT) [10,11] methods, which go beyond the archaic broken-symmetry formalism [12–14], have offered viable

alternatives for studying S–T splittings and other properties of biradicals, including the ones of experimentalist interest, since these methods can treat considerably large molecular systems than their *ab initio* counterparts. Taking into account the recent development of linear scaling techniques for DFT, we expect that REKS and spin-flip TD-DFT methods and other similar approaches will start playing a prominent role in rational drug design, serving as reliable tools for prediction of S–T splittings in various aromatic biradicals formed by Bergman cyclization or other drugs activation processes.

In this Letter, we report the first application of a novel approach which takes one step further on the evolutionary ladder of spin-flip TD-DFT compared to previously developed approaches [10,11]. The improvement introduced in our implementation of spin-flip TD-DFT is twofold: first, we introduce a non-collinear exchange–correlation kernel [11], which is capable to handle hybrid exchange–correlation functionals and in this way overcome the technical limitations of previous implementation by Wang and Ziegler [11] in which only ‘pure’ exchange–correlation functionals can be used in the spin-flip TD-DFT calculations; second, we base our implementation on the open-shell spin-restricted Kohn–Sham formalism and in this way eliminate one source of spin-contamination of the spin-flip excited states, namely the spin-contamination of the reference triplet state. This new development in spin-flip TD-DFT ensures that it is capable to describe the various states of biradicals with better accuracy than before, since one now can obtain better localization in extended systems due to the use of hybrid exchange–correlation functionals with a large fraction of exact Hartree–Fock exchange. Here, we will demonstrate these features of our implementation by evaluating the S–T splitting in a selected set of aromatic σ,σ -biradicals.

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2. Spin-flip TD-DFT: from collinear to hybrid non-collinear exchange–correlation kernels

Since its introduction by Shao et al. [10], the spin-flip TD-DFT approach has been advertised as a one of the most successful solutions in DFT for treatment of molecules with ground states with a significant biradical character. However, the initial form implemented by Shao et al. [10], with a collinear exchange–correlation kernel, as well as in the later development by Wang and Ziegler of a non-collinear reformulation [11], have only been applied to study biradicals containing systems on a few occasions beyond the initial benchmarking works [15–17]. Probably, the main reason behind the yet limited popularity of spin-flip TD-DFT is that the hybrid exchange–correlation functionals, which provide in many cases superior description of the electronic structure of molecular systems, cannot be used with available implementations which use non-collinear exchange–correlation kernels. This circumstance has significantly narrowed the types of molecules which can be treated accurately by spin-flip TD-DFT. The underlying reason is the well known failure of local density (LDA) and generalized gradient approximation (GGA)-based exchange–correlation to describe the localization of electron density of extended molecular systems, something that leads to significant errors for larger biradicals. This deficiency of LDA and GGA type exchange–correlation functionals is corrected in hybrid functionals, which contain a large fraction of exact Hatree–Fock exchange. In order to improve the performance of spin-flip TD-DFT it is therefore essential to enable the handling of hybrid functionals in non-collinear exchange–correlation kernels of spin-flip TD-DFT. We have implemented this extension in a development version of the DALTON quantum chemistry package [18]. This non-collinear spin-flip TD-DFT can thus handle LDA, GGA, hybrid and long range corrected, like CAM-B3LYP, exchange–correlation functionals in the spin-flip TD-DFT calculations. Furthermore, in order to reduce the spin-contamination of excited states obtained by spin-flip TD-DFT, we have based our implementation on an open-shell spin-restricted Kohn–Sham formalism. In this way we eliminate the spin-contamination of the high spin triplet reference states [19,20], which are featured in previous implementations based on the unrestricted Kohn–Sham formalism. However, in our implementation of spin-flip TD-DFT method, excited states remain still spin-contaminated, since we use ordinary spin-flip down excitation operator, which is not spin-adapted, in parameterization of time evolution of electron density. The general form of spin-flip operators, which are spin-adapted, along with corresponding derivation of spin-flip TD-DFT equations is given in work by Vahtras and Rinkevicius [21] and we are currently working on the incorporation of general spin-flip excitation operators in spin-flip TD-DFT approach. The technical details of our implementation of the spin-flip TD-DFT approach as well as detailed descriptions of the capabilities of this method will be given elsewhere. We also refer interested readers to the seminal works by Shao et al. [10], Ziegler and Wang [11], and Vahtras and Rinkevicius [21]. In the following we will critically examine the performance of our implemented variant of spin-flip TD-DFT for the evaluation of S–T splittings of benzenes, which have been extensively studied by various theoretical approaches as well as by experimentalists. We also apply this approach to study S–T splittings in a selected set of σ,σ -biradicals, which can serve as simplified models of biradicals encountered in DNA cleavage by enediyne anti-tumor drugs.

3. Benchmarking spin-flip TD-DFT: singlet–triplet splittings in benzenes

The o-, m- and p-benzynes (see Fig. 1) are probably the most studied species among the aromatic σ,σ -type biradicals owing to

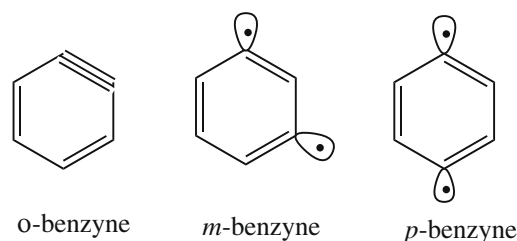


Fig. 1. Ortho-, meta- and para-benzynes.

their fundamental importance for understanding σ,σ -biradical reactivity and function in various chemical processes as well as to the availability of reliable experimental data for these compounds [5,6,10,20,22]. A variety of quantum chemistry methods have been applied to determine the ordering of the lowest singlet and triplet states as well as to determine the S–T splittings in these compounds. In line with experimental observations, most previous studies carried out using multi-reference *ab initio* methods or collinear spin-flip TD-DFT predict a singlet ground state for these compounds, in which the biradical character increases going from o-benzyne to p-benzyne. In Table 1 we tabulated our spin-flip TD-DFT results along with a few selected results obtained in earlier works devoted to benzenes. As one can see from the inspection of Table 1, S–T splittings obtained using the BHLYP exchange–correlation functional are in close agreement with SF-CCSD(dT) results, which are probably the most accurate *ab initio* results available up to date, and the discrepancies between the two methods do not exceed 0.1 kcal/mol for o- and p-benzynes. Compared to previous spin-flip TD-DFT results by Shao et al. [10], which were obtained using a collinear exchange–correlation kernel, the non-collinear spin-flip TD-DFT outperforms the older method if we take the SF-CCSD(dT) results as reference. Also, our results are in very good agreement with experimental data. This agreement is somewhat worse if we add the zero point vibrational correction (ZPVE)

Table 1

Adiabatic S–T splittings in o-benzyne, m-benzyne and p-benzyne computed using non-collinear spin-flip TD-DFT.^{a,b}

Molecule	o-Benzyne	m-Benzyne	p-Benzyne
BHLYP	37.28	18.82	3.98
Birad. char. ^c %	5.1	12.18	32.8
SF50/50 ^d	41.70	22.30	3.50
SF-OD ^e	37.63	19.30	3.94
SF-CCSD(dT) ^f	37.34	20.57	3.97
Experiment ^g	37.5 ± 0.3	21.0 ± 0.3	3.8 ± 0.3
ZPVE ^h	−0.65	0.99	0.48
Effective S–T ⁱ	38.15 ± 0.3	20.01 ± 0.3	3.32 ± 0.3

^a S–T splittings are given in kcal/mol with respect to singlet state, i.e., $\Delta = E(^3T) - E(^1S)$.

^b Spin-flip TD-DFT calculations carried out using hybrid BHLYP functional [24–27] in TZV2P basis set [28]. Benzenes geometries for singlet and triplet states optimized at broken-symmetry unrestricted B3LYP/Turbomole-TZVP level of theory [25–30].

^c Biradical character computed by taking square of double HOMO²–LUMO² excitation weight in spin-flip response residue vector for singlet state.

^d S–T splittings computed using spin-flip TD-DFT with collinear exchange–correlation kernel. See Ref. [10] for definition of 50/50 exchange–correlation functional.

^e S–T splittings computed using spin-flip optimized orbital coupled cluster doubles (SF-OD) method. See Ref. [22] for details.

^f S–T splittings computed using spin-flip coupled cluster singles, doubles with non-iterative perturbative triples correction (SF-CCSD(dT)) method. See Ref. [23] for details.

^g S–T splittings obtained from ultraviolet photoelectron spectroscopy. See Ref. [5] for details.

^h Zero point vibrational correction to S–T splitting computed using spin-flip TD-DFT with collinear exchange–correlation kernel. See Refs. [10,22], for details.

ⁱ Effective S–T splitting estimated by adding ZPVE to experimentally determined S–T splittings.

to the experimental S–T splitting. We point out that the ZPVEs are taken from work of Shao et al. [10] which for p-benzyne is surprisingly large and contradicts the commonly observed trend in other well localized aromatic σ,σ -biradicals, where the ZPVE to S–T splittings almost in all cases are vanishing, not exceeding 0.5 kcal/mol (see for example, work by Cramer and Thompson [31]). Taking this into account, we conclude that probably for the p-benzyne case it is more realistic to compare directly the S–T splittings with spin-flip TD-DFT results ignoring Shao's ZPVE corrections. For larger biradicals the evaluation of ZPVE can be very costly and if this contribution cannot be neglected any prospective for modeling of S–T splitting in realistic systems would be computationally very demanding.

Let us here turn to another important issue, namely the biradical character of the singlet ground state in these compounds. As one can see from Table 1, our spin-flip TD-DFT results nicely reproduce the expected increase of biradical character going from o-benzyne to p-benzyne. Furthermore, we observe that the change of biradical character going from one benzyne to the other correlate with the S–T splitting in these compounds (obviously three data points are too few to make any sound conclusion about such a correlation). We conclude that the spin-flip TD-DFT with non-collinear exchange–correlation kernel combined with the BHLYP functional is capable to reproduce the S–T splittings in o-, m- and p-benzynes with an accuracy compared to best correlated *ab initio* methods, but at the fraction of the computational cost.

4. Singlet–triplet splittings in model σ,σ -biradicals

For the further validation of our spin-flip TD-DFT approach we selected six model systems (Fig. 2), which have been extensively studied in connection to the biradicaloid mechanism of bioactivity of enediyne antibiotics. The first two compounds, **I** and **II**, are interesting prototype cases for substitution effects on p-benzyne, as only the latter compound is predicted to be an effective hydrogen abstraction agent. Substitution of the CH group with a nitrogen atom in p-benzyne (see compound **I** in Fig. 2) leads to a profound decrease of the biradical character, from 32.8% to 13.9%, which is accompanied with a sharp increase of the S–T splitting, 3.98–10.50 kcal/mol (see BHLYP results in Tables 1 and 2). This change in electronic structure makes the retro-Bergman cyclization reaction become favorable in compound **I** and consequently renders it the ability to serve as an effective hydrogen abstraction agent [32,33]. Protonation of nitrogen in compound **I** produces com-

ound **II**, which has almost two times larger biradical character than compound **I** and a comparable S–T splitting with p-benzyne (4.44 kcal/mol vs. 3.98 kcal/mol, respectively). Therefore the protonation severely alters the nature of compound **I** and restores the ability of its protonated form to participate in a hydrogen abstraction reaction as the primary active component. For both compounds, **I** and **II**, our spin-flip TD-DFT results agree fairly well with the most accurate results by Cramer using a composite method (see Ref. [30] for details), the discrepancies do not exceed 1.1 kcal/mol. Broken-symmetry unrestricted DFT at the BPW91 level predicts the S–T splitting in good agreement with our spin-flip TD-DFT results for compound **II**, but for compound **I** the difference becomes quite large (3.5 kcal/mol). Here, we note that Cramer's CASPT2 calculations predict S–T splittings to be systematically larger than ones obtained by spin-flip TD-DFT or Cramer's composite method due to the overstabilization of the singlet biradical state [32,33]. In light of this finding we restrain ourselves from using CASPT2 results as reference data for benchmarking of our spin-flip TD-DFT method. The next two compounds, **III** and **IV**, in our test suite are the 1,4-naphthalene and 1,5-naphthalene biradicals for which we test the ability of spin-flip TD-DFT to predict S–T splittings in σ,σ -biradicals with extended π systems. Here, we note that extension of the π system going from p-benzyne to 1,4-naphthalene has negligible impact on the biradical character and the S–T splitting, as one can see from Tables 1 and 2. From this point of view p-benzyne can be used as a small model for 1,4-naphthalene. In compound **IV**, and differently from compound **III**, one unpaired electron is located on one of the six-membered ring and another electron is located on the other six-membered ring. This change of position of the unpaired electron from the fourth to the fifth carbon slightly decreases the biradical character of the naphthalene type biradical and consequently increases the S–T splitting, by roughly 3 kcal/mol. A similar result for a pair of these radicals has also been obtained by Squires and Cramer at the CASPT2 level of theory [6], though their S–T splittings are systematically larger than our spin-flip TD-DFT results due to the above mentioned limitation of the CASPT2 method. Here, we would like to draw the readers attention to the fact that the broken-symmetry unrestricted DFT approach fails to predict the correct ordering of the lowest singlet and triplet states in 1,4-naphthalene and therefore cannot be used to study naphthalene type biradicals. The last two compounds, **V** and **VI**, in benchmarking set are 4,8-didehydroindene and 4,7-didehydroindene, which are typically formed in Myers–Saito cyclization reaction [31]. We included these two compounds into our test suite in order to test the impact of substitu-

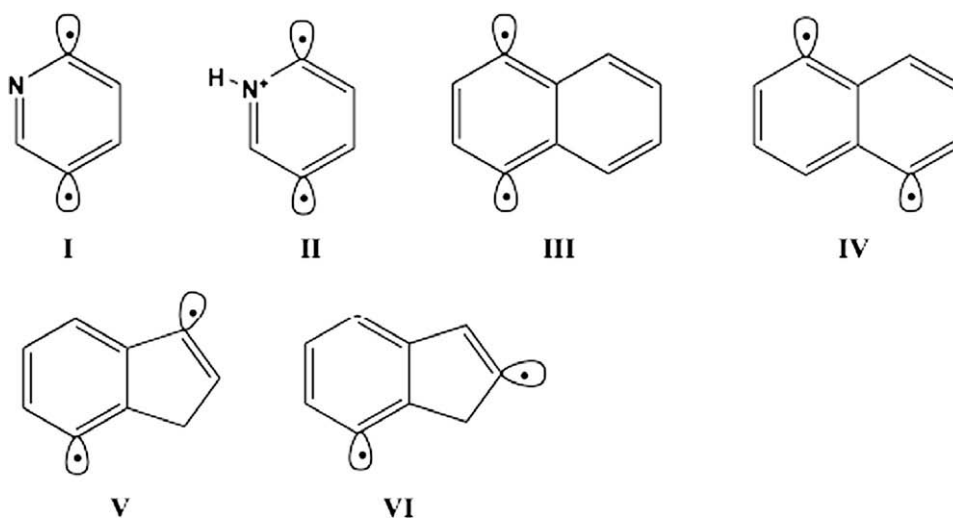


Fig. 2. Six model σ,σ -biradicals included in our benchmarking set of performance of spin-flip TD-DFT approach.

Table 2Adiabatic S–T splittings in model σ,σ -biradicals computed using non-collinear spin-flip TD-DFT^{a,b}.

Compound	I	II	III	IV	V	VI
BHLYP	10.50	4.39	4.01	7.18	7.22	2.20
Birad. char. ^c , %	13.9	20.4	32.49	29.59	27.04	23.23
CASPT2 ^d	14.1	5.6	5.6	7.8	7.4	0.4
BCCSD(T) ^e	11.6	5.6	6.3	0.5
Composite ^f	11.6	4.0
BS-BPW91 ^g	14.0	4.3	-1.0	1.6	6.0	0.6

^a S–T splittings are given in kcal/mol with respect to singlet state, i.e., $\Delta = E(^3T) - E(^1S)$.^b Spin-flip TD-DFT calculations carried out using hybrid BHLYP functional [24–27] in TZV2P basis set [28]. Benzynes geometries for singlet and triplet states optimized at broken-symmetry unrestricted B3LYP/Turbomole-TZVP level of theory [25–30].^c Biradical character computed by taking square of double HOMO²–LUMO² excitation weight in spin-flip response residue vector for singlet state.^d S–T splittings computed using complete active space second-order perturbation theory (CASPT2) method. See Refs. [32,33] for compounds I and II, Ref. [6] for compounds III and IV and Ref. [30] for compounds V and VI.^e S–T splittings computed using Brueckner couple cluster with singles, doubles and perturbative triples (BCCSD(T)) method. See Refs. [32,33] for I and II and Ref. [30] for compounds V and VI.^f S–T splittings estimated using composite method based on Brueckner and conventional coupled cluster methods. See Ref. [33] for definition of method and computational details.^g S–T splittings computed using broken-symmetry unrestricted DFT method using BPW91 exchange–correlation functional, denoted here as BS-PW91. See Refs. [32,33] for compounds I and II, Ref. [34] for compounds III and IV and Ref. [31] for compounds V and VI.

tion of the six-membered ring with the five membered ring in the residence site of one unpaired electron. Overall, compounds V and VI exhibit slightly lower biradical character than 1,5-naphthylene (see Table 2). The S–T splitting in compound V is close to the one obtained for 1,5-naphthylene, while the situation is completely different for compound VI, which has the smallest S–T splittings among the six model σ,σ -biradicals considered in our test set. For 4,8-didehydroindene the spin-flip TD-DFT predicts an S–T splitting in a good agreement with the BCCSD(T) results by Cramer and Thompson [31], while for 4,7-didehydroindene our approach overestimates the BCCSD(T) data by 1.7 kcal/mol (see Table 2, 2.2 kcal/mol vs. 0.5 kcal/mol). The reason behind this discrepancy is not immediately clear and further investigation with more accurate *ab initio* methods, like SF-CCSD(dT), is needed in order to resolve this issue.

After discussing the model σ,σ -biradicals in pairs let us summarize our findings. Overall, for the six model compounds, which have biradical character from 13.9% to 32.49%, considered in this Letter, spin-flip TD-DFT predicts the correct ordering of the lowest singlet and triplet states and gives S–T splittings in good agreement with the best available *ab initio* calculations. Furthermore, spin-flip TD-DFT outperforms the commonly used broken-symmetry unrestricted DFT approach, which fails to predict the correct ordering in compound III, i.e., 1,4-naphthalene. Based on these findings, we are confident that the spin-flip TD-DFT approach will in the near future become the method of choice for studying S–T splittings in σ,σ -biradicals and open a way for more comprehensive modeling of reactive intermediates encountered in various enediyne antibiotics which go beyond currently used simplified model systems.

5. Conclusions

In this Letter we have presented the first application of a spin-flip TD-DFT approach with a hybrid non-collinear exchange–corre-

lation kernel. We have demonstrated the capability of the approach by computing singlet–triplet splittings in σ,σ -biradicals, including the ones which are used in modeling of bioactivity mechanisms of enediyne antibiotics. Overall, our spin-flip TD-DFT approach in combination with the hybrid BHLYP exchange–correlation functional provides a state of the art methodology for prediction of S–T splittings in σ,σ -biradicals. It is comparable in accuracy with best available *ab initio* methods, but at the same time significantly less demanding for computational resources. The presented approach outperforms the commonly used broken-symmetry unrestricted DFT method and can therefore be recommended as a more accurate alternative to this archaic method. We hope that the results presented in this Letter motivate the spin-flip TD-DFT approach to become more widely used, for instance in modeling of S–T splittings of various biradicals and chemical reactions involving biradicaloid intermediates, like the ones encountered in biochemistry of enediyne antibiotics.

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