

Reply to the 'Comment on "trans-1,2-Disiloxybenzocyclobutene, an adequate partner for the auto-oxidation: EPR/spin trapping and theoretical studies"' by H.-G. Korth, P. Mulder and T. Paul, Phys. Chem. Chem. Phys., 2017, 19 , C6CP04187F

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Reply to the 'Comment on "*trans*-1,2-Disiloxybenzocyclobutene, an adequate partner for the auto-oxidation: EPR/spin trapping and theoretical studies"' by H.-G. Korth, P. Mulder and T. Paul, *Phys. Chem. Chem. Phys.*, 2017, 19, C6CP04187F†

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The proposal and the comments made by Korth *et al.* on a biradical intermediate along the isomerization path of the reaction of *trans*-1,2-*tert*-butyldimethyldisilyloxybenzocyclobutene **1** with dioxygen are unsuitable in our case. The mechanism scenario that we proposed is in agreement with our experimental observations. Moreover, new calculations were able to give an answer to the crucial question, "is the biradical an intermediate or a transition state?" together with the localization of the two radicals. This full article is a response to the "Comment on "*trans*-1,2-Disiloxybenzocyclobutene, an adequate partner for the auto-oxidation: EPR/spin trapping and theoretical studies" by J. Drujon *et al.*, *Phys. Chem. Chem. Phys*. 2014, **16**, 7513".

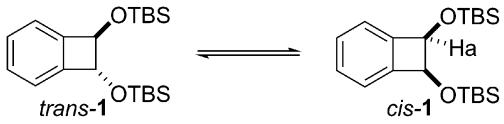
I. Introduction

In 2014, in a previous paper[1] entitled "*trans*-1,2-Disiloxybenzocyclobutene, an adequate partner for the auto-oxidation: EPR/spin trapping and theoretical studies", we have reported both EPR/spin trapping and theoretical studies to understand and explain the mechanism of spin-forbidden addition of triplet oxygen $O_2(^3\Sigma_g)$ to *trans*-1,2-disiloxybenzocyclobutene **1** to give the corresponding *endo*-peroxide **7**. Two years later, H.-G. Korth and co-workers have published some comments related to our work.[2] To address the main points of controversy, we present herein several pieces of evidence based on both experimental and theoretical studies. Moreover some remarks will also be provided in the references section and in the ESI† to address minor points taken up by Korth *et al.*

II. Discussion

(1) Isomerization or not? Experimental evidence

The major point of their claim comes from the fact that we did not consider a possible isomerization of *trans*-**1** to *cis*-**1** (Scheme 1) in our postulated mechanism of the addition of triplet oxygen $O_2(^3\Sigma_g)$ to *trans*-**1**.



Scheme 1 Isomerization of *trans*-**1** to *cis*-**1**.

First of all, no characteristic proton NMR chemical shift of *cis*-**1** was ever observed in the crude ^{1}H NMR spectrum of the reaction. Despite H.-G. Korth and co-workers' assertion ("*The resolution of the ^{1}H and ^{13}C NMR spectra displayed in the ESI to ref. 1 is insufficient to prove or disprove the presence of cis-**1**.*"), we wish to insist that in the ^{1}H NMR spectrum recorded in C_6D_6, the chemical shifts of the Ha protons of *cis*-**1** (singlet at 5.27 ppm) and *trans*-**1** (singlet at 5.10 ppm) are too different to be mistaken.

Nevertheless, a complementary experiment has been performed in order to detect the isomerization of *trans*-**1** to *cis*-**1**, which we could have missed in our previous work. For this purpose, *trans*-**1** was heated alone at 45 °C in degassed C_6D_6. Even after 18 h of heating, no isomerization occurred, since the chemical shift of the Ha proton of *cis*-**1** was never detected in the ^{1}H crude NMR spectrum (Fig. 1).

Furthermore, in a previous paper[3] related to cycloaddition reaction studies of *trans*-1,2-disiloxybenzocyclobutene **1** with

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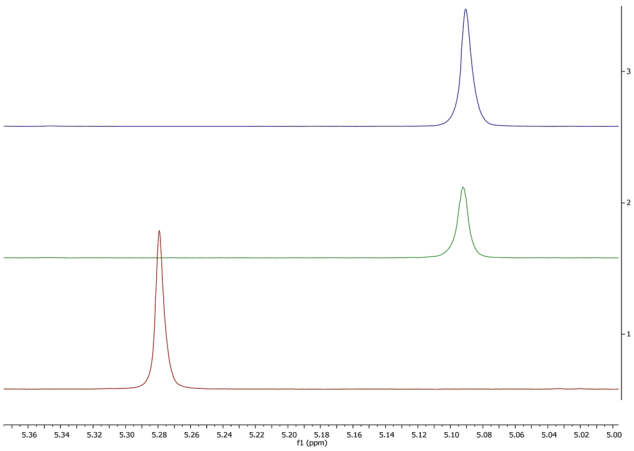


Fig. 1 (1) ^{1}H NMR spectra of *cis*-**1a**; (2) ^{1}H NMR spectra of *trans*-**1a** at t = 0; (3) ^{1}H NMR spectra of *trans*-**1a** at t = 18 h after heating at 45 °C.

γ-alkylidenebutenolides towards the synthesis of natural products, we have never detected the presence of *cis*-1,2-disilyloxybenzocyclobutene in the crude mixture, even after 3 days of reaction!

In their comment, the authors also stated that "*In 1999, we reported on the reaction of meso-1,2-diphenyl-1,2-dimethoxybenzocyclobutene (meso-**5**) with molecular oxygen to produce the related endo-peroxides 6 (Scheme 2). The reaction proceeded smoothly at 20 °C.*" (Fig. 2). Nevertheless, the reaction time is very long, as they explain in their article[4] published in 1999: "*Therefore, the isomerization of meso-**1c** was also carried out in the presence of molecular oxygen. In oxygen-saturated [D$_3$]acetonitrile solution, a variety of new ^{1}H- and ^{13}C-NMR resonances appeared over a period of days at 20 °C.*" In our case, the reaction time of O_2 trapping by the *trans*-1,2-disilyloxybenzocyclobutene **1** is *ca.* 3–4 hours only.

The major structural difference between *meso*-**5** and *trans*-**1**, together with the very different reaction time, certainly explains why we have never observed any isomerization. Actually, modifying the substitution certainly has a dramatic influence on the stabilities of expected bisradicaloid species formed after homolytic scission of cyclobutene. Moreover, it is important to note that, in our case, the conversion rate of O_2 trapping is quasi quantitative.

On the basis of all these observations and experimental evidence, it is quite clear that in our case the isomerization can be neglected.

The new calculations of H.-G. Korth and co-workers based on relative enthalpies and free energies of (1) electrocyclic ring opening of different *trans*- and *cis*-1,2-disubstituted-benzocyclobutenes and (2) dioxygen addition to *E*,*E*-dimethoxy-*o*-quinodimethane are interesting (and complete ours!), nevertheless they only illustrate the observations of D. J. Danishefsky and co-workers[5] who reported that

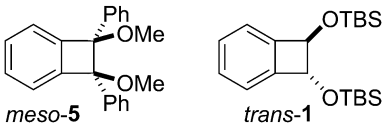


Fig. 2 Structure of *meso*-**5** and *trans*-**1**.

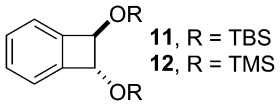


Fig. 3 Structure of **11** and **12**.

a TMS-analog of *cis*-**1** (Fig. 3) is not reactive in the cycloaddition conditions; the following sentence being sufficiently explicit "*Although trans-**11** could be purified, **12** was used as a mixture of trans and non-reactive cis isomer.*"

(2) About the nature of the postulated intermediate

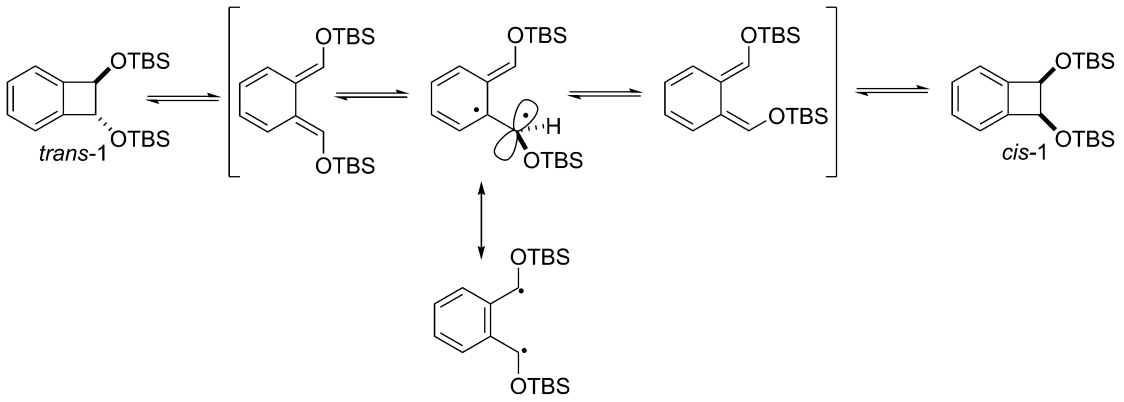
No reliable calculations of isomerization reaction (*rac*-benzocyclobutene to *meso*-benzocyclobutene) support the formation of *cis*-**1** from *trans*-**1**. More precisely, no calculation supports the hypothesis of Korth *et al.* that the isomerization reaction proceeds *via* a biradical intermediate (which does not occur fast enough at the time scale in which we performed the reaction *vide supra*) (Scheme 2).

This assumption was made by Korth *et al.*,[4] as follows "*Roth provided evidence that for [methyl and phenyl benzocyclobutene molecules][6] double-bond isomerization [...] is unlikely. It was suggested that the system avoids the energetically unfavorable disrotatory pathway by following the biradical one.*" Then follows a discussion about the nature of this diradical molecule: is it an intermediate or a transition state? In the following paragraph, the authors continue to base their work on Roth's: "*For the [corresponding orthoquinodimethane],[6] a difference of 20.5 kJ mol^{-1} between the activation barriers for the 'forbidden' and the conrotatory isomerization was estimated. This difference dropped to just 4.2 kJ mol^{-1} in the case of [diphenyl benzocyclobutene],[6] an effect attributed to the higher (benzyl-type) stabilization [...] in the transition state/intermediate. Following this argument, we can assume that for [our case] the energy difference [...] should be of the same order, [...]. Thus, the energetic difference between the 'allowed' and 'forbidden' reaction pathways might have virtually vanished*". From these quotes, we intend to make four following important points.

(1) First of all, Korth *et al.* are conscious that the system they base their reasoning on differs from our molecule because of the presence of phenyl groups;

(2) The very nature of the hypothetical diradical is not clear: is it a transition state or an intermediate? This constitutes a crucial difference! In both cases, it is possible to optimize the geometries and to identify the nature of the structure: if it is an intermediate, it must be a minimum of the potential energy surface. If it is a transition state, it should be a minimum along all internal coordinates except the reaction coordinate, along which it should reach a maximal energy. Since the early 1990's[7] methods have existed which allow finding of such intermediates or transition states as we shall show in the following section;

(3) Korth *et al.*, in their comments, admit that "*Numerous attempts to locate single-bond rotational transition states or biradical intermediates [...] have been unsuccessful*". Despite this, they



Scheme 2 Isomerization pathway.

suggest: "*However, a biradical pathway may still be feasible.*" based on the fact that multireference calculations should be performed.

(4) The argumentation concerning the diradical intermediate/transition state is only based on Roth's work. If Roth's arguments vanish (and we shall demonstrate in the following that they do), this diradical intermediate/transition state has no more reason to be considered.

The latter point deserves to be addressed. To do so, let us turn to Roth's work. This article deals with the opening of benzocyclobutene derivatives and the capture of NO.[8] It compares experiments and calculations. Three striking points may be noted in it:

(1) The diradical hypothesis is proposed in Scheme 10 on a methyl-substituted *o*-quinodimethane. Calculations seem to support the fact that both pathways, the rotatory process and a diradical process, are almost isoenergetic;

(2) The obvious stabilization effect of phenyl groups is emphasized "*Im Hinblick auf die höhere Stabilisierung von [the intermediate]*[6] *(Benzyl-Stabilisierung) gegenüber [a non phenyl substituted intermediate]*[6] *sollte der Enthalpie-Unterschied für kon- und disrotative Ringöffnung beim Diphenyl-Isomedeutlich kleiner sein.*"[9]

(3) The discussion about the nature of the intermediate/transition is the basis of the one formulated by Korth *et al.* as the following table shows.

(4) All calculations, on which Roth *et al.* base their reasoning, are performed with a force field extracted by Roth *et al.* in 1994 published in 1995.[11] This ambitious force field aimed at computing heats of formation of hydrocarbons with high accuracy taking into account the multireference character of their electronic structures through a valence bond based approach. We shall show in the following lines that this very ambitious approach is likely to fail in describing diradical rotations leading thus Roth to wrong conclusions, which annihilates Korth and coworker's view of the diradical intermediate/transition state.

(3) New insight into the evidence of a biradical transition state

Finally, we turn our attention to the results obtained with the MMEVBH force field in his seminal paper. As mentioned above, the ambition of this force field was very high and this is to be put to the credit of the authors. Yet, nowadays, very few methods, even based on quantum chemistry, would claim to be able to get very accurate results for a large family of diradical species. This is even truer when the diradical character of the electronic structure is not in the equilibrium geometry.

In order to definitively discard the diradical hypothesis, quantum mechanical methods should be employed to explicitly treat the electronic effects, while a force field does take into account electronic effects only implicitly. Using a method derived from the string method of Liotard,[7] we have computed the fully relaxed energy profile along the dihedral angle (Fig. 4 and 5),

Roth (1995)	Korth (1999)	Korth (2016)
Das hier vorgeschlagene Bild ist insofern verwirrend, als das orthogonale Diradikal 17 zwei Reaktionen [...] als Ubergangszustand zugesprochen wird, was der Definition des Ubergangszustandes widerspricht. Dieser Widerspruch verschwindet, wenn man akzeptiert, daβ das orthogonale Diradikal [...] nicht zwangslaufig ein Ubergangszustand sein muss[10]	A difficulty then arises in that 13 would thus represent a common transition state for two independent processes, (*E*,*Z*)-2 → (*Z*,*Z*)-2 and *meso*-1 → *rac*-1, an obvious contradiction to the definition of the transition state. Roth *et al.* circumvented this problem by arguing that the biradical structure derived from the (*E*,*Z*)-2 → (*Z*,*Z*)-2 process is not necessarily a transition state, but rather could be an intermediate. 13 would then represent a common intermediate of the (*E*,*Z*)-2 → (*Z*,*Z*)-2 and *meso*-1 → *rac*-1 reactions	Now the problem arises that on paper 8 would represent the same transition state for two different processes, namely nonconcerted benzocyclobutene ring opening and double bond rotation in an *o*-quinodimethane. This is obviously a contradiction to the definition of a transition state. It should be remembered, however, that a certain transition structure is characterized by the coordinates of all atoms, thus a transition state like 8 might indeed differ (different vibrational modes leading to the bond breaking/bond forming processes) for benzocyclobutene ring opening and *o*-quinodimethane double bond rotation. A further possibility to circumvent the contradiction is to assume that 8 is in fact a common intermediate for the two processes

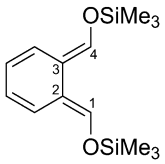


Fig. 4 Numbering of carbon atoms.

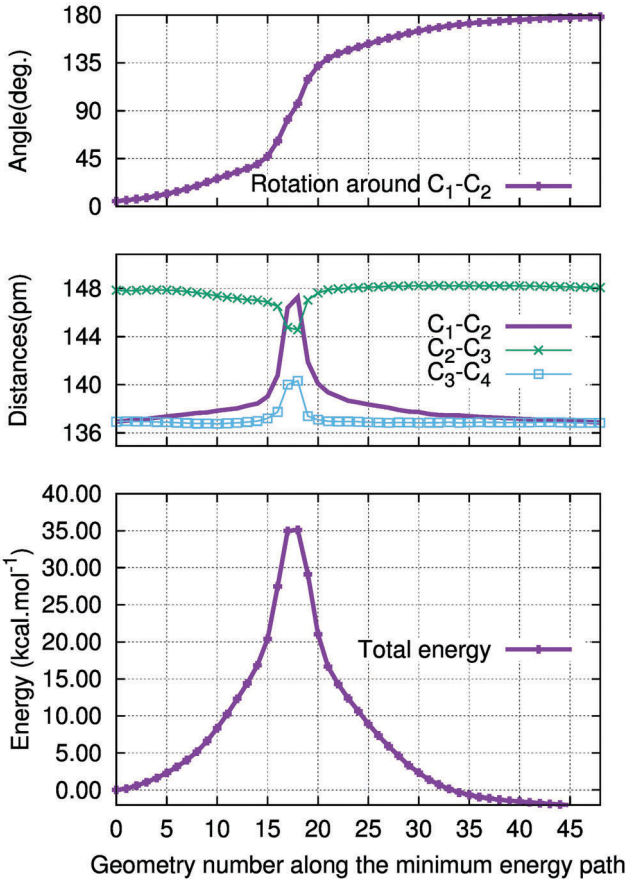
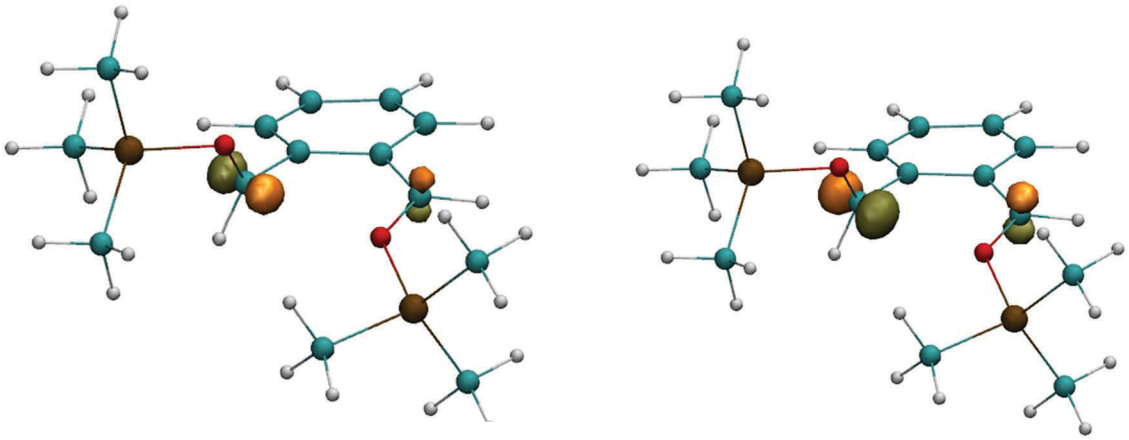


Fig. 5 Torsion angle (upper graph), bond lengths (middle graph) and total energy (graph at the bottom) along the rotation pathway.

which corresponds to the rotation suggested by Korth *et al.* By "fully relaxed", we mean that all geometrical parameters were optimized along the minimum energy pathway which connects the *E*,*Z* and *E*,*E*-isomers.

As can be seen from Fig. 5, the total energy admits a maximum in the 18th geometry. This point shall be considered as a transition state, as it is a maximum along one coordinate and a minimum along all the others. At this geometry, the rotation angle is 96.8° and the three investigated bonds admit an extremum: C3–C4 is 3.5 pm longer, C2–C3 is 3.5 pm shorter and C1–C2 bond increases by 10.4 pm (8% variation) with respect to the initial geometry. By this means, we obtain an activation energy of 35.1 kcal mol^{-1}. This value is to be compared to the activation energy of the opening, which we computed to be 26.8 kcal mol^{-1}. This 8.3 kcal mol^{-1} difference in activation energy leads to $t_{1/2}$ of the rotation process of 6.2×10^5 in favor of the opening at 40 °C.[12]

Along this minimum energy pathway calculation, the unrestricted calculation exhibits a large spin contamination at geometries 17 and 18 (⟨S^2⟩ is 0.84 and 0.96 for these two geometries).[13,14] Thus, a multireference calculation at the CASSCF(8,8) level was performed. In order to unambiguously determine the position of the two radicals, we analyzed the CASSCF wavefunction. Occupation numbers of the 8 natural orbitals of the CAS space are 2.0, 1.9, 1.9, 1.2, 0.8, 0.1, 0.1, and 0.0. Only the 4th and the 5th orbitals will be discussed as their occupation numbers express the open shell character of the wavefunction. As can be seen from Fig. 6, these orbitals show that one radical is on C1 and the other lies on C4. This can be understood by considering the electronic structure of this transition state as the electronic structure of the benzyl radical on one side (formed by the benzene ring and C4) and the radical alone on the other (on C1). Finally, the dynamic correlation was added on top of the CASSCF wavefunction by means of the NEVPT2 method. Both these methods agree quantitatively with our previous DFT calculations: the activation energy is found to be 42.5 kcal mol^{-1} at the CASSCF level and drops to 36.8 kcal mol^{-1} after addition of the NEVPT2 correction.[15]



culation with occupation number 1, 2 (left) and 0.8 (right).

Finally, at the end of their comment, H.-G. Korth and coworkers hammer home their point of view relative to the isomerization of benzocyclobutene nevertheless the advanced demonstration reveals a simplistic analysis. Thus, the final comment "*Evidence for such a process would be provided by observation of trans-**1** → cis-**1** isomerization in the absence of oxygen. From the free energy differences ΔG(**10c–9c**) = 1.3, ΔG(**10d–9d**) = 2.4 kcal mol*$^{-1}$ *(Table 1), a steady-state content (at 25 °C) of cis-1 in the 1–10% range can be expected. Such an amount should be easily detectable by high-field NMR.*"[17] is misleading. The statement "*a steady-state content at 25 °C of cis-**1** in the 1–10% range can be expected*" is based only on thermodynamic considerations and does not take into account kinetic controlled parameters.

III. Conclusion

We have experimentally and theoretically demonstrated that no isomerization could occur with our system despite the arguments advanced by Korth *et al.* We still believe that our EPR/spin trapping and theoretical studies are correct. In addition, new calculations were able to give an answer to the question, "is the biradical an intermediate or a transition state" together with the localization of the two radicals during a plausible rotation.

IV. Experimental section

Computational section

The minimum energy pathway search was done using the woelfling algorithm implemented in TURBOMOLE at the PBE/def2-TZVP level.[16–18] All multi-configurational calculations were performed with the RIJCOSX approximation with the def2-TZVP basis set and respective fitting basis as provided by ORCA.[19–21]

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2 The only relevant comment was the fact that we used the term "disrotatory" in place of "conrotatory" (Scheme 3 p7514 of ref. 1).

3 S. Dubois, F. Rodier, R. Blanc, R. Rahmani, V. Héran, J. Thibonnet, L. Commeiras and J.-L. Parrain, *Org. Biomol. Chem.*, 2012, **10**, 4712.

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5 J. G. Allen, M. F. Hentemann and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2000, **122**, 571.

6 The square brackets replace the notation used in the article in order to avoid confusion with the notation used in the current work.

7 D. A. Liotard, *Int. J. Quantum Chem.*, 1992, **44**, 723.

8 W. R. Roth, V. Rekowski, S. Börner and M. Quast, *Liebgs Ann.*, 1996, 409.

9 Translation into English: Because of the strong stabilization due to the phenyl groups, the reaction enthalpy for the con and disrotatory ring opening should be smaller for the diphenyl isomer.

10 Translation into English: The proposed hypothesis would be confusing if the orthogonal biradical 17 were considered as the transition state of two reactions, which is a contradiction to the definition of the transition state. This contradiction disappears if we accept that the orthogonal biradical must not necessarily be a transition state.

11 W. R. Roth, V. Staemmler, M. Neumann and C. Schmuck, *Liebigs Ann.*, 1995, 1061.

12
$$\frac{t_{1/2}^{\text{open}}}{t_{1/2}^{\text{rot}}} = \exp\left(\frac{E_{\text{A}}^{\text{open}} - E_{\text{A}}^{\text{rot}}}{RT}\right)$$

13 For all geometries, ⟨S^2⟩ is strictly 0.00.

14 For a better understanding see the video in the ESI†.

15 Concerning note number 15, in which a comment is made on the level of calculation we used, we shall mention the following points. First of all, it is interesting to note that in the studies of Korth *et al.*[3] the authors have used the semi empirical PM3 method that is, to date, unambiguously not reliable for a such study. Secondly, we did a careful benchmark of some functionals against CCSD(T)/def2-QZVP, which was recently published in the opening of benzocyclobutene derivatives (P. Nava and Y. Carissan, *Phys. Chem. Chem. Phys.*, 2014, **16**, 16196). It turns out that B3LYP gives the worst thermodynamic values in our set. This is the reason why the functional chosen was PBE0 and not B3LYP. Next, the authors state that multireference calculations should be done but, just like us, they provide DFT calculations only: CBS schemes are extrapolation schemes, which provide accurate results if, and only if, the method used (in this case DFT with the B3LYP functional) describes properly the physics of the system. We have shown that B3LYP was a poor choice.

16 TURBOMOLE V7.1 2016, a development of University of Karlsruhe and Forschungszentrum Karlsruhe GmbH, 1989–2007, TURBOMOLE GmbH, since 2007, available from http://www.turbomole.com.

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