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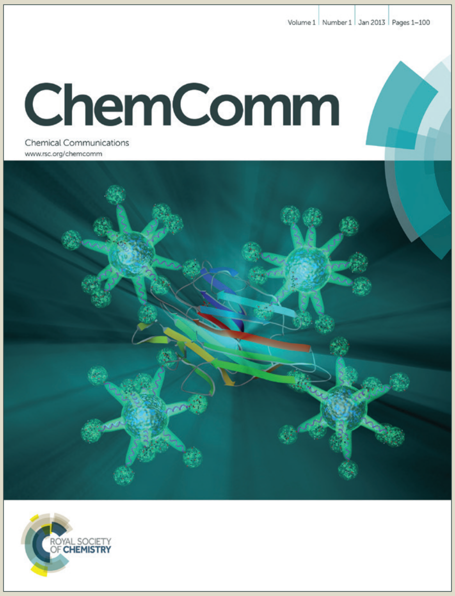

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Is it Possible to Achieve a Complete Desaturation of Cycloalkanes Promoted by *o*-Benzyne?

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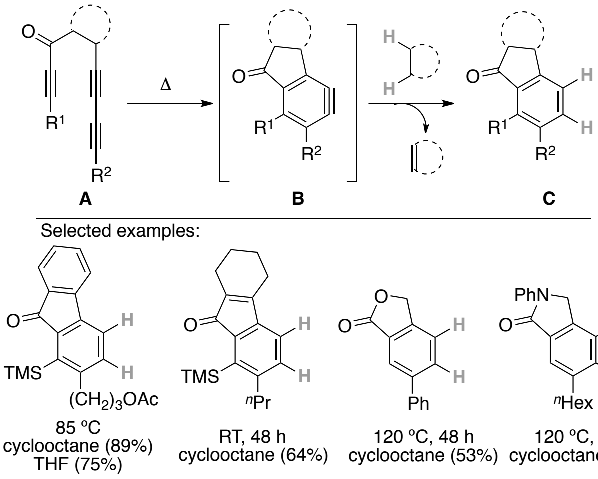
The competence between the possible reaction pathways in the reaction of different cycloalkanes and *o*-benzyne has been computationally explored. Systems able to undergo complete desaturation by consecutive double hydrogen atom transfer reactions are suggested.

Very recently, Hoye and co-workers reported an interesting process which leads to the desaturation of alkanes promoted by benzynes.[1] As shown in Scheme 1, species **B**, generated through a hexadehydro-Diels Alder (HDDA) reaction[2] of triyne **A**, is able to accept two vicinal hydrogen atoms from a suitable alkane 2H donor. As a result, the corresponding (oxidized) alkene and the (reduced) benzenoid species **C** are formed. This transformation is compatible with different HDDA-generated benzynes and cyclic alkanes or heterocycles (from cyclopentane or tetrahydrofuran to cyclooctane) and can even occur at room temperature, thus showing the synthetic usefulness and ease of the process.[1]

This transformation is suggested to occur through an intermolecular and simultaneous double hydrogen atom transfer from the cycloalkane to benzyne. Therefore, this process is analogous to other Double Group Transfer reactions (DGTR) like the double hydrogen atom migrations occurring from ethane to ethylene,[3] type-II dyotropic reactions,[4] the diimide reduction of double or triple bonds,[5] the Meerwein-Ponndorf-Verley reduction (MPV) of carbonyl groups,[6] and even the Noyori-type hydrogenations of polar double bonds.[7] All these $[\sigma 2_s+\sigma 2_s+\pi 2_s]$ transformations share a common feature, namely, they proceed concertedly and suprafacially on both reaction sites through an in-plane aromatic six-membered ring transition state.[3,8]

Considering the efficiency of the process described by Hoye and co-workers,[1] we hypothesized that, in the presence of an excess of benzyne, different cycloalkanes could be totally desaturated through consecutive double hydrogen atom transfers. For instance, cyclohexane could be converted directly into benzene, which would constitute an alternative to the production of benzene and aryl derivatives (typically carried out under expensive transition-metal catalysts in the chemical industry).[9] However, potential issues associated with using stoichiometric amounts of salts and/or costly highly activated intermediates must also be taken into account. A careful balance of arguments in favour and against of the potential of transition metals-free reactions is required in each case. As a consequence, exploring (and predicting) the potential of novel and alternative methods for the transition metal-free desaturation of alkanes is very relevant, aside from posing a tantalizing challenge to both experimental and theoretical chemists. To check the viability of this transition metal-free complete desaturation process, we carried out a computational study at the M06-2X/6-311+G(d,p) level[10] to explore the corresponding potential energy surfaces involving different cycloalkanes.



Scheme 1. HDDA-alkane desaturation cascade described by Hoye et al. (see reference 1).

We first investigated the envisioned conversion of cyclohexane (**1**) into benzene (**3**) in the presence of *o*-benzyne (**2**). The corresponding reaction profiles are shown in Figure 1, which gathers the relative gas-phase free energies computed at 298 K. In agreement with the findings by Hoye and co-workers,[1] cyclohexane is converted into cyclohexene (**4**) via transition state **TS**$_{1\text{-}4}$, which is associated with the concerted and synchronous double hydrogen atom migration from **1** to benzyne (**2**) with concomitant formation of one equivalent of benzene (**3**). A closer inspection of the geometry of **TS**$_{1\text{-}4}$ reveals that cyclohexane undergoes this transformation from its less stable boat conformation, which lies 4.9 kcal/mol over the corresponding chair conformation. This is due to the fact that the hydrogen atoms in the chair conformation are least disposed towards the required suprafacial transfer as compared to those in the boat form. Interestingly, this process occurs with a low activation barrier ($\Delta G^{\ddagger}$ = 23.0 kcal/mol) as compared to other intermolecular DGTRs reactions (typically $\Delta G^{\ddagger}$ > 40.0 kcal/mol) in a highly exergonic transformation (ΔG_R = –64.4 kcal/mol).[3] This can be ascribed to the relief of the ca. 50 kcal/mol of strain in *o*-benzyne, which constitutes the driving force for the process.

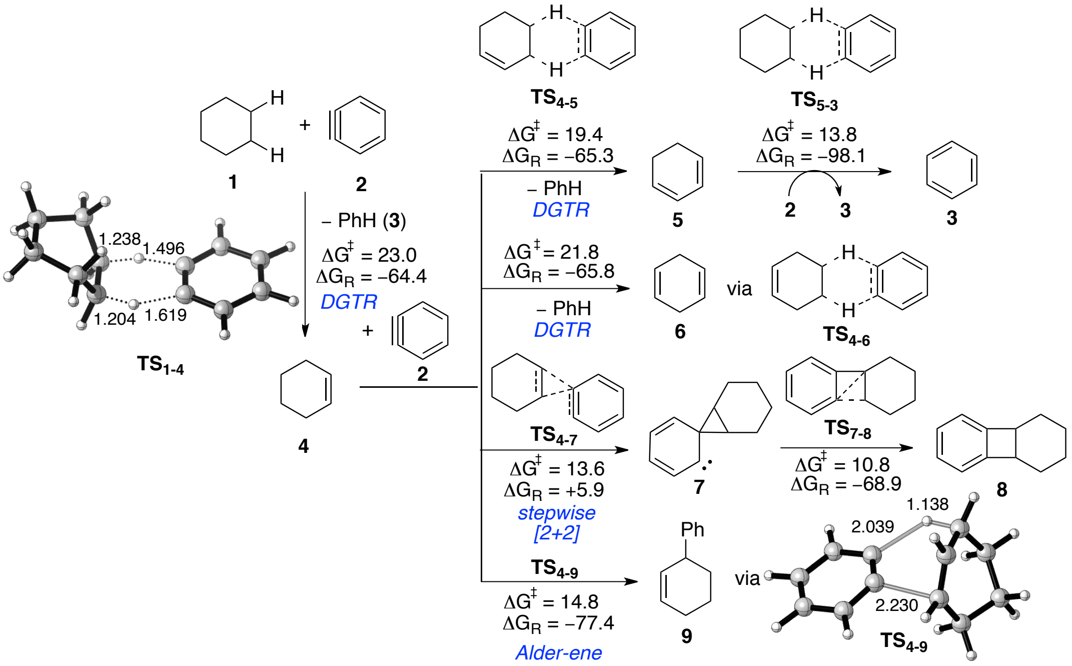


Figure 1. Computed reaction profile of the reaction between cyclohexane (**1**) and o-benzyne (**2**). Free energies (at 298 K) and bond distances are given in kcal/mol and angstroms, respectively. All data have been computed at the M06-2X/6-311+G(d,p) level.

Similarly, cyclohexene (**4**) can be transformed into 1,3-cyclohexadiene (**5**) by reaction with benzyne via **TS**$_{4\text{-}5}$. Interestingly, both the barrier and reaction energies are more favourable than those computed for the process involving cyclohexane. This is very likely due to the hyperconjugation in cyclohexene, which increases the HOMO-LUMO interaction thus leading to a lower barrier process.[11] Finally, 1,3-cyclohexadiene (**5**) evolves to benzene (**3**) via **TS**$_{5\text{-}3}$ in a process which involves a dramatic reduction of the computed barrier energy to only 13.8 kcal/mol. This is mainly ascribed to, besides the relief of the benzyne-strain, the formation of an additional aromatic benzene molecule, which is reflected in the high exergonicity (ΔG = –98.1 kcal/mol) computed for this final step. The gain of aromaticity and the benzyne-strain relief can be considered as the driving forces of the complete oxidation of cyclohexane into benzene promoted by *o*-benzyne.

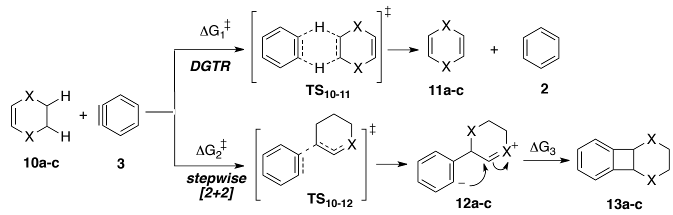
Despite that, different side-reactions can be envisaged in this cascade process, which may hamper the production of benzene from cyclohexane. For instance, once cyclohexene (**4**) is formed, it can alternatively undergo a similar DGTR with benzyne via **TS**$_{4\text{-}6}$ to produce 1,4-cyclohexadiene (**6**) instead of 1,3-cyclohexadiene (**5**). The exergonicity of this side-reaction is comparable to that associated with the formation of 1,3-cyclohexadiene, which highlights the stabilization provided by homoconjugation in **6**.[12] However, this process occurs with a higher activation barrier ($\Delta\Delta G^{\ddagger}$ = 2.4 kcal/mol), which translates into a **5**:**6** ratio of 98:2 (at 298.15 K). Therefore, the side reaction **4** → **6** seems to be not competitive against the **4** → **5** transformation.

Alternatively, it has been shown that acyclic alkenes present two additional modes of reaction with *o*-benzyne, namely the stepwise [2+2]-cycloaddition to produce benzocyclobutanes and Alder-ene reactions.[13,14] Our calculations indicate that both processes involving cyclohexene (**4**) proceed with lower activation barriers than the DGTR's leading to cyclohexadienes **5** or **6**. It is noteworthy that this kind of processes has been found in the environmentally relevant soot formation in hydrocarbon combustion.[15] In addition, the Alder-ene reaction is also the most thermodynamically favourable reaction channel (ΔG = –77.4 kcal/mol). This latter result suggests that 3-phenylcyclohexene (**9**) would be the main (or exclusive) product formed in the process. Our computational finding is in nice agreement with an early experimental study by Crews and Beard, which reported the exclusive formation of **9** in the reaction of *o*-benzyne (generated from benzenediazonium 2-carboxylate) and cyclohexene.[16] Therefore, the highly favourable Alder-ene reaction actually thwarts any hope for achieving the complete desaturation of cyclohexane to benzene.

This initial study involving cyclohexane encouraged us to investigate the divergent reaction channels for related cycloalkanes in order to find a system able to undergo the complete desaturation by consecutive DGTR's. In a first approach, the obvious solution to prevent the undesired Alder-ene reaction consists of replacing the allylic hydrogen atoms in cyclohexene by atoms or groups unable to be transferred to benzyne. Thus, 2,3-dihydro-1,4-dioxine (**10a**), formed upon initial DGTR from 1,4-dioxane ($\Delta G^{\ddagger}$ = 26.6 kcal/mol, ΔG_R = −67.8 kcal/mol), was then considered.

From the data in Table 1, it can be seen that the initial step for the formal [2+2]-cycloaddition is clearly kinetically favoured over the DGTR ($\Delta\Delta G^{\ddagger}$ = 14.3 kcal/mol). Note that this reaction does not lead to the formation of a spiranic carbene intermediate as it occurs with cyclohexane (intermediate **7**, Figure 1) but to a zwitterionic species (**11**) as a consequence of the nucleophilic addition induced by the lone-pair of the oxygen atom. In order to make this initial nucleophilic attack more difficult, we also considered compounds **10b** and **10c**, where the nitrogen atoms are directly attached to electron withdrawing groups. However, a kinetic bias towards the formation of the corresponding benzocyclobutenes ($\Delta\Delta G^{\ddagger}$ = 11.9 and 10.2 kcal/mol) is also predicted in these systems. Despite that, it is noteworthy that the DGTR is favoured under thermodynamic control, particularly for tetrahydropyrazines **10b** and **10c** ($\Delta\Delta G_R$ = −2.0 and −6.7 kcal/mol, respectively). This is due to the endergonicity computed for the nucleophilic addition reaction (ΔG_R = +8.8 to +11.8 kcal/mol, see Table 1) in spite of the exergonicity of the subsequent ring closure forming benzocyclobutanes **13**.

Table 1. Possible reaction pathways for the reaction of compounds **10a-c** and *o*-benzyne.[a]

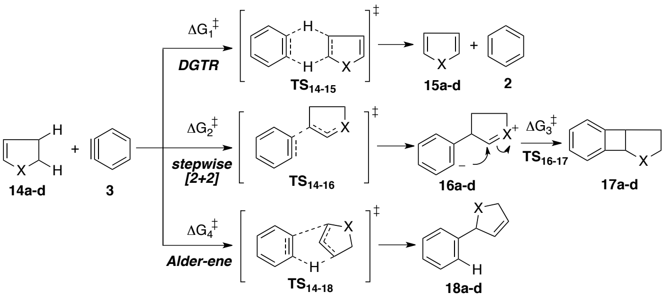


X	$\Delta G_1^{\neq}$ ($\Delta G_{R,1}$)	$\Delta G_2^{\neq}$ ($\Delta G_{R,2}$)	($\Delta G_{R,3}$)
O (**10a**)	29.1 (-60.8)	14.8 (+11.8)	(-70.9)
NCF_3 (**10b**)	25.2 (-61.8)	14.0 (+10.7)	(-70.5)
NCO_2Me (**10c**)	22.1 (-65.5)	11.9 (+8.8)	(-67.6)

[a] All data have been computed at the M06-2X/6-311++G(d,p) level.

The latter result suggests that the DGTR leading to the complete desaturation can be favoured by increasing the thermodynamic stability of the corresponding dehydrogenated product. In this sense, we considered the formation of five-membered heteroaromatic rings (Table 2). At variance with the six-membered rings considered above, in these cases the Alder-ene reaction channel must be taken into account as well.

Table 2. Possible reaction pathways for the reaction of compounds **14a-d** and *o*-benzyne.[a]



X	$\Delta G_1^{\neq}$ ($\Delta G_{R,1}$)	$\Delta G_2^{\neq}$ ($\Delta G_{R,2}$)	$\Delta G_3^{\neq}$ ($\Delta G_{R,3}$)	$\Delta G_4^{\neq}$ ($\Delta G_{R,4}$)
O (**14a**)	15.4 (-82.3)	9.7 (+3.2)	2.5 (-69.1)	14.3 (-75.6)
NCF_3 (**14b**)	15.8 (-83.0)	11.4 (+3.2)	2.1 (-70.0)	15.6 (-75.6)
NCO_2Me (**14c**)	15.8 (-81.6)	9.8 (+2.8)	2.6 (-68.0)	14.1 (-75.9)
$N^+(H)CF_3$ (**14d**)	16.5 (-58.0)	–	–	14.2 (-84.4)

[a] All data have been computed at the M06-2X/6-311++G(d,p) level.

From the data in Table 2, it becomes clear that again the stepwise formal [2+2]-cycloaddition of the initial cyclic alkenes **14a-c**, formed through a DGTR between benzyne and the corresponding tetrahydro-derivative, is kinetically favoured over the DGT and Alder-ene reactions (which exhibit similar reaction barriers, $\Delta G^{\ddagger}$ ca. 15 kcal/mol). Interestingly, whereas the barrier computed for the Alder-ene reactions remains practically unaltered (a similar barrier of 14.8 kcal/mol was also computed for cyclohexene, see Figure 1), the barrier for the DGTR strongly depends on the nature of the initial cycloalkene ($\Delta G^{\ddagger}$ ranging from 29.1 kcal/mol for **10a** to 19.4 kcal/mol for cyclohexene and to only 15.4 kcal/mol for **14a**). In addition, the gain in aromaticity by forming heterocycles **15** is reflected in the remarkable exergonicity ($\Delta G_{R,1} > -80$ kcal/mol) computed for these DGTR's. As a result, this makes the DGTR the thermodynamically preferred transformation over the [2+2] and Alder-ene reactions. Hence, it can be concluded that the complete desaturation leading to highly valuable chemicals like furan (**15a**) or pyrroles (**15b-c**) via consecutive DGTR's might be achieved by fine-tuning of the experimental reaction conditions. Of course, these aromatic species are known to undergo a Diels-Alder reaction with a new molecule of benzyne[17,18] (if available) therefore forming the corresponding tricyclic 1,4-dihydronaphtalene derivatives, which would constitute the final reaction products experimentally observed.[19]

In a final attempt to suppress the kinetically favoured nucleophilic addition leading to zwitterions **16**, we protonated the nitrogen atom in **14b** and considered the processes involving cation **14d**. However, although the [2+2]-reaction is hampered (all attempts to locate the corresponding transition state met with no success), the Alder-ene process becomes now the most favourable process under both kinetic and also thermodynamic control, as a consequence of the aromaticity loss in **15d** by protonation (see Table 1).

Our computational study clearly shows that, rather than producing benzene, three different reaction products may be formed in the reaction of cycloalkanes and *o*-benzyne. These products include, benzocyclobutanes derived from a formal stepwise [2+2]-cycloaddition reaction, products derived from Alder-ene reactions and complete unsaturated products as a result of consecutive double hydrogen atom transfer reactions. The preference for a reaction channel over the others strongly depends on the nature of the initial cycloalkane as well as on the thermodynamic stability of the reaction products. Indeed, it has been found that although DGTR's are, in general, not kinetically preferred, the unsaturated compounds are the products formed under thermodynamic control, particularly for typical five-membered heteroatomic rings such as furan or pyrrole-derivatives. In our opinion, the results herein described may serve as a guide for experimentalists in order to achieve a transition-metal free complete desaturation of cycloalkanes.

Acknowledgments

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Notes and references

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† Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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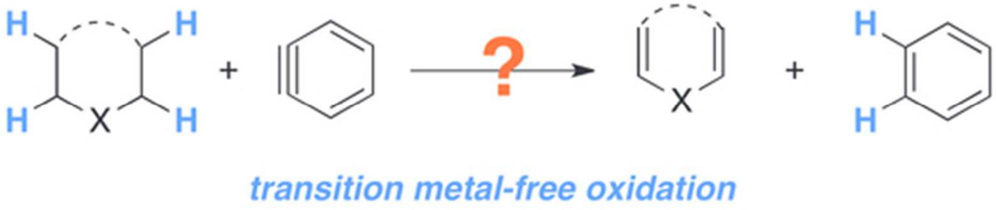

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