Alkane desaturation by concerted double hydrogen atom transfer to benzyne

Dawen Niu1, Patrick H. Willoughby1, Brian P. Woods1, Beeraiah Baire1 & Thomas R. Hoye1

The removal of two vicinal hydrogen atoms from an alkane to produce an alkene is a challenge for synthetic chemists1–3. In nature, desaturases and acetylenases are adept at achieving this essential oxidative functionalization reaction, for example during the biosynthesis of unsaturated fatty acids4, eicosanoids, gibberellins5 and carotenoids6. Alkane-to-alkene conversion almost always involves one or more chemical intermediates in a multistep reaction pathway; these may be either isolable species (such as alcohols or alkyl halides) or reactive intermediates (such as carboxations, alkyl radicals, or σ-alkyl-metal species). Here we report a desaturation reaction of simple, unactivated alkanes that is mechanistically unique. We show that benzyne precursors are capable of the concerted removal of two vicinal hydrogen atoms from a hydrocarbon. The discovery of this exothermic, redox-neutral process was enabled by the simple thermal generation of reactive benzynes from suitable substrates through the hexadehydro-Diels–Alder cycloisomerization of triyne substrates. We are not aware of any single-step, bimolecular reaction in which two hydrogen atoms are simultaneously transferred from a saturated alkane. Computational studies indicate a preferred geometry with eclipsed vicinal C–H bonds in the alkene donor.

 Arynes7–9 engage in myriad trapping reactions that functionalize adjacent sp-hybridized carbons in the π-aryne ring. We recently reported a general strategy for the formation and subsequent in situ trapping of benzynes by means of the hexadehydro-Diels–Alder (HDDA) reaction10,11,12. The simplest imaginable variant (Fig. 1b) is the reaction of 1,3-butadiyne (2) with ethyne (1, the diynophile) to produce o-benzylene (3). The free energy change for this process is computed to be exothermic by approximately 50 kcal mol−1 (refs 6, 12). Trapping of 3 permits the synthesis of many useful benzene derivatives (4). In practice (Fig. 1c), the HDDA cycloisomerization is effected intramolecularly simply by heating a tethered triyne substrate such as 5 to produce a fused bicyclic benzyne intermediate such as 6. Trapping leads to a highly substituted benzenoid product such as 7. In addition to the preparative value of this 2H transfer reaction, the HDDA reaction provides the opportunity to uncover previously unprecedented aryne trapping modes13,14 (for example, the insertion of the aryne into the silyl ether bond as in Fig. 1a). We now report a 2H transfer reaction in which the HDDA-generated benzyne simultaneously accepts two vicinal hydrogen atoms from a suitable 2H donor substrate (H–Csp3–Csp3–H). This gives the corresponding (oxidized) alkene and (reduced) benzenoid products.

For example, when we heated triyne 8 in cyclooctane to 85 °C, the only isolated product (89%) was the reduced fluorenone derivative 10-h2, 10-d2 (Fig. 2a, b). Using 1H NMR spectroscopy, we observed that a comparable amount of cyclooctene had been formed by desaturation15 (see Fig. 3b). The only well-characterized example of benzene reduction by means of the net addition of two hydrogen atoms is a previous study6 in which a benzene intermediate derived from a bis-diynyl-bridged, dinuclear metal complex was reduced to the arenne. They demonstrated that the solvent (tetrahydrofuran; THF) was the source of the hydrogen (and, in the case of 10-h2, deuterium16) atoms that appeared in the reduced benzenoid product. When we heated substrate 8 in THF-h2, 10-h2 was the only product isolated (75%, Fig. 2a, b). Similarly, when 8 was heated in THF-d2, the dideuterated analogue 10-d2 (mass spectrometry and 1H NMR) was the only product isolated.

To probe the mechanism of this process further and, in particular, to distinguish between pathways involving sequential hydrogen atom abstractions from two solvent molecules versus a transfer of two hydrogen atoms from a single molecule, we repeated the generation and trapping of benzylene 9, this time in the presence of an equimolar mixture of THF-h2 and THF-d2. Intriguingly, only the dideuterobenzenoid and dideuterobenzenoid products 10-h2 and 10-d2 were produced; none of the mono-H/mono-D analogue (10-hd) was detected. The observed 10-h2:10-d2 product ratio was 6:1, indicating a significant H/D kinetic isotope effect for the 2H transfer. In a complementary experiment, we used a 1:6 molar ratio of THF-h2:THF-d6, which gave a nearly 1:1 ratio of products 10-h2:10-d2. The lack of an observable level of monodeuterated...
product in any of these experiments is consistent with the concerted transfer to the benzynic of two hydrogen atoms from a single THF molecule as represented in the depiction of the transition structure 11 (Fig. 2c). Although such a description might seem unusual, it can be noted that the generally accepted mechanism for the reduction of alkynes by diimide (HN=NH) and for dyotropic reactions in which two hydrogen atoms are shuffled intramolecularly involves a similar simultaneous transfer.

We next screened a series of cyclic hydrocarbons to explore their relative ability to engage an aryne in a similar hydrogen transfer reaction (Fig. 3). We were surprised to observe that cyclohexane was significantly less efficient than the other cycloalkanes in its reduction of the benzynoid 10-h2, b. Isotope profiling using THF-h8. THF-d8 and mixtures thereof shows that both hydrogen atoms in the product originate from a single molecule of 2H donor. Asterisk, mono-deuterated product (10-hd) was not observed (1H NMR analysis; estimated limit of detection was 6%). c. Representation (11) of simultaneous double hydrogen transfer between an aryne and a THF molecule. Analogous six-atom arrays are involved in the transition structures of 2H transfer by diimide to an aryne acceptor and in the class of intramolecular reorganizations known as dyotropic reactions.

The ratio of the alkene resonances of cyclooctene to cyclopentene (adjusted for the molar ratio of solvents) provides the relative rate ratio (krel) between the two hydrocarbon donors (2.6 for this example). The relative intensity of alkene to arene resonances (from 14) as well as the absence of resonances indicative of aromatic by-products shows the overall cleanliness of the reaction.

As stated earlier, cyclohexane (Fig. 3a, entry 5 in the inset table) is a considerably poorer 2H donor than the other cyclic hydrocarbons (entries 1–4). We speculated that this implies a preference for an eclipsed conformation, is least disposed towards transfer of two of its hydrogen atoms, whereas the other hydrocarbons all have low-lying conformers with norbornene comprises a strained alkene.

Next, using density functional theory (DFT) methods (see Supplementary Information) we computed the transition structure geometry and the free energy of activation (ΔG‡) for the double hydrogen atom transfer between o-benzene (3) and each of the seven cyclic donors shown in entries 1–7 (Fig. 3a). For all 2H donors the calculations indicate a relatively early transition structure (for example, compare the two distances shown in 15a). This is consistent with the highly exothermic nature of the 2H transfer step (for example, we computed the free energy of reaction to be −65.6 kcal mol⁻¹ for o-benzene (3) + cyclopentane to benzene + cyclopentene). The computed geometries for the cyclopentane and cyclohexane transition structures (15a and 15b) are shown in Fig. 3c. It is not accidental that the energy difference between the chair and boat conformers of cyclohexane (approximately 6 kcal mol⁻¹) is similar to the computed difference in ΔG‡ between 15a.
and (the boat-like) 15b. The $\Delta G^2$ values computed for all seven donors are given in the inset table in Fig. 3a. There is a remarkably good correlation between the computed $\Delta G^2$ values and the observed $k_{rel}$ values. These observations are most consistent with the idea of substantial dependence on dihedral angle for the process, which can only be true if the double hydrogen atom transfer event is concerted.

Products 16a–g (Fig. 3d) arose from incubating the corresponding triyne precursor (inferred from the dashed line in each structure; see Supplementary Information for details) in cyclooctane under the indicated conditions. Notable features include the following: a variety of functional groups, present in both the triyne precursor and benzyne product, are readily tolerant of these benign reducing conditions; benzyne representatives a breadth of electronic activation and/or perturbation engage in the reaction; most of the products 16 represent a breadth of electronic activation and/or perturbation. Notable features include the following: a variety of hydrocarbon (and cyclic ether) 2H donors for the reduction of arynes in cyclooctane under the indicated conditions (starting substrate concentration 10 mM). RT, room temperature; Ts, toluenesulfonyl; TMS, trimethylsilyl; TIPS, triisopropylsilyl; $^3$Pr, n-propyl; $^3$Hex, n-hexyl.

Finally, an ancillary but important practical consideration has emerged. The most common method for generating simple benzyne derivatives, italicized H3 and H4 denote the resonances for the newly introduced pair of hydrogen atoms to benzyne. This is consistent with both the results reported above for the relative efficiencies of THF and 1,4-dioxane in cyclooctane (approximately 25 equivalents). We suggest that all traditional benzyne generation methods performed in the presence of a potential 2H donor (most typically, THF) are at risk to the unwanted, benzyne-depleting, 2H transfer process, especially when the benzyne trapping event is inherently slow. Indeed, we infer that this has already been encountered. Recent reports show THF to be an inferior medium (compared with 1,4-dioxane or diethyl ether) for some benzyne trapping reactions. This is consistent with both the results reported above for the relative efficiencies of THF and 1,4-dioxane as a 2H donor (Fig. 3a, entries 6 and 7 in the inset table), and also our arguments for angle dependence during the 2H transfer.

Figure 3 | Dihydrogen transfer between arynes and cyclic hydrocarbons. a, Relative efficiency (percentage yield and $k_{rel}$ compared with cyclopentane) of various hydrocarbon (and cyclic ether) 2H donors for the reduction of arynes to benzenoid products, are readily tolerant of these benign reducing conditions; benzyne represents a breadth of electronic activation and/or perturbation engagement in the reaction; most of the products 16 represent a breadth of electronic activation and/or perturbation.

| Entry | 2H donor | Yield (%) | $k_{rel}$ | $\Delta G^2$ (kcal mol$^{-1}$) |
|-------|----------|-----------|---------|-----------------------------|
| 1     | Cyclooctane | 97%       | 2.6     | 17.6                         |
| 2     | Cycloheptane | 94%       | 2.3     | 17.7                         |
| 3     | Cyclopentane | 84%       | 1.0     | 18.7                         |
| 4     | Norbornane  | 66%       | 0.60    | 18.5                         |
| 5     | Cyclohexane | 20%       | 0.01    | 24.1                         |
| 6     | THF        | 60%       | 0.4     | 19.2                         |
| 7     | 1,4-Dioxane | 0%        | –       | 27.1                         |

| Entry | 2H donor | Yield (%) | $k_{rel}$ |
|-------|----------|-----------|-----------|
| 1     | Cyclooctane | 97%       | 2.6       |
| 2     | Cycloheptane | 94%       | 2.3       |
| 3     | Cyclopentane | 84%       | 1.0       |
| 4     | Norbornane  | 66%       | 0.60      |
| 5     | Cyclohexane | 20%       | 0.01      |
| 6     | THF        | 60%       | 0.4       |
| 7     | 1,4-Dioxane | 0%        | –         |

**LETTER**

**RESEARCH**

**Macmillan Publishers Limited. All rights reserved**
We have described the essential mechanistic features of a double hydrogen atom transfer process. Both (vicinal) hydrogen atoms come from the same donor molecule. There is substantial dependence on dihedral angle; donors with a greater degree of eclipsing among their low-energy conformers are more reactive. This is reinforced by the nearly planar geometry of the six reacting atoms in the computed transition structures. Our observations support a pathway in which both hydrogen atoms are transferred simultaneously from the saturated alkane to the benzyne carbon atoms—a process that could be viewed as a metal-free, double C–H activation event.²⁶

METHODS SUMMARY

A typical double hydrogen atom transfer reaction comprised heating a solution of HDDA triyne precursor (substrate) in cyclooctane (approximately 0.01 M) in a closed glass reaction vessel (for example, a screw-capped vial or culture tube). After the specified time, the reaction mixture was loaded directly onto a bed of silica gel and eluted first with hexanes to remove the excess cyclooctane and then with ethyl acetate to capture the reduced benzenoid products. These were further purified by chromatography on silica gel. Relative rate data (Fig. 3a, b) were collected by ¹H NMR spectroscopy at 300 MHz using No-D NMR²² and quantitative NMR²² techniques. Details are given in Supplementary Information. Details for the preparation of all new compounds, their full spectroscopic characterization data and the computational methods used are also provided in Supplementary Information.

Received 9 March; accepted 18 July 2013.

1. Linstead, R. P., Braude, E. A., Mitchell, P. W. D., Woolridge, K. R. H. & Jackman, L. M. Transfer of hydrogen in organic systems. Nature 169, 100–103 (1952).
2. Bloomfield, D. K. & Bloch, K. The formation of 1H NMR spectroscopy at 500 MHz using No-D NMR²² and quantitative NMR²² techniques. Details are given in Supplementary Information. Details for the preparation of all new compounds, their full spectroscopic characterization data and the computational methods used are also provided in Supplementary Information.
3. Bhattacharya, A. Characterization of the fungal gibberellin desaturase as a 1,2-aryne intermediate with a silver catalyst. J. Am. Chem. Soc. 135, 4668–4671 (2013).
4. Voica, A.-F., Mendoza, A., Gutekunst, W. R., Fraga, J. O. & Baran, P. S. Guided desaturation of unactivated aliphatics. Nature Chem. 4, 629–635 (2012).
5. Tsui, J. A. & Sternenberg, B. T. A metal-templated 4 + 2 cycladdition reaction of an alkyne and a diyne to form a 1,2-aryne. Angew. Chem. Int. Ed. 52, 2–4 (2013).
6. Moran, N. A. & Jarvik, T. Lateral transfer of genes from fungi underlies carotenoid growth. J. Nat. Prod. 72, 1211–1214 (1993).
7. Hoffmann, R. W. & Suzuki, K. A 'hot, energized' benzyne. J. Am. Chem. Soc. 119, 9917–9918 (1997).
8. Paul, G. F., Jak, B. & Lankin, D. A. Routine experimental protocol for qHNMR transfer reactions. J. Org. Chem. 74, 9480–9481 (2009).
9. Corey, E. J., Pasto, D. J. & Modk, W. L. Chemistry of diimide. II. Stereochemistry of hydrogen transfer to carbon–carbon multiple bonds. J. Am. Chem. Soc. 83, 2957–2958 (1961).
10. Miyawaki, K., Suzuki, R., Kawano, T. & Ueda, I. Cycloaromatization of a non-dehydro-Diels–Alder reaction. Tetrahedr. Lett. 35, 353–357 (1961).
11. Bradley, A. Z. & Johnson, R. P. Thermolysis of 1,3,8-nonatriyne: evidence for intramolecular [2 + 4] cycloaromatization to a benzene intermediate. J. Am. Chem. Soc. 119, 9917–9918 (1997).
12. Hoffman, R. W. & Suzuki, K. A 'hot, energized' benzyne. Angew. Chem. Int. Ed. 52, 2–4 (2013).
13. Hoffmann, R. W. & Suzuki, K. A 'hot, energized' benzyne. Angew. Chem. Int. Ed. 52, 2–4 (2013).
14. Yun, S. Y., Wang, K.-P., Lee, N.-K., Mamidipalli, P. & Lee, D. Alikane C–H insertion by arylene intermediates with a silver catalyst. J. Am. Chem. Soc. 135, 4668–4671 (2013).
15. Voica, A.-F., Mendoza, A., Gutekunst, W. R., Fraga, J. O. & Baran, P. S. Guided desaturation of unactivated aliphatics. Nature Chem. 4, 629–635 (2012).
16. Tsui, J. A. & Sternenberg, B. T. A metal-templated 4 + 2 cycladdition reaction of an alkyne and a diyne to form a 1,2-aryne. Angew. Chem. Int. Ed. 52, 4906–4908 (2009).
17. de Almeida, G., Townsend, L. C. & Bertozzi, C. R. Synthesis and reactivity of dibenzoelenacyclopentynes. Org. Lett. 15, 3038–3041 (2013).
18. Hüning, S., Müller, H. & Thier, W. Reductions mit diimid. Tetrahedr. Lett. 2, 353–357 (1961).
19. Corey, E. J., Pasto, D. J. & Modk, W. L. Chemistry of diimide. II. Stereochemistry of hydrogen transfer to carbon–carbon multiple bonds. J. Am. Chem. Soc. 83, 2957–2958 (1961).
20. Fernández, I., Siess, F. P. & Sierra, M. A. Dyotropic reactions: mechanisms and synthetic applications. Chem. Rev. 109, 6687–6711 (2009).
21. Fernández, I., Siess, M. A. & Cassio, F. P. In-plane aromaticity in double-group transfer reactions. J. Org. Chem. 72, 1488–1491 (2007).
22. Hoye, T. R., Eklov, B. M., Ryba, T. D., Voloshin, M. & Yao, L. J. No-D NMR (no deuterium proton NMR spectroscopy: a simple yet powerful method for analyzing reaction and reagent solutions. Org. Lett. 6, 953–956 (2004).
23. Himeshima, Y., Sonoda, T. & Kobayashi, H. Fluoride-induced 1,2-elimination of o-trimethylsilylphenyl triflate to benzyne under mild conditions. Chem. Lett. 12, 1211–1214 (1983).
24. Ma, Z.-X., Feltenberger, J. B. & Hsung, R. P. Total syntheses of chelidonine and norchelidonine via an enamide–benzyne–[2+2] cycladdition cascade. Org. Lett. 14, 2742–2745 (2012).
25. Sumida, Y., Kato, T. & Hosoya, T. Generation of arynes via ate complexes of aryloboronic esters with an ortho-leaving group. Org. Lett. 15, 2806–2809 (2013).
26. Davies, H. M. L., Du Bois, J. & Yu, J.-Q. C–H functionalization in organic synthesis. Chem. Soc. Rev. 40, 1855–1856 (2011).
27. Paul, G. F., Jak, B. & Larkin, D. A. Routine experimental protocol for qHNMR illustrated with taxol. J. Nat. Prod. 70, 589–595 (2007).
28. Author Contributions D.N. made the initial key observations and performed most of the scope studies. P.H.W. performed most of the mechanistic studies. B.P.W. and B.B. also performed aspects of the experimental work. All authors interpreted the data and wrote the manuscript.
29. Author Information Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Correspondence and requests for materials should be addressed to T.R.H. (hoye@umn.edu).