Reduction of Benzenes

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Electron Transfer to Benzenes by Photoactivated Neutral Organic Electron Donor Molecules**

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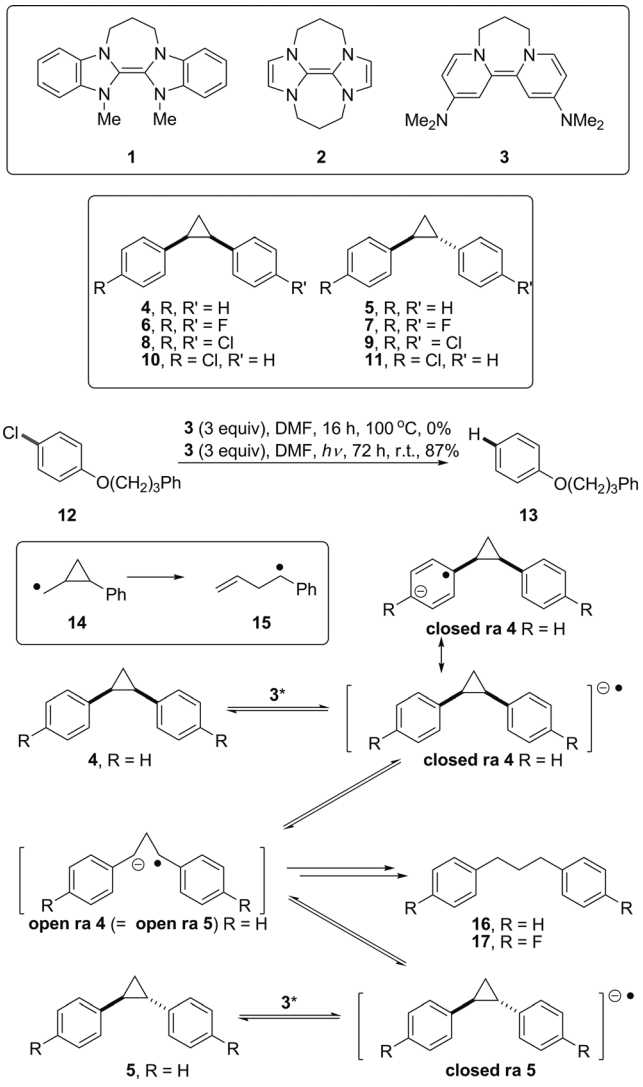
Benzene ($E^0 = -3.42$ V vs. a saturated calomel electrode, SCE[1]) and its close analogs are among the most challenging organic substrates for reduction. Very few chemical entities have the power to add an electron to ground-state benzene, and these are all derived from highly reactive metals. Thus, the alkali metals sodium ($E^0 = -2.71$ V) and lithium ($E^0 = -3.04$ V) dissolve in liquid ammonia to form solvated electrons together with the corresponding metal cations,[2] and similarly calcium ($E^0 = -2.89$ V) and lithium dissolve in aliphatic amines.[3] These solvated electrons can convert benzene to its radical anion. In the Birch reduction, a protonation step follows for the arene radical anion, but this step is independent of the electron-rich metal. Very recently, a complex derived from samarium(II) iodide, also in the presence of an amine, joined this exclusive set of reagents, in the reduction of the substrate, 4-methoxybenzyl alcohol.[4,5] We now explore whether a completely organic molecule can convert close analogs of benzene to their radical anions, mirroring the behavior of the metals described above. The choice of arene substrate determines the level of the challenge. E^0 values are not routinely available for benzenes,[1] other than those activated by electron-withdrawing groups. However, comparison of the computed lowest unoccupied molecular orbital (LUMO) energies of a range of arenes shows[6] (see Table S1 in the Supporting Information) that benzenes substituted by saturated carbon groups have LUMO energies that lie within 0.2 eV of the value for benzene itself. In contrast, both extended arenes and arenes substituted by electron-withdrawing groups (e.g. CN, CO_2Me) have much lower LUMO energies and are much easier to reduce. Accordingly, in choosing a discriminating test for a reducing agent, the latter substrates are not appropriate. We have chosen 1,2-diphenylcyclopropanes **4** and **5** and their derivatives **6**–**11** as the substrates for our study. Both **4** and **5** have LUMO energies within 0.2 eV of that of benzene, are relatively involatile, and can report the intermediacy of radical anions through the opening of the cyclopropane ring (see Scheme 1).

Our recent research has probed the ground-state donor properties of highly reactive neutral organic reducing agents. Thus, we have shown that the neutral ground-state organic electron donor **1**[7,8] (Scheme 1) reduces iodoarenes[9,10] to aryl radicals[11] while the stronger donors **2**[12] and **3**[13] under milder conditions, afford aryl anions from the same substrates



Scheme 1. Reactions of organic electron donors with substrates.

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through transfer of two electrons. These donors also reduce sulfonamides, acyloin derivatives, and Weinreb amides.[13]

Nevertheless, our efforts to reduce more challenging arenes, for example, chlorobenzenes, had been unsuccessful, and so this was the starting point for studies with the photoactivated donor **3**.

Donor **3** is deep purple in color with absorption maxima at 260, 345, and 520 nm and so is susceptible to near-UV excitation. A carousel arrangement of 12×8 W F8T5-BLB lamps with emission at 365 nm was selected for the initial set of experiments with **3**. The emission spectrum of these lamps shows good overlap with the absorption of donor **3** centered at 345 nm (see the Supporting Information). To set a benchmark for the photoactivation process, substrate **12** was selected for reaction with donor **3**. Previous experiments had shown that in the presence of **3** (3 equiv) at 100 °C, but with no irradiation, no reduced product **13** was produced; instead, 95 % of the starting material **12** was recovered. In the current work, irradiation at room temperature in the presence of donor **3** now led to the reduced product **13** in 87 % yield (see Scheme 1). Blank reactions determined that the chloride **12** did not react under these irradiation conditions, in the absence of donor **3**. This successful reductive dechlorination encouraged us to explore whether the photoexcited donor **3** might be capable of transferring an electron to the more challenging non-halogenated benzenes.

Phenylcyclopropylcarbinyl radicals, for example, **14** have previously been used as probes for very fast radical reactions by the teams of Newcomb[14a] and Ingold[14b] through diagnostic ring-opening to phenylbutenyl radicals **15**. Our plan was to take a single isomer of 1,2-diphenylcyclopropane, for example, **4** and to use the excited donor **3** to transfer an electron to it to afford the radical anion, **ra 4**, and then to monitor the outcome of the experiment for formation of the ring-opened product **16** or for partial equilibration of the stereochemistry of the initial isomer.[15–17] The ring-opening of closed **ra 4** to open **ra 4** should be fast, but the fate of open **ra 4** was not certain. Since back electron transfer is common in photochemical processes, the cyclopropane could form again from open **ra 4**. However, since the 3-carbon chain in open **ra 4** should be conformationally fluid, the stereochemical purity of the re-formed cyclopropane should be diminished. Alternatively, the open radical anion **ra 4** could 1) receive another electron to become a dianion, or 2) abstract a proton or a hydrogen atom, on its way to the diarylpropane **16**. The *cis*-isomers of 1,2-diarylcyclopropanes **4**, **6**, and **8** and their respective *trans*-isomers **5**, **7** and **9**, were prepared from known stilbenes. Irradiation of each separate isomer with donor **3** (Table 1, entries 1–4) was undertaken in inert atmosphere and, for each irradiation, a blank experiment (in which no donor **3** was present) was conducted simultaneously by placing two otherwise identical vessels in the irradiation chamber at the same time. The products were monitored by ^{1}H NMR spectroscopy, which was used for both quantitation and identification of the products. The product identities were confirmed by GCMS in these experiments.

With the 1,2-diphenylcyclopropane study, the *cis* starting material represented as **4** contained a 2:98 ratio of the *trans*:*cis* isomers **5**:**4**. The blank experiment performed in the absence of donor **3** afforded an unchanged 2:98 ratio of these isomers, while the product of irradiation in the presence of donor **3** afforded a 19:81 ratio (79 % recovery) as shown in Table 1 (entry 1) together with the entries for the other substrates **5**, **6**, and **7**. All the isomers show stereomutation, with the effects being more pronounced for the *cis*-substrates, as expected.

The experiment was also carried out for both of the chlorophenyl substrates **8** and **9**. These cases showed dechlorination as a competitive reaction, providing further evidence of the involvement of radical anions of the substrates (see the Supporting Information).

We applied computational studies to get deeper insights.[18] The intermediates and transition states were optimized with UB3LYP/6-31 + G(d)[19] or CBS-QB3 and energies were subsequently calculated at UCCSD(T)/6-31G(d)//UB3LYP/6-31 + G(d).[20] The calculated reaction profiles for the diphenylcyclopropanes **4** and **5** are shown above (Figure 1). Using UB3LYP/6-31 + G(d), we calculate a very small barrier for the ring opening of the *cis* radical anion. At CBS-QB3, the ring opening is even spontaneous upon optimization of **ra 4** (the radical anion of **4**). Further assessment of the ring opening with UCCSD(T)/6-31G(d)

Table 1: Outcome of the irradiation of arene substrates in the presence of donors **2** or **3**. For entries 1–4, the products were isolated and the isomer ratios determined by ^{1}H NMR spectroscopy. For entries 8-12, ^{1}H NMR calibration against an added internal anisole standard was performed (CPs = cyclopropanes, DPs = diarlypropanes).

Entry	Arene	CPs starting *trans/cis* ratio	Electron donor (equiv)	Irradiation time [h] (energy [W])	Isolated *trans/cis* ratio of CPs	Isolated yield [%]	CPs *trans/cis* yield [%]	DPs (yield [%])
1	**4**	2:98	**3** (3)	24 (8×12)	19:81	79	n.a.	n.a.
2	**6**	2:98	**3** (1.5)	24 (8×12)	14:86	59	n.a.	n.a.
3	**5**	99.5:0.5	**3** (3)	24 (8×12)	95:5	88	n.a.	n.a.
4	**7**	99:1	**3** (1.5)	17 (8×12)	95:5	35	n.a.	n.a.
5	**4**	2:98	**3** (2)	90 (2×100)	n.a.	n.a.	46.8; 19.6	**16** (6.1)
6	**6**	2:98	**3** (2)	90 (2×100)	n.a.	n.a.	28.3; 31.3	**17** (2.8)
7	**5**	99.5:0.5	**3** (2)	90 (2×100)	n.a.	n.a.	54.2; 7.0	**16** (13.7)
8	**7**	99:1	**3** (2)	90 (2×100)	n.a.	n.a.	41.8; 5.3	**17** (5.6)
9	**4**	2:98	**2** (2)	90 (2×100)	n.a.	n.a.	17.7; 17.7	**16** (35.1)
10	**6**	2:98	**2** (2)	90 (2×100)	n.a.	n.a.	6.5; 54.5	**17** (21.2)
11	**5**	99.5:0.5	**2** (2)	90 (2×100)	n.a.	n.a.	32.7; 3.3	**16** (34.8)
12	**7**	99:1	**2** (2)	90 (2×100)	n.a.	n.a.	35.3; 1.8	**17** (23.9)

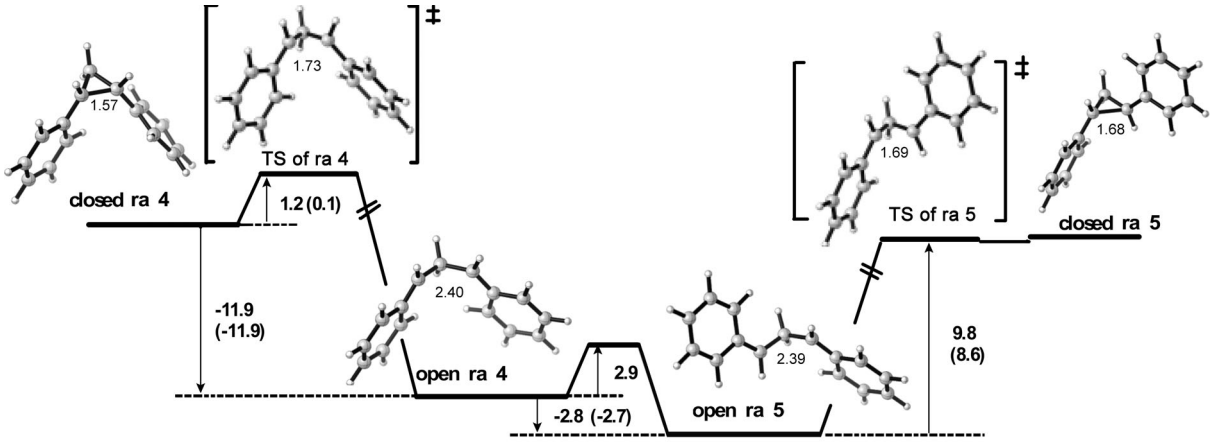

Figure 1. Reaction path energy profile for 1,2-diphenylcyclopropane. The electronic energies are shown (in kcal mol^{-1}) and the enthalpies are given in parentheses (at UB3LYP/6-31 + G(d) level of theory). For additional levels of theory, see the text.

energies confirms that there is essentially no barrier for the ring opening ($\Delta\Delta E^{\neq} = -0.1$ kcal mol^{-1}). The cleavage is exothermic by 11 kcal mol^{-1} at DFT and CCSD(T) levels of theory, disfavoring therefore the reverse ring-closing process. The rotational barrier from the ring-opened *cis* radical anion open **ra 4** to the corresponding *trans* isomer open **ra 5** (and vice versa) is low and feasible (see Figure 1). Ring closure of the *trans* radical anion, open **ra 5**, is calculated to have a barrier of 9.8 kcal mol^{-1} at B3LYP and 8.2 kcal mol^{-1} at CCSD(T), but the ring-closed *trans* radical anion closed **ra 5** (obtained following the intrinsic reaction coordinate) is in fact of essentially the same energy as the transition state (TS) itself.[21]

This suggests that ring closure of the radical anions is disfavored. The ring-opened radical anion intermediates (*cis* or *trans*) could readily undergo back electron transfer to the corresponding singlet biradical in the reaction. Optimization of the singlet biradical intermediate indeed showed spontaneous ring closure upon optimization (see the Supporting Information). The alternative triplet biradical is energetically disfavored (it is $\Delta H_{rxn} = 15.3$ kcal mol^{-1} higher in energy than diphenylcyclopropane **4**).

Thus, the data suggest that initial ring opening can take place through reduction. Subsequent isomerization (i.e. rotation) takes place through the radical anion intermediates and upon oxidation of the ring-opened *cis* or *trans* radical anion, very fast ring closure of the singlet biradical takes place. A triplet biradical, if formed, might give rise to rotation and isomerization also, but would be in competition with decay to the singlet biradical and subsequent spontaneous ring closure.

Returning to laboratory experiments, in efforts at increasing the amount of stereomutation, the photoactivated reactions were then repeated for substrates **4**, **5**, **6**, and **7**, but with more intense irradiation (UVP Black-Ray lamps, 2 × 100 W, 365 nm focused irradiation) and for an extended reaction time of 90 h using two equivalents of the donor. This afforded higher percentages of isomerization (Table 1, entries 5–8) and identification of minor components as the 1,3-diarylpropanes (**16** and **17**, respectively), the expected products of reductive trapping of the radical anion.[22]

Our previous studies had shown that donors **2** and **3** have similar oxidation potentials in their ground state, and so we also explored the reactions of donor **2** (see Table 1, entries 9–12). The qualitative results are the same, although donor **2** is more effective in promoting the formation of the 1,3-diphenylpropanes, with about 35% being formed from each isomer of 1,2-diphenylcyclopropane.

In summary, we showed that in the presence of the simple photoexcited super electron donors **2** and **3**, ring opening of the diphenylcyclopropanes results. This is the first time that a neutral organic reducing agent, upon photoexcitation, has achieved such a challenging reduction reaction, and yet the active electron donors are simple structures derived from pyridine and imidazole rings composed exclusively of carbon, hydrogen, and nitrogen elements. Pyridines and imidazoles occur widely in the pool of chemicals that are biosynthesized naturally and so it is noteworthy that nature could evolve very powerful reductive reactions even in environments that are depleted in redox-active metals.

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