

Chemically Induced Anion Radical Cycloadditions: Intramolecular Cyclobutane of Bis(enones) via Homogeneous Electron Transfer

Jingkui Yang, Greg A. N. Felton, Nathan L. Bauld,* and Michael J. Krische*

University of Texas at Austin, Department of Chemistry and Biochemistry, Austin, Texas 78712

Received September 19, 2003; Revised Manuscript Received November 18, 2003

The extensive body of cation radical cycloaddition chemistry brought forth in recent years clearly establishes this reaction type as a preferred and efficient reaction mode for cation radicals in their combinations with neutral molecules.^{1,2} The possibility that a similarly robust body of chemistry involving *anion radicals* might exist is therefore of substantial interest. Indeed, the first examples of anion radical cycloaddition, which involve the cyclobutane of activated alkenes initiated by heterogeneous electron transfer from electrodes, have recently been reported.³ We now wish to report the first examples of anion radical cycloaddition induced by homogeneous electron transfer from chemical agents.^{4,5} Specifically, upon exposure to chrysene anion radical, bis(enone) substrates are found to engage in stereoselective intramolecular [2 + 2] cycloaddition. These studies, along with the corresponding electrochemically initiated reactions, provide insight into this fundamentally new pattern of reactivity and support the feasibility of expanding this novel reaction type.

Recently, an intramolecular Co-catalyzed [2 + 2] cycloaddition of bis(enones) was discovered by one of the present authors.⁴ Mechanistic studies pertaining to this transformation implicate Co-complexed anion radicals as reactive intermediates.^{3c,4} This finding stimulated interest in the broader, more significant question of whether pericyclic processes are generally amenable to promotion via single-electron transfer. To explore this possibility, bis(enone) **1a** was exposed to an assortment of aromatic anion radicals. Gratifyingly, exposure of **1a** to chrysene anion radical at $-78\text{ }^{\circ}\text{C}$ in THF results in the formation of the [2 + 2] cycloaddition product *cis*-**2a** and the [4 + 2] cycloaddition Diels–Alder adduct **3** as single stereoisomers. Reductive cyclization–aldolization product **4** and the simple reductive cyclization product **5** are also obtained.⁶ The anion radicals of anthracene and naphthalene were found to induce cycloaddition; however, the most favorable results are obtained using chrysene anion radical. Transformations carried out at higher temperatures were found to produce large quantities of oligomeric and polymeric materials. The [2 + 2] cycloaddition mechanism is believed to involve nonconcerted C–C bond formation via intermediacy of a distonic anion radical, as previously proposed for the electrochemically promoted transformation (Scheme 1).

Under these conditions, anion radical cycloaddition of assorted aromatic bis(enones) was explored. It can be noted from Table 1 that the yields of *cis*-**2** are modest in the case of substrates **1a** and **1b** primarily because of the competing formation of **4** and **5**. Products **4** and **5** appear to derive from dianions formed by over-reduction of the intermediate distonic anion radical.⁷ That is, the distonic anion radical can either engage in cycloaddition to afford the cyclobutane or Diels–Alder products or accept a further electron to give a dianion. Protonation of the latter can lead to either **4** or **5**. It is noteworthy and expected that, when the benzoyl substituents of **1a** are replaced by acetyl or carboethoxy groups, neither cyclobutane nor Diels–Alder products are formed, since the second bond-forming step would then require placement of the anion radical moiety in the LUMO of an acetyl or ester group, either of which is much higher in energy than the LUMO of a benzoyl group.

Scheme 1. Postulated Mechanism for Chemically Induced Anion Radical [2 + 2] Cycloaddition of Bis(enones)

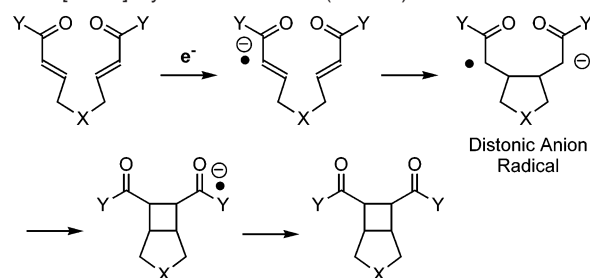


Table 1. Cyclobutane of Bis(enones) **1a–1f** Promoted by Chrysene Anion Radical^a

substrate	<i>cis</i> - 2 (yield%) ^b	3 (yield%) ^b	4 (yield%) ^b	5 (yield%) ^b
1a	31.5	9.2	20.1	2.9
1b	35.0	5.0	35.8	-
1c	60.4	-	14.0	4.0
1d	61.7	-	18.0	10.0
1e	50.8	9.8	16.4	16.4
1f	41.4	4.0	8.0	6.2

^a Representative Procedure: To a solution of **1c** (50 mg, 0.109 mmol, 100 mol %) in THF (3 mL, 0.036 M) at $-78\text{ }^{\circ}\text{C}$, was added over a period of 15 s a solution of chrysene anion radical (0.077 mmol, 70 mol %) in THF (0.9 mL, 0.086 M). After a reaction time of 3.5 min, the reaction mixture was quenched with aqueous ammonium chloride solution and then partitioned between water and dichloromethane. The organic layer was separated, dried (Na_2SO_4), filtered, and evaporated to give the crude reaction products. ^b Isolated yield after purification by silica gel chromatography.

The proposed stepwise nature of the cycloaddition suggests that, if the anion radical moiety in the cyclobutane product could reside in a still lower-energy LUMO than that of the parent benzoyl group, the rate of the second C–C bond formation might be enhanced such that formation of cyclobutane products would be favored over formation of dianionic products. This hypothesis was investigated by examining the reactions of **1c** and **1d**, which provide more extensive delocalization of the anion radical moiety than does the benzoyl moiety. In both of these cases the yield of pericyclic products is observed to be substantially increased and that of the dianion-type products diminished. Of special interest is the observation that the Diels–Alder products **3c** and **3d** were not observed. Since neither the *trans*-cyclobutane nor the Diels–Alder product

is formed, cycloaddition in these cases is highly stereo- and periselective.

The pronounced *cis*-diastereoselectivity is presumed to derive from relatively strong electrostatic interactions between the sodium ion and both carbonyl oxygens in the transition state for cyclization. Although the anion radical moiety is presumed to reside primarily upon just one of the aroyl groups in the product anion radical, it appears plausible that in the transition state the anion radical moiety is substantially delocalized over both benzoyl groups. The circumstances under which the Diels–Alder product is not formed at all are attractive synthetically but are also of particular interest mechanistically. The most intriguing possibility is that, as a result of enhanced thermodynamic driving force, the cyclobutanation may have become concerted. The more likely possibility, however, is that the second cyclization step may have become so rapid that the bond rotations which may be necessary in order to generate the conformations appropriate for Diels–Alder formation may be too slow to compete with the covalent bond formation which leads to the cyclobutane product.

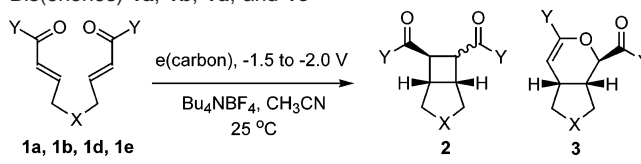
The further possibility of accelerating the rate of the second cyclization step, and therefore increasing the yield of pericyclic products, by installing electron-withdrawing groups on the aromatic ring was also investigated. As demonstrated by the reaction of substrate **1e**, a 4-chloro substituent is indeed observed to significantly enhance the yield of cyclobutane product *cis*-**2e**, but in contrast to the results obtained for **1c** and **1d**, a small amount of Diels–Alder adduct **3e** is also formed. Notably, products of dechlorination are not observed. Finally, with increased chloro substitution, as in the case of 3,4-dichlorobenzoyl-derived bis(enone) **1f**, the yield of pericyclic products is relatively modest. In this case a large amount of polymer formation is observed, suggesting the anion radical moiety may now be too stabilized for efficient intramolecular cycloaddition.

In all cases, these chemically induced cycloadditions appear to be stoichiometric, rather than catalytic radical chain processes. Optimum yields were obtained when about 70–120 mol % of the chrysene anion radical was used relative to the substrate. Quite possibly, tight ion-pairing of the sodium ions with the product anion radicals in the somewhat nonpolar solvent has the effect of retarding the rate of intermolecular electron transfer to substrate molecules, which would be required for chain propagation. Notably, although four products are formed in some cases, the cyclobutane products *cis*-**2a**–*cis*-**2f** are predominantly the major reaction products (Table 1). Finally, use of samarium iodide failed to generate any cyclobutane products. Instead, the previously mentioned aldol-type products were formed in a reaction requiring 2 mol of samarium iodide.

For selected substrates, electrochemical promotion of the cycloaddition was examined. For cycloadditions conducted under electrochemical conditions, reduction of the distonic anion radical intermediate does not contribute as a competitive reaction pathway. However, both *cis*- and *trans*-cyclobutane isomers are formed, as would perhaps be expected considering the relatively more polar solvent involved and the steric characteristics of the tetrabutylammonium counterion, both of which would tend to diminish ion-pairing interactions. The total yields of pericyclic products are seen to be quite good, and since the *cis*-cyclobutanes are readily converted to the more stable *trans*-cyclobutanes,⁴ the procedure affords a high-yielding approach to the latter. As with the chemical procedure, no pericyclic products are formed when the COY groups are acetyl or ester. An especially attractive feature of the electrochemical procedure is that it is electrocatalytic, furnishing modest turnovers of between 3 and 5 (Table 2).

In summation, we report the first anion radical cycloadditions mediated by chemical agents in solution. The present results clearly suggest the feasibility of expanding this new reaction type through

Table 2. Electrochemically Promoted Cyclobutanation of Bis(enones) **1a**, **1b**, **1d**, and **1e**^a



substrate	<i>cis</i> - 2 (yield%) ^b	<i>trans</i> - 2 (yield%) ^b	3 (yield%) ^b	pericyclic products (total yield%)
1a	17.1	58.6	12.6	88.3
1b ^c	38.8	20.9	28.4	88.1
1d	14.4	28.9	8.2	51.3
1e	11.1	52.0	11.6	74.7

^a *Representative Procedure:* To a flask charged with **1a** (100 mg, 0.329 mmol, 100 mol %) under a positive flow of N₂(g) was added 22 mL of a 0.1 M solution Bu₄NBF₄ in acetonitrile. This solution was added to the working electrode (WE) compartment, and a further 6 mL of the electrolyte solution was placed in the counter electrode (CE) compartment. Reticulated carbon electrodes were used for the WE and CE, alongside a silver wire “pseudo-standard” reference electrode (RE) encased in porous Vycor glass. The solution was subjected to electrolysis at constant voltage, with stirring under an atmosphere of N₂(g) at room temperature, between –1.5 and –2.0 V vs RE. Upon complete consumption of starting material, the reaction mixture was partitioned by between water and benzene. The organic layer was separated, dried (Na₂SO₄), filtered, and evaporated to give the crude reaction products. ^b Isolated yield after purification by silica gel chromatography. ^c For **1b**, MgClO₄ was used as electrolyte and electrolysis was performed at –2.5 to –3.0 V.

further variation of the single-electron reductant. The scope of these transformations, including intermolecular cross-cyclobutanation and Diels–Alder cycloaddition, and their reaction mechanisms are currently under active investigation in these laboratories.

Acknowledgment. This research was supported, in part, by the Robert A. Welch Foundation (F-149, N.L.B.) and the NIH (RO1 GM65149-01, M.J.K.).

Supporting Information Available: Spectral data for all new compounds (¹H NMR, ¹³C NMR, IR, HRMS) (PDF). Single-crystal X-ray crystallographic data for compounds *cis*-**2b**, *trans*-**2b**, **3b**, and **4b** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- Bauld, N. L. *Tetrahedron* **1989**, *45*, 5307.
- Bauld, N. L. In *Electron Transfer in Chemistry*; Balzani, V., Ed.; Wiley-VCH: Weinheim, 2001; Vol. 2, p 133.
- For electrochemically induced anion radical cyclobutanation, see: (a) Delaunay, J.; Mabon, G.; Orliac, A.; Simonet, J. *Tetrahedron Lett.* **1990**, *31*, 667. (b) Jannsen, R.; Motevalli, M.; Utey, J. H. P. *J. Chem. Soc., Chem. Commun.* **1998**, 539. (c) Roh, Y.; Jang, H.-Y.; Lynch, V.; Bauld, N. L.; Krische, M. J. *Org. Lett.* **2002**, *4*, 611.
- Anion radicals have been implicated as reactive intermediates in the Co-catalyzed [2 + 2] cycloaddition of bis(enones): (a) Baik, T.-G.; Wang, L.-C.; Luiz, A.-L.; Krische, M. J. *J. Am. Chem. Soc.* **2001**, *123*, 6716. (b) Wang, L.-C.; Jang, H.-Y.; Lynch, V.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 9448.
- For other pericyclic reactions of anion radicals, see: (a) Bauld, N. L.; Chang, C.-S.; Farr, F. R. *J. Am. Chem. Soc.* **1972**, *94*, 7164. (b) Bauld, N. L.; Cessac, J.; Chang, C.-S.; Farr, F. F.; Holloway, R. *J. Am. Chem. Soc.* **1976**, *98*, 4561. (c) Fox, M. A.; Hurst, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 7626. (d) Borhani, D. W.; Greene, F. D. *J. Org. Chem.* **1986**, *51*, 1563. (e) Witmer, M.; Altmann, E.; Young, H.; Sancar, A.; Begley, T. P. *J. Am. Chem. Soc.* **1989**, *111*, 9264. (f) Pasto, D. J.; Yang, S.-H. *J. Org. Chem.* **1989**, *54*, 3544.
- β,β -Coupling of bis(enones) with and without subsequent aldolization has previously been observed under the conditions of electron transfer. For selected examples, see: (a) Enholm, E. J.; Kinter, K. S. *J. Am. Chem. Soc.* **1991**, *113*, 7784. (b) Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 4.
- It appears unlikely that the aldol-type cyclization occurs at the stage of distonic anion radical in view of the fact that aldol type products are not formed in the electrochemical reactions, which also involve distonic anion radical intermediates.

JA030543J