

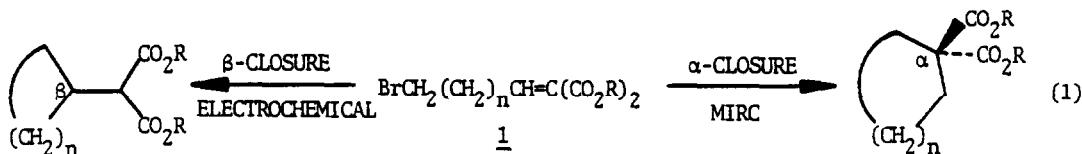
ELECTROREDUCTIVE CYCLIZATION A COMPARISON OF
 THE ELECTROCHEMICAL AND ANALOGOUS CHEMICAL (MIRC) REACTION[¶]

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ABSTRACT. Several examples which illustrate the contrasting and complementary aspects of electroreductive cyclization and MIRC reactions are presented. A brief mechanistic discussion of the electrochemical reaction is given and two examples of the use of an electrochemically generated base are provided.

We report the contrasting and complementary behavior of ω -bromoalkylidenemalonates (1) when subjected to hydride (L-Selectride) initiated ring closure (a MIRC reaction¹) and electrochemically initiated closure. Thus, while the former leads to the usual closure involving the α -carbon atom of the enolate¹, the electrochemical counterpart of the reaction, termed electroreductive cyclization (ERC), affords a ring with one carbon atom fewer in the cycle; that is, closure occurs from the β , rather than from the α -carbon atom.² Generalized expressions for these transformations are illustrated below.



The electrochemical reactions were conducted at a constant potential (-1.85V vs. SCE) in a modified H-cell³ using a BAS SP-2 power supply, a mercury pool cathode, a platinum foil anode, freshly dried DMF as the solvent, and n-Bu₄NBr (0.16 N) as the supporting electrolyte. Workup was initiated when the current had dropped to about 5% of the initial value. The Selectride runs were conducted at 0°C (with 2) or at reflux (with 3) in THF.^{1c,d}

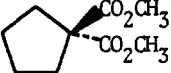
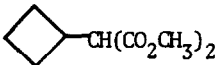
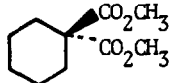
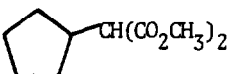
Several examples are illustrated in Table I. It is of particular interest to note that the electrochemical process provides a simple and efficient route to the cyclobutane ring system, thereby suggesting that the reaction may serve as one of a limited number of satisfactory methods which can be utilized for the construction of four membered rings. This possibility is presently the basis of a more detailed investigation.

Cyclic voltammetry studies using the compounds listed in Table II illustrate that (a) the reduction potential required for the ERC reaction is considerably more positive (ca. 0.3V)

[¶] An account of this work was presented by S.N. at the 1981 Pacific Conference on Chemistry & Spectroscopy, Anaheim, California, October, 1981

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TABLE I

STARTING MATERIAL	REACTION WITH	PRODUCT	YIELD (%)
$\text{Br}(\text{CH}_2)_3\text{CH}=\text{C}(\text{CO}_2\text{CH}_3)_2$ (2)	$\text{Li}(\underline{s}\text{-Bu})_3\text{BH}$, THF, 0°C		65
(2)	-1.85 V (SCE), DMF, $\underline{n}\text{-Bu}_4\text{NBr}$, room temp.		65-80
$\text{Br}(\text{CH}_2)_4\text{CH}=\text{C}(\text{CO}_2\text{CH}_3)_2$ (3)	$\text{Li}(\underline{s}\text{-Bu})_3\text{BH}$, THF, reflux		45
(3)	-1.85 V (SCE), DMF, $\underline{n}\text{-Bu}_4\text{NBr}$, room temp.		60

than that required for the reduction of *n*-butyl bromide, thereby suggesting that the electrochemical reaction does not begin by an initial carbon-bromide bond cleavage. (b) the replacement of one of the C_4 hydrogen atoms of butyl bromide with a malonic ester unit to afford 4 has no effect on the reduction potential, *i.e.*, the reduction of 4 takes place at the same potential as that for *n*-butyl bromide; (c) the reduction of an alkylidenemalonate which is not ω -bromo substituted (*e.g.*, 5) leads to an anodic shift in the reduction potential of ca. 0.1V relative to butyl bromide and 4. However, the observed potential is still not shifted sufficiently to account for the fact that the reduction potential for substrates 2 and 3 is -1.85V

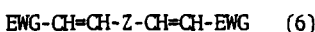
TABLE II

COMPOUND	OBSERVED REDUCTION POTENTIAL (V vs. SCE)
$\underline{n}\text{-BuBr}$	-2.18 ^a
$(\text{MeO}_2\text{C})_2\text{CH}(\text{CH}_2)_4\text{Br}$ (4)	-2.18
$(\text{MeO}_2\text{C})_2\text{C}=\text{CH}(\text{CH}_2)_2\text{CH}_3$ (5)	<-2.00 ^b
$(\text{MeO}_2\text{C})_2\text{C}=\text{CH}(\text{CH}_2)_3\text{Br}$ (2)	-1.85
$(\text{MeO}_2\text{C})_2\text{C}=\text{CH}(\text{CH}_2)_4\text{Br}$ (3)	-1.85

a. See also Lambert, F., Kobayashi, K. *J. Am. Chem. Soc.*, 1960, 82, 5324-5328 and ref. therein.

b. No reduction curve was observed, only catholyte discharge.

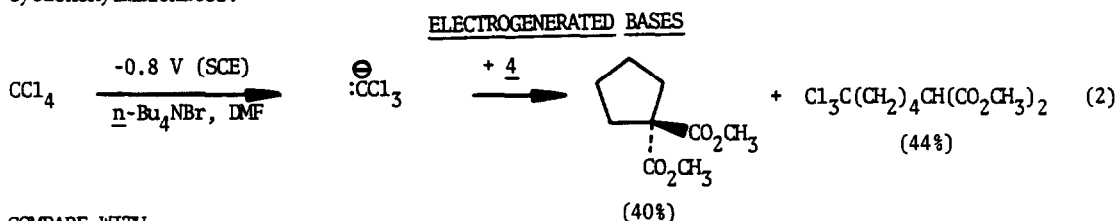
Previously, in conjunction with detailed studies of the electrohydrocyclization (EHC) of bisactivated olefins, Baizer and coworkers argued that the observation of an anodic shift in the reduction potential for a bisactivated olefin (6) when compared with a simple monoactivated system, was indicative of a "concerted reduction-cyclization during the transfer of the first electron in the potential-determining step."⁴⁻⁶ While more definitive studies are clearly in order, one could *perhaps* interpret the present findings in a similar way.



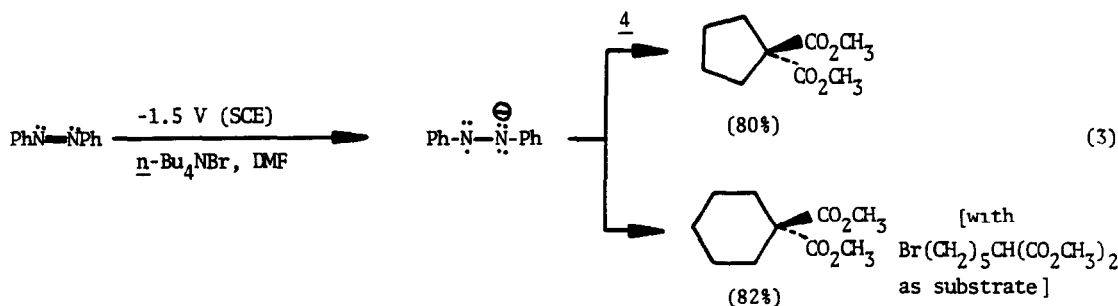
EWG = electron-withdrawing group

For the systems presently under investigation, coulometry shows that the reductive cyclization occurs as an overall two electron process. However, the precise timing of events is not yet known. The voltammetry results, as well as analogy with the suggestion of Baizer and coworkers, *suggests the possibility* of a concerted one electron transfer and ring closure step. Alternatively, of course, a one or a two electron transfer prior to ring closure would lead to the formation of a radical anion or a dianion (most likely formed by disproportionation of the radical anion rather than by direct electron transfer).⁷

In addition to the electrochemical reductive cyclization discussed above, we have briefly investigated the possibility of utilizing electrogenerated bases (EGB)⁸ to initiate ring forming reactions of ω -haloalkylmalonates. Thus, for example, the reaction of malonate 4 with the trichloromethyl anion generated by reductive cleavage of carbon tetrachloride (-0.8V vs. SCE), led to the formation of 84% of ca. a one-to-one mixture of the desired ring closed product along with the product resulting from $\text{S}_{\text{N}}2$ displacement (note eq. 2). The $\text{S}_{\text{N}}2$ displacement product was avoided by using the radical anion of azobenzene as the base instead of CCl_3^- . As illustrated in eq. 3, this method was used efficiently to produce both dimethylcyclopentyl- and cyclohexylmalonates.



COMPARE WITH,



Further studies are in progress and will be reported in due course.

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REFERENCES AND NOTES

1. (a) Little, R.D.; Dawson, J.R. J. Am. Chem. Soc., 1978, 100, 4607-4609. (b) Little, R.D.; Dawson, J.R. Tetrahedron Letters, 1981, 21, 2609-2612. (c) Little, R.D.; Verhe', R.; Monte, W.T.; Nugent, S.; Dawson, J.R. J. Org. Chem., in press. (d) Fortunato, J.M.; Ganem, B. J. Org. Chem., 1976, 41, 2194-2200 and ref. therein.
2. For other examples of reactions which occur at the β -carbon atom of an electroreduced unsaturated system see: (a) Satoh, S.; Sugimone, H.; Tokuda, M. Tetrahedron Letters, 1981, 22, 1895-1898. (b) Lund, H.; Degrand, C. Ibid., 1977, 3593-3594 and ref. therein. (c) reference 3 below.
3. See, for example, Lund, H.; Iversen, P.E. in Ch. IV of "Organic Electrochemistry, An Introduction and a Guide," Baizer, M.M., Ed., 1973, Marcel Dekker, New York.
4. (a) Petrovich, J.P.; Anderson, J.D.; Baizer, M.M. J. Org. Chem., 1966, 31, 3897-3903. (b) Anderson, J.D.; Baizer, M.M.; Petrovich, J.P. Ibid., 1966, 31, 3890-3897. (c) Fry, A.J. "Synthetic Organic Electrochemistry", 1972, Harper & Row, New York, p. 250.
5. For a discussion of the relation of electrochemical potential and activation energy see. Bard, A.J.; Faulkner, L.R. "Electrochemical Methods", Ch. 3, John Wiley & Sons Inc., 1980, New York.
6. Rifi has also argued in favor of the existence of a concerted process in conjunction with the electrochemical ring closure of a variety of α,ω -dibromoalkanes based upon the observation of an anodic shift in the reduction potential for the dibromides relative to their monobromide counterparts. However, this suggestion has been criticized by Fry and Britton. Rifi, M.R. Tetrahedron Letters, 1969, 1043. Fry, A.J.; Britton, W.E. Ibid. 1971, 4363 and Fry, A.J.; Britton, W.E. J. Org. Chem. 1973, 38, 4016.
7. In view of the studies of House, the formation of a radical anion, wherein the β -carbon has radical character, seems more likely than the direct formation of a dianion. Regardless, it is likely that the β -carbon has greater total *localized* electron density since the two ester groups provide a means of *delocalizing* electron density away from the α -carbon. *Perhaps* this provides a rationale for the observed β -closure. Bowers, K.W.; Giese, R.W.; Grimshaw, J.; House, H.O.; Kolodny, N.H.; Kronberger, K.; Roe, D.K. J. Am. Chem. Soc. 1970, 92, 2783.
8. For other examples of the use of electrogenerated bases see: (a) Hallcher, R.C.; Baizer, M.M. Liebigs Ann. Chem., 1977, 737-746. (b) Iversen, P.E.; Lund, H. Tetrahedron Letters, 1969, 3523-3524 and ref. therein.
9. *Added in Proof:* See Gassman, P.G.; Rasmay, O.M.; Murdock, T.O.; Saito K. J. Org. Chem. 1981, 46, 5457-5458.

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