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Dramatic effects of the electrolyte cation on the selectivity of electroreductive cycloaddition reactions of bis(enones)

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Abstract—The nature of the electrolyte cation (Li, Na, K, Ag, Mg, Ba) exerts a dramatic effect upon the diastereoselectivity of the intramolecular cyclobutanation reactions of several bis(enones). The formation of *cis* as against *trans* cyclobutanes is strongly favored by magnesium ions, presumably via a chelation effect, and becomes exclusive in the case of barium. The latter ion has the additional surprising effect of enhancing the amount of Diels–Alder cycloaddition as opposed to cyclobutanation.

1. Introduction

Intramolecular anion radical pericyclic reactions of tethered bis(enones) have been described from these laboratories.[1] These anion radical reactions are of special interest because they represent rare examples of intramolecular anion radical cycloaddition, rather than the more common electrohydrocyclization (EHC). The focus of this work has been in the comparison of electrochemical methods to chemical reduction routes,[2] and the elucidation of the full mechanism of cyclization.[3] While undertaking this investigation we became aware that the electrolyte choice was having a strong effect upon the ratio of products obtained from each reduction. To further explore this feature, the effect of several perchlorate electrolytes was studied. The commonly used $LiClO_4$,[1,3–7] $Mg(ClO_4)_2$,[1–5,7–10] $NaClO_4$,[6,7,10–12] $KClO_4$,[12] and $AgClO_4$[13] were investigated, as well as what may represent the first use of $Ba(ClO_4)_2$[6–8] in an electrosynthetic application. This work represents the first observation of such an electrolyte effect in cyclobutanation. A similar effect has been observed in a handful of EHC systems, with a relatively limited array of electrolytes.[4,5] The use of a strong acid or base (as the electrolyte) has been seen to affect the isomer ratios of products in ketone to alcohol reductions,[14,15] and in diketone to diol EHC.[16] Indeed solvent choice has also been observed to affect the ratios of product isomers in EHC[16] and reductive cleavage,[17] as well as in nonelectrochemical deprotonations.[18] However, such solvent effects tend to be of a more modest magnitude than those observed in the present work. There are also numerous cases of electrolyte choice affecting the ability of a reaction to proceed.[19]

The bis(enones) studied have been observed to readily undergo cycloaddition under electrochemical reduction conditions.[1] This cycloaddition is considered to occur via a two-step mechanism,[3] involving a distonic anion radical intermediate, shown below (Fig. 1). Virtually all products issue from this distonic species, and the three primary pericyclic (two cyclobutanation and one Diels–Alder) products result from its subsequent cyclization/cyclobutanation. The proportion of products **4** and **5**, which represent two-proton EHC processes, is determined by the lifetime of the distonic intermediate

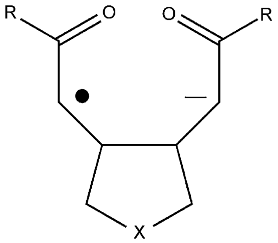

Figure 1. The distonic anion intermediate formed from the initial cyclization; products **1** through **5** are all formed in competing reactions from this intermediate species.

Keywords: Electrolyte effect; Cyclobutanation; Barium ion; Chelation; Diastereoselectivity.

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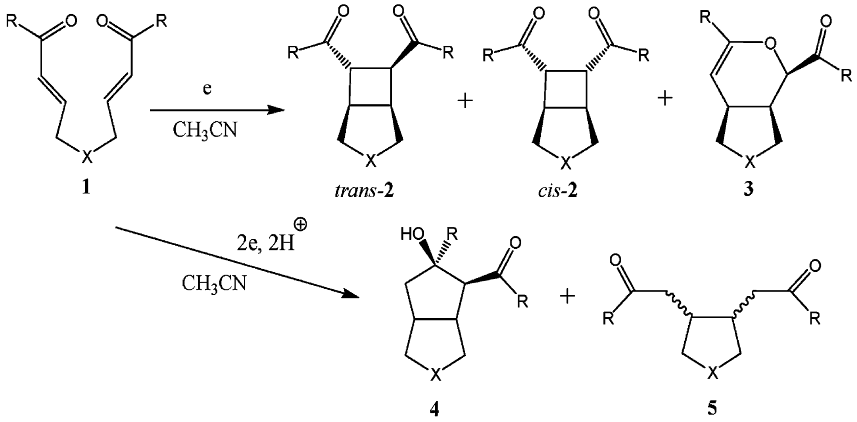
(in turn controlled in part by the relative SOMO stabilizing power of the R group). Use of an alkylammonium electrolyte is favored for these pericyclic conversions, partly for its higher electrocatalysis (generally representing $0.2\,F\,mol^{-1}$ processes) and partly for the greater pericyclic yields obtained.[3] However, perchlorate electrolytes also display modest electrocatalysis (0.6–$0.8\,F\,mol^{-1}$), along with reasonable pericyclic yields, which are somewhat diminished by the competing formation of products **4** and **5** (Fig. 2).

2. Electrolyte variation: the reduction of substrate 1a

The 4-chlorophenyl bis(enone) substrate **1a** was chosen for the preponderance of the electrolyte variation experiment, primarily because of its greater tendency to form the three pericyclic products exclusively. Lithium and magnesium perchlorate were studied initially. They reveal a large variation in the isomer product ratio upon switching from the +1 to the +2 cation (Table 1). The Mg^{2+} greatly retards the formation of the thermodynamically favored *trans*-**2a** cyclobutane isomer (discussed below). This clearly suggests a much stronger chelation of the Mg^{2+} ion with the distonic anion and, in particular, in the transition state leading from this latter to the product anion radical. Effectively, the divalent metal ion steers the two oxygen functions of the intermediate distonic anion radical into the relatively close positioning involved in *cis*-**2a** and **3a**, where the chelating interaction can be maintained in the product anion radical, and away from the distant positioning required in *trans*-**2a**, where the metal cation would be able to interact with only one of the two oxygen functions. The formation of a small amount of **4** indicates that even the aldol cyclization route can compete in what is essentially an aprotic system.

The use of barium perchlorate as the electrolyte takes this effect to a rather stunning and unprecedented extreme, where all *trans*-**2a** formation is suppressed. In fact, *cis*-**2a** and **3** are formed in nearly equal amounts, and in a slight excess over **4**. This result is especially intriguing in that, because of the much smaller charge-to-size ratio of the barium ion than the magnesium ion (the ionic size of Ba^{2+} is 0.134 nm, whereas that of Mg^{2+} is only 0.064 nm), the former is expected to be inherently much less efficiently solvated than the latter. Evidently, the greater size of the barium ion provides a better fit to the chelation cavity available in the distonic anion radical than does the much smaller Mg^{2+}, thus enabling Ba^{2+} to efficiently interact with both oxygen functions. The data suggest that the Ba^{2+} cation also favors the Diels–Alder cyclization route, as this nearly 1:1 ratio to *cis*-**2a** is one of the highest seen in these experiments. It is appropriate to note that the two oxygen functions in **3** are in relatively close proximity, permitting a five-membered chelation ring.

The normal effect of changing the charge to size ratio can be observed in the Li^+, Na^+, and K^+ series (Table 1, expts. 1, 4, and 5), where we see that, as the charge-to-size ratio decreases, chelation is rendered progressively less efficient, such that *trans*-**2a** formation can dominate. In fact, this *trans* preference approaches a factor of 10 with potassium. The looseness of the ion pairing with the potassium ion even allows for an electrogenerated base-catalyzed product to form (usually only seen with the weakly ion-pairing alkylammonium salts).[3] It is known that the *trans*-**2** isomer is the thermodynamically more stable cyclobutane product. However, in most cases the *cis*-**2** isomer is formed in excess initially, indicating a kinetic advantage in the formation of this isomer, probably due to the strength of cationic chelation, which tends to maintain the *cis* relationship



Substrate	R	X
1a	4-Cl-Ph	CH_2
1b	3,4-Cl_2-Ph	CH_2
1c	β–Naphthoyl	CH_2
1d	4-Ph-Ph	CH_2
1e	Ph	O

Figure 2. The bis(enone) substrates studied, the primary pericyclic products (**1**–**3**), and two proton EHC products (**4**–**5**).

Table 1. Product isomer variation with electrolyte using substrate **1a** in acetonitrile

	Electrolyte	Ratio of *trans*-**2a**	Ratio of *cis*-**2a**	Ratio of **3a**	Ratio of **4a**	%Reaction completion[20]	Maximum% of charge used[21]
1	0.1 M $LiClO_4$	1	1.4	0.45	—	77	86
2	0.5 M $LiClO_4$[a]	1	1.0	1.5	0.12	91	15
3	0.1 M $LiClO_4$ + 0.006 M $AgClO_4$	1	2.3	0.57	1.9	59	95[b]
4	0.1 M $NaClO_4$	1	0.77	0.32	—	86	16
5	<0.05 M $KClO_4$	1	0.12	0.21	—[c]	100	14
6	0.1 M $Mg(ClO_4)_2$	1	6.4	2.9	0.58	81	27
7	0.1 M $Ba(ClO_4)_2$	—	1	0.94	0.72	79	53

[a] Using THF as the solvent.

[b] Competing silver ion reduction, 25 C were used, substrate and silver ion used correspond to 9.1 and 17.2 C, respectively.

[c] 0.51 Ratio of an electrogenerated base product.[3]

Table 2. The effect of length of electrolysis upon isomer ratios, using 0.1 M $LiClO_4$ as electrolyte

Substrate	Ratio of *trans*-**2**	Ratio of *cis*-**2**	Ratio of **3**	Ratio of **4**	Ratio of **5**	%Reaction completion[20]	Maximum% of charge used[21]
1a	1	1.4	0.45	—	—	77	86
1a	1	0.44	0.46	—	0.46	100	100
1b[a]	1	1.6	0.41	0.95	—	66	33
1b[a]	1	1.1	0.37	0.82	—	100	74
1e[b]	1	0.97	0.09	—	—	99	63
1e[b]	1	0.17	0.17	—	—	100	78

[a] $LiClO_4$ (0.2 M) was used.

[b] Ratios from PTLC separated yields.

of the two carbonyl groups in the transition state for the cyclization reaction. Clearly, the weaker chelation provided by the Na^+ and K^+ ions no longer provides this advantage.

The use of silver perchlorate is complicated by the reduction of Ag^+ to Ag metal. Used in isolation, silver metal forms on the Working Electrode, and the solution is unable to sustain a potential negative enough for substrate reduction. However, a small amount of $AgClO_4$ could be used in conjunction with $LiClO_4$. In this experiment (expt. 3), an effect of added silver ion upon the products ratios is clearly evident, so that any analysis of the data must assume a superimposed silver ion effect. The experiment was also run for longer times than other experiments due to continued Ag^+ reduction, which consumed much of the charge that flowed. This increased length of reaction tends to favor the enhanced formation of **4** (see Section 4), but cannot be the basis for the slight increase in the amount of *cis*-**2a**. This increase may be due to Ag^+ chelation.

3. Solvent effect

Solvent variation was not extensively examined in this study. However, an experiment utilizing the less polar solvent tetrahydrofuran (THF) did reveal an interesting effect, viz., a greater tendency toward the formation of the Diels–Alder product (**3**). The basis for this novel periselectivity effect is uncertain, but could indicate that chelation effects are still more important in the less polar solvent, and that these effects may be especially strong in the transition state leading to **3**.

4. Product reduction effects

Through the course of the reaction, as the substrate is consumed, the electrocatalysis not surprisingly becomes less efficient. The product ratios observed can be altered at this advanced stage of an electrolysis. This is not thought to be a large effect, and has been shown to proceed via reversion of the *cis*-**2** isomer back to the distonic intermediate. Reduction of the *trans*-**2** isomer in isolation gives no reaction, yet similar reduction of isolated *cis*-**2** gives all products (**2**–**5**), after a relatively large amount of charge has passed.[3] It seems apparent that reduction of the substrate is greatly favored over reduction of the products; otherwise *cis*-**2** yields would be greatly lowered. Similarly, more extensive formation of product **5** would also be expected, as a result of further reduction or protonation of the distonic intermediate, if this reversion were occurring earlier in the course of the reaction. To examine this possibility, the continued reduction of substrate **1a** was examined, using exactly 100% of the required charge, ignoring electrocatalysis, and therefore representing extensive over reduction (see Table 2). This lowered the *cis*-**2a** isomer ratio, with increased formation of product **5**, a product not seen when the reaction is stopped sooner. This large drop in *cis*-**2a** isomer ratio is repeated when **1e** is over reduced. Although in this case products **4** and **5** are not seen, the *cis*-**2e** isomer ratio is reduced 5-fold, and the **3** isomer ratio is doubled. However, it should be remembered that the distonic anion formed from substrate **1e** will have a slightly different chelation profile, due to the bridging ethereal oxygen. Indeed this structural feature may also fractionally lower the reduction potentials of the products, so that reversion to the

Table 3. The effect of using $LiClO_4$ or $Mg(ClO_4)_2$ as electrolyte upon the electrolysis of varied bis(enone) substrates

Substrate	Electrolyte	Ratio of *trans*-**2**	Ratio of *cis*-**2**	Ratio of **3**	Ratio of **4**	Ratio of **5**	%Reaction completion[20]	Maximum% of charge used[21]
1b	0.2 M $LiClO_4$	1	1.1	0.37	0.82	—	100	74
1b	0.1 M $LiClO_4$ + 0.1 M $Mg(ClO_4)_2$	1	3.1	1.8	0.85	—	100	76
1c	0.1 M $LiClO_4$	1	3.1	0.48	0.52	0.48	78	86
1c	0.1 M $Mg(ClO_4)_2$	1	5.6	2.2	2.3	1.6	71	94
1d	0.1 M $Mg(ClO_4)_2$	1	4.1	5.2	1.9	1.3	73	54
1e[a]	0.1 M $LiClO_4$	1	0.97	0.09	—	—	99	63
1e[a]	0.1 M $Mg(ClO_4)_2$	1	1.9	1.4	—	—	67	50

[a] Ratios from PTLC separated yields.

distonic anion may be more prevalent. A third example, involving substrate **1b**, with a somewhat more modest over reduction, leads to a smaller effect. In this case, the *cis*-**2b** isomer ratio is merely lowered by a third, while other ratios remain effectively constant (Table 3).

These results clearly highlight the limited effect of *cis*-**2** reduction upon the isomer ratios, at least until the advanced stages of an electrolysis. Such an electrolysis run to near completion (say 90%), should see minimal interference to product isomer ratios from *cis*-**2** reversion. The base-catalyzed interconversion of the *cis*-**2** to *trans*-**2** isomer is a formal possibility, yet the lack of formation of any electrogenerated base products in all but the weakest of chelated cation systems (namely K^+) seems to discount such an interfering effect.

5. Isomer ratio variation in other substrates

Several other substrates were also examined with regard to the major effect observed when the electrolyte is varied from $LiClO_4$ to $Mg(ClO_4)_2$. The different aroyl substituents yield slightly differing results, but the broad picture remains unchanged. The stronger Mg^{2+} chelation leads to a strong inhibition of *trans*-**2** formation, and subsequent increase of other product yields, in particular in those of *cis*-**2**. For the two experiments with substrate **1b**, it seems reasonable to assume that the stronger chelation of the Mg^{2+} ion leads to the majority of reduction occurring with this cation chelated. This leads to the most dramatic increase in the *cis*-**2** ratio observed for this substrate, a tripling of the *cis*-**2b** ratio (although a 6-fold increase was observed for substrate **1a**).

A further interesting feature of these results, also noted above for Ba^{2+}, is the enhancement of the Diels–Alder cyclization route (product **3**) provided by the +2 cations. This effect, observed for all of the substrates, is especially interesting to consider in terms of the ratio of the Diels–Alder adduct to each of the individual cyclobutane isomers. Formation of **3** is generally seen to increase 5-fold in comparison to *trans*-**2** for all of the substrates examined, but the change in the relative amount of **3** compared to *cis*-**2** is more variable and appears to be dependent upon the SOMO-stabilizing ability of the R group. The result is that only a small enhancement (ca. 50%) in the relative amount of **3** is observed for substrates **1a** and **1b**, whereas this effect increases to a 2.5-fold enhancement for **1c**, and an 8-fold enhancement for **1e**.

6. Conclusion

Variation of the nature of the cation of the supporting electrolyte leads to dramatic variations in the product ratios for a variety of bis(enone) intramolecular cycloadditions initiated by electrochemical reduction. It is proposed that the strength of the chelating interaction between the metal cation and the two oxygen functions of the distonic anion radical intermediate directly relates to these product ratios. This effect is prominently observed when +2 cations are used in place of +1 cations. The resulting increase in chelation strength leads to greatly retarded formation of the *trans*-cyclobutane product. The most dramatic results are observed in the use of $Ba(ClO_4)_2$, where all *trans*-**2a** formation is inhibited. This effect is interpreted in terms of a size effect, in which the much larger barium ion just fits into the chelation cavity of the intermediate distonic anion radical. Stronger cation chelation is also observed to correlate with enhancement in the formation of the Diels–Alder product **3**. It is noted that the two oxygen functions in **3** are proximate enough to maintain an efficient chelation interaction.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.09.094.

References and notes

1. Roh, Y.; Jang, H.-Y.; Lynch, V.; Bauld, N. L.; Krische, M. J. *Org. Lett.* **2002**, *4*, 611–613.
2. Yang, J.; Felton, G. A. N.; Bauld, N. L.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*(6), 1634–1635.
3. Felton, G. A. N.; Bauld, N. L. *Tetrahedron* **2004** (in press).

4. Bode, H. E.; Sowell, C. G.; Little, R. D. *Tetrahedron Lett.* **1990**, *31*, 2525–2528.
5. *Novel Trends in Electroorganic Synthesis*; Konno, A., Bode, H. E., Little, R. D., Eds.; Springer: Tokyo, 1998; pp 211–212.
6. Blanchard, P.; Huchet, L.; Levillain, E.; Roncali, J. *J. Electrochem. Commun.* **2000**, *2*, 1–5.
7. Nagayma, H.; Hojo, M.; Ueda, T.; Nishimori, Y.; Okamura, M.; Daike, C. *Jpn. Soc. Anal. Chem.* **2001**, *17*, 1413–1420.
8. Aramata, A.; Delahay, P. *J. Phys. Chem.* **1964**, *68*, 880–883.
9. Saito, M.; Ikuta, H.; Uchimoto, Y.; Wakihara, M.; Yokoyama, S.; Yabe, T.; Yamamoto, M. *J. Electrochem. Soc.* **2003**, *6*, A726–A731.
10. Dutkiewicz, E.; Jakubowska, A. *Colloid Polym. Sci.* **2002**, *280*, 1009–1014.
11. Bond, A. M.; Lamprecht, A.; Tedesco, V.; Marken, F. *Inorg. Chim. Acta* **1999**, *291*, 21–31.
12. Kim, D. Y.; Kim, J. K.; Lee, J. Y.; Rhee, H. W.; Kim, C. Y. *Polym. Adv. Technol.* **1998**, *8*, 184–188.
13. Flätgen, G.; Wasle, S.; Lübke, M.; Eickes, C.; Radhakrishnan, G.; Doblhofer, K.; Ertl, G. *Electrochim. Acta* **1999**, *44*, 4499–4506.
14. Nonaka, T.; Kusayanagi, Y.; Fuchigami, T. *Electrochim. Acta* **1980**, *25*, 1679–1683.
15. Nonaka, T.; Kusayanagi, Y. *Electrochim. Acta* **1981**, *26*, 893–898.
16. Nonaka, T.; Asai, M. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2976–2982.
17. Walborsky, H. M.; Aronoff, M. S.; Schulman, M. F. *J. Org. Chem.* **1971**, *36*, 1036–1040.
18. Munchhof, M. J.; Heathcock, C. H. *Tetrahedron Lett.* **1992**, *33*, 8005–8006.
19. Cipris, D. *J. Electrochem. Soc.* **1980**, *127*, 104–1045.
20. Based upon estimated recovered substrate (see Supplementary data for experimental details).
21. Corrected for recovered substrate, using 96,485 C mol^{-1}.