Evidence for α-lactone intermediates in addition of aqueous bromine to disodium dimethyl-maleate and -fumarate

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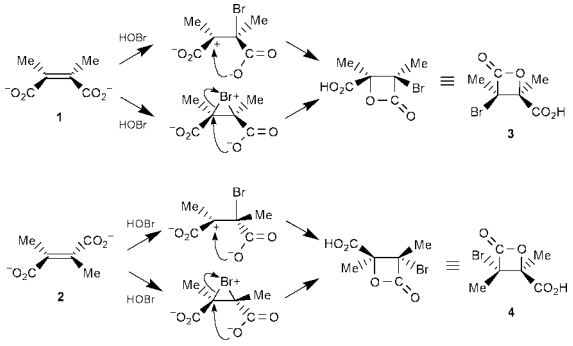
Crystallographic analysis of the bromo-β-lactones obtained by addition of bromine to aqueous solutions of disodium 2,3-dimethylmaleate and 2,3-dimethylfumarate reveals stereochemistries opposite to those originally assigned and suggests that the first-formed intermediate in each case is an α-lactone.

It is widely accepted that the addition of halogens to an alkene occurs in two stages and in an *anti* manner.[1] In 1937, Tarbell and Bartlett[2] found that the disodium salts of 2,3-dimethylmaleic acid and 2,3-dimethylfumaric acid (**1** and **2**) reacted stereospecifically with aqueous bromine, each yielding a single crystalline bromo-β-lactone; similar results were obtained with chlorine. The stereospecific nature of the reaction implied that the addition of the two components to the alkene was concerted. The authors proposed that the addition of bromine to give a carbocation was followed 'in the quickest possible succession' by attack of the carboxylate group leading directly to a β-lactone. The structures of the lactones (**3** and **4**, respectively) were assigned on this basis, corresponding to *anti* addition at the double bond. This work shortly predated the important paper by Roberts and Kimball[3] proposing cyclic halonium ion intermediates for halogen addition to alkenes. In Scheme 1 we have illustrated the two possible interpretations given at that time.[2,4]

We suspected that the reaction might be more complex than had been supposed, and have therefore prepared the two bromolactones from **1** and **2** by the published method[2] and established their structures by X-ray crystallography. The structures found (**4** from **1**,† and **3** from **2**,‡ Fig. 1) correspond to overall *syn* addition to the alkene. This unequivocal result is in contrast to the *anti* addition supposed by the Tarbell and Bartlett mechanism or arising from direct attack by carboxylate anion on a cyclic bromonium ion intermediate.[4,5] We believe that the most satisfactory explanation of our results (Scheme 2) involves formation of an α-lactone intermediate[6] (**5** and **6**) as the first step in the decomposition of the bromonium ion. Subsequently the other carboxylate group attacks the α-lactone, with a second inversion of configuration, to give the β-lactone. This scheme accounts simply and satisfactorily for the overall



Scheme 1

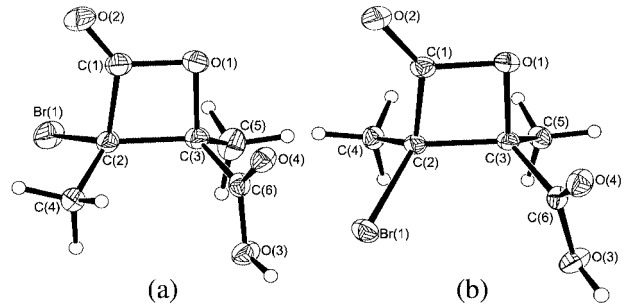
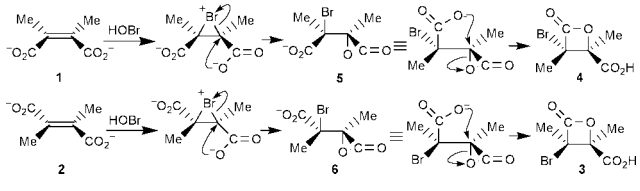


Fig. 1 X-Ray crystallographic structures for bromo-β-lactones: (a) compound **4** from disodium 2,3-dimethylmaleate; (b) compound **3** from disodium 2,3-dimethylfumarate.

stereochemical outcome. Furthermore, both of the individual steps, the formation of the α-lactone from the bromonium ion followed by formation of the β-lactone, are favoured *exo* processses in the Baldwin sense.[7–10] It is known that β-lactones are formed as kinetically controlled products in halolactonisation of salts of β,γ-unsaturated acids,[11,12] involving ring opening of the halonium intermediate in an *exo* manner.[13] Scission of the bromonium ion derived from a salt of an α,β-unsaturated monocarboxylic acid to give a β-lactone directly has been recognised as a relatively unfavourable pathway,[7,12–14] and can only be achieved under certain conditions.[13–16]

In support of our proposed mechanism, it is known that halogenation of certain allylic alcohols leads to epoxides by rearrangement of the halonium ion.[17–22] More pertinent is the behaviour of maleic acid and fumaric acid towards halogens; bromine in ether converts the free acids into the dibromides expected from *anti* addition.[23] On the other hand, treatment of disodium maleate with aqueous chlorine affords the *erythro* chlorohydrin[24] or, in the presence of an excess of chloride ions, the *erythro* (*meso*) dichloro compound,[25] the products of overall *syn* addition; disodium fumarate reacts *via* both *anti* and *syn* addition (80 : 20).[24,26] During the course of this work we became aware of the suggestion by Badea,[27] without experimental evidence, that an α-lactone intermediate might account for the *syn* addition.

α-Lactones are known to undergo intramolecular nucleophilic attack under aqueous conditions. Reaction of 2-amino-2-deoxy-D-gluconic acid with nitrous acid affords 2,5-anhydro-D-gluconic acid by double inversion *via* an α-lactone intermediate.[28] Similar reactions of L-glutamic acid and L-



Scheme 2

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glutamine result in the γ-lactone of L-α-hydroxyglutaric acid.[29,30] It appears that in the system we have studied ring closures are facilitated by alkyl substitution (the 'Thorpe–Ingold' effect);[31] there is no evidence for β-lactone formation during the chlorination of disodium maleate,[24–26] nor in the deamination of L-asparagine.[30]

Despite their high instability,[32] α-lactones may be more prevalent as reaction intermediates than has generally been imagined. Computational studies are in progress to evaluate structural and energetic aspects of the alternative mechanisms in Schemes 1 and 2 in order to elucidate the factors determining the preferred course of reactivity *via* the α-lactone intermediate.

Notes and references

† **4**, [3*S*(3*R*),4*S*(4*R*)]-3-Bromo-4-carboxy-3,4-dimethyloxetan-2-one, mp 92–94 °C (lit.,[2] 95–96 °C); δ_H [400 MHz, $(CD_3)_2SO$] 1.81 (s, 3H, Me), 1.93 (s, 3H, Me); δ_C [100 MHz, $(CD_3)_2SO$] 22.9 (Me), 23.1 (Me), 64.4 (C-3), 83.6 (C-4), 166.5 (C=O), 168.2 (C=O). *Crystal data*: $C_6H_7BrO_4$, M = 223.03, monoclinic, a = 10.4057(9), b = 6.4044(4), c = 12.0468(11) Å, β = 92.812(4)°, U = 801.86(11) Å^3, T = 170(2) K, space group $P2_1/c$, Z = 4, μ(Mo-Kα) = 5.090 mm^{-1}, 8001 reflections (R_{int} = 0.0514), R_1 = 0.0364 and wR_2 = 0.1021 based on 1328 F^2 data with $F_o > 4\sigma(F_o)$. Software used SHELXS,[33] SHELXL[34] and ORTEX.[35] CCDC 149760. See http://www.rsc.org/suppdata/cc/b1/b100335f/ for crystallographic data in .cif or other electronic format.

‡ **3**, [3*R*(3*S*),4*S*(4*R*)]-3-Bromo-4-carboxy-3,4-dimethyloxetan-2-one, mp 148 °C (lit.,[2] 148–150 °C); δ_H [400 MHz, $(CD_3)_2SO$] 1.77 (s, 3H, Me), 1.99 (s, 3H, Me); δ_C [100 MHz, $(CD_3)_2SO$] 18.3 (Me), 21.0 (Me), 61.4 (C-3), 85.0 (C-4), 166.7 (C=O), 168.9 (C=O). *Crystal data*: $C_6H_7BrO_4$, M = 223.03, triclinic, a = 6.0820(4), b = 6.3270(4), c = 11.6600(8) Å, α = 81.416(4), β = 88.333(5), γ = 62.060(4)°, U = 391.52(4) Å^3, T = 170(2) K, space group $P\bar{1}$ (No. 2), Z = 2, μ(Mo-Kα) = 5.212 mm^{-1}, 4102 reflections (R_{int} = 0.0675) $R1$ = 0.0330 and $wR2$ = 0.0918 based on 1469 F^2 data with $F_o > 4\sigma(F_o)$. Software used SHELXS,[33] SHELXL[34] and ORTEX.[35] CCDC 149759. See http://www.rsc.org/suppdata/cc/b1/b100335f/ for crystallographic data in .cif or other electronic format.

1 P. B. D. de la Mare and R. Bolton, *Electrophilic Additions to Unsaturated Systems*, 2nd edn., Elsevier, New York, 1982.
2 D. S. Tarbell and P. D. Bartlett, *J. Am. Chem. Soc.*, 1937, **59**, 407.
3 I. Roberts and G. E. Kimball, *J. Am. Chem. Soc.*, 1937, **59**, 947.
4 S. Winstein and H. J. Lucas, *J. Am. Chem. Soc.*, 1939, **61**, 1576.
5 E. S. Gould, *Mechanism and Structure in Organic Chemistry*, Holt, Rinehart and Winston, New York, 1959, pp. 522 and 611.
6 C. F. Rodriquez and I. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1997, 959 and references therein.
7 J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734 (p.736).
8 J. G. Buchanan and A. R. Edgar, *Carbohydr. Res.*, 1969, **10**, 295; J. A. Mills, *Adv. Carbohydr. Chem.*, 1955, **10**, 1 (p. 8).
9 J. G. Buchanan and H. Z. Sable, in *Selective Organic Transformations*, ed. B. S. Thyagarajan, Wiley, New York, 1972, vol. 2, p. 53.
10 G. Stork and J. F. Cohen, *J. Am. Chem. Soc.*, 1974, **96**, 5270.
11 W. E. Barnett and W. H. Sohn, *J. Chem. Soc., Chem. Commun.*, 1972, 472, and references therein.
12 K. E. Harding and T. H. Tiner, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, Pergamon, Oxford, **1991**, vol. 4, p. 363, and references therein.
13 F. Homsi and G. Rousseau, *J. Org. Chem.*, 1999, **64**, 81.
14 C. A. Kingsbury and G. Max, *J. Org. Chem.*, 1978, **43**, 3131.
15 C. C. Price and H. W. Blunt, *J. Org. Chem.*, 1969, **34**, 2484.
16 D. Solas and J. Wolinsky, *Synth. Commun.*, 1981, **11**, 609.
17 S. Winstein and L. Goodman, *J. Am. Chem. Soc.*, 1954, **76**, 4373.
18 B. Ganem, *J. Am. Chem. Soc.*, 1976, **98**, 858.
19 R. D. Evans, J. W. Magee and J. H. Schauble, *Synthesis*, 1988, 862.
20 B. O. Lindgren and C. M. Svahn, *Acta. Chem. Scand.*, 1970, **24**, 2699.
21 M. Santelli and J. Viala, *Tetrahedron Lett.*, 1977, 4397.
22 M. M. Midland and R. L. Halterman, *J. Org. Chem.*, 1981, **46**, 1229.
23 A. McKenzie, *J. Chem. Soc.*, 1912, **101**, 1196.
24 R. Kuhn and F. Ebel, *Ber.*, 1925, **58**, 919;
25 E. M. Terry and L. Eichelberger, *J. Am. Chem. Soc.*, 1925, **47**, 1067.
26 R. Kuhn and T. Wagner-Jauregg, *Ber.*, 1928, **61**, 504.
27 F. Badea, *Reaction Mechanisms in Organic Chemistry*, Abacus Press, Tunbridge Wells, Kent, 1977, p. 496.
28 A. B. Foster, *Chem. Ind. (London)*, 1955, 627.
29 H. Sachs and E. Brand, *J. Am. Chem. Soc.*, 1954, **76**, 3601.
30 A. T. Austin and J. Howard, *J. Chem. Soc.*, 1961, 3278; A. T. Austin and J. Howard, *J. Chem. Soc.*, 1961, 3284; A. T. Austin and J. Howard, *J. Chem. Soc.*, 1961, 3593.
31 A. J. Kirby, *Adv. Phys.Org.Chem.*, 1980, **17**, 183.
32 C. F. Rodriquez and I. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1997, 953.
33 G. M. Sheldrick, *Acta Cryst.*, 1990, **A46**, 467.
34 G. M. Sheldrick, *SHELXL–97*, a computer program for crystal structure refinement, University of Göttingen, 1997.
35 P. McArdle, *J. Appl. Cryst.*, 1995, **28**, 65.