Experimental and computational evidence for α-lactone intermediates in the addition of aqueous bromine to disodium dimethyl-maleate and -fumarate†

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Structural 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 in 1937: *cis* alkene yields *erythro* lactone, and *trans* alkene yields *threo* lactone. B3LYP/6-31+G(d) calculations using a PCM description of aqueous solvation confirm the validity of our proposed mechanism, in which the first-formed intermediate in each case is an α-lactone. The cyclic bromonium species is not an intermediate. An alternative pathway leading directly from *cis* alkene to *cis* lactone, *via* an unusual frontside displacement mechanism, is over 20 kJ mol^{-1} higher in free energy. Hydrolysis of the bromo-β-lactones yields bromohydrins whose stereochemistries as determined by X-ray crystallography indicate stereospecific formation by acyl–oxygen cleavage of the lactone ring, again contrary to the original view.

Introduction

α-Lactones are Cinderella species, whose existence is often overlooked: they are often totally excluded from discussions of lactones as cyclic esters in popular textbooks. If mentioned at all, it is usually in the context of neighbouring group participation, as the intermediate responsible for the double inversion (that leads to overall retention of stereochemistry) observed in the classic work by Ingold and co-workers on alkaline hydrolysis of α-halocarboxylates.[1] However, despite the clear proposals of Kenyon in regard to deamination of amino acids[2] and substitutions of α-tosyloxycarboxylates,[3] Ingold consistently avoided naming them as α-lactones: they were zwitterions with a configuration-protecting α-carboxylate substituent interacting electrostatically with the carbocation centre.[4] Winstein described the intermediate in hydrolysis of α-bromopropionate as an α-lactone, but denied that this term implied a completely covalent species; instead he reasoned that "there is a very large ionic character to the new carbon–oxygen bond".[5,6] α-Lactones are formed in inert matrices at low temperature by the addition of carbenes to CO_2,[7] and they polymerise readily, or decompose by extrusion of CO or CO_2.[8] Generally they do not survive warming to room temperature in solution; bis(trifluoromethyl)oxiranone is stable at ~20 °C,[9] and an extremely bulky perfluoro-derivative ($C_{12}F_{22}O_2$) survives at room temperature for a few days.[10]

The electrophilic addition of halogens to a non-conjugated alkene yields a dihalide with overall *anti* addition.[11,12] In 1937 Roberts and Kimball[13] proposed that a cyclic halonium ion intermediate[14] was formed as the first step, followed by attack, with inversion, at one of the carbon atoms by halide ion. The geometry of the transition state for the second step became clear when it was realised that in conformationally biased cyclohexenes such as in certain steroids[15] or *tert*-butyl derivatives[16] the major product under conditions of kinetic control was a diaxial dihalide. This corresponds to the diaxial ring opening of the analogous epoxides under a variety of conditions (the Fürst–Plattner rule).[17,18] The intermediate halonium ion can be captured by other nucleophiles.[11] A cyclic product results when the nucleophilic group is already present in the alkene:[19] the most common example of the latter is halolactonisation.[20,21]

Tarbell and Bartlett[22] 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 crystalline β-lactone, together with a bromohydrin; similar results were obtained with chlorine. Although the stereospecificity of the addition strongly suggested a concerted ring closure by a carboxylate group, the authors realised that there were geometrical difficulties; they suggested instead that reaction with a cationic centre occurred 'in the quickest possible succession' to form the β-lactone. On this basis the structures **3** and **4**, respectively, were assigned to the lactones, corresponding to *anti* addition to the double bond. Later authors, however, regarded it as a concerted process.[5,13,23] Scheme 1 shows the two possible interpretations. We shared the reservations of Tarbell and Bartlett, particularly in the light of analogous intramolecular reactions of epoxides[24–27] and activated cyclopropanes,[28] where such concerted ring closures are not favoured.[29] We therefore decided to reinvestigate the reactions using X-ray crystallography and NMR spectroscopy to establish unequivocally the structure and stereochemistry of the products.

Experimental results and discussion

The two bromolactones were prepared from **1** and **2** by the published method and their structures (Fig. 1) determined by

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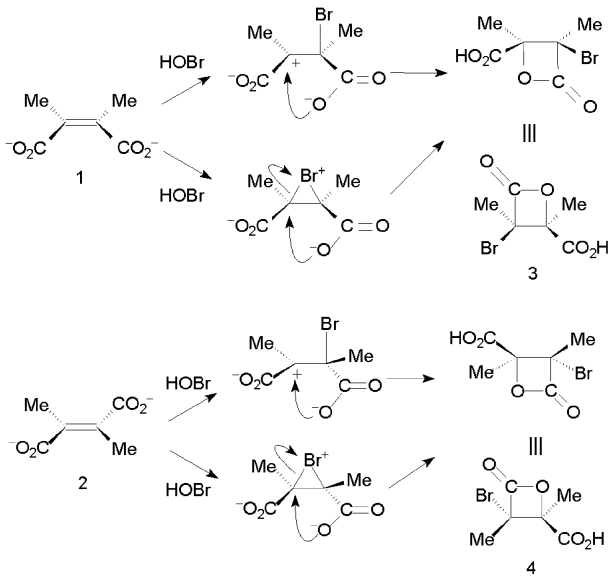
† Electronic supplementary information (ESI) available: Cartesian co-ordinates for optimised structures; crystal structure data. See DOI: 10.1039/b711538e



Scheme 1 Original interpretations of the results of Tarbell and Bartlett.

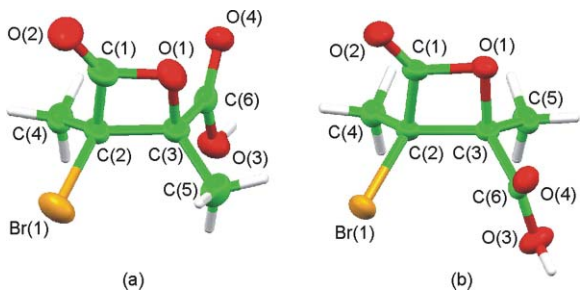


Fig. 1 X-Ray crystallographic structures for bromo-β-lactones: (a) *erythro* compound **4** from 2,3-dimethylmaleate; (b) *threo* compound **3** from 2,3-dimethylfumarate.

X-ray crystallography.[30] They proved to be those arising from overall *syn* addition to the alkenes, *i.e.* **4** from **1** and **3** from **2** (Scheme 2) and not as previously supposed. In order to account for these results, we have proposed[30,31] that an α-lactone intermediate[32] (**5** or **6**) is formed as the first step in the breakdown of the bromonium ion. The other carboxylate group then attacks the α-lactone, with a second inversion of configuration, to give the β-lactone.

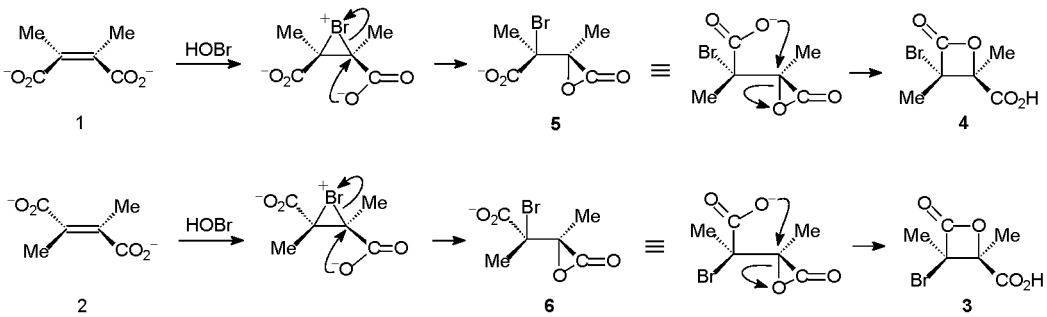
This scheme accounts simply and satisfactorily for the overall stereochemical outcome. An important feature is that both of the individual steps, the formation of the α-lactone from the bromonium ion, followed by formation of the β-lactone, are favoured *exo* processes in the Baldwin sense.[29] In agreement with this, Barnett and others have shown that in the halolactonisation of salts of β,γ-unsaturated acids the products formed under kinetic control are β-lactones arising from ring opening of the halonium ion in an *exo* manner.[33–35] Direct scission of the halonium ion derived from a salt of an α,β-unsaturated monocarboxylic acid to give a β-lactone in one step[36] has been recognised as an unfavourable pathway and achieved only under certain conditions,[19,37–41] vindicating the original view of Tarbell and Bartlett.[22]

There are many examples of the rearrangement of cyclic halonium ions to form other three-membered rings. Certain allylic alcohols are converted into haloepoxides;[42–46] de la Mare showed that rearranged halohydrins are formed from allyl halides and hypohalous acids, presumably by migration of the epihalonium ring.[47] Directly relevant 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.[48] Disodium maleate, however, affords only the *erythro* chlorohydrin when treated with aqueous chlorine,[49] or the *erythro* (*meso*) dichloride in the presence of added chloride ions;[50,51] these are the products of overall *syn* addition. Disodium fumarate, on the other hand, affords the products of both *anti* and *syn* addition (80 : 20).[49,51,52]

Similar suggestions involving intermediate formation of an α-lactone have been made by Kingsbury[55] in connection with the bromination of the sodium salts of citraconic and mesaconic acid, and by Badea[56] to account for the reactions of disodium maleate, but no rationalisation was offered for this behaviour.

α-Lactones are believed to be intermediates in the deamination of α-amino acids by nitrous acid and are responsible for the observed retention of configuration in the hydroxy acid products.[2,57] In aqueous solution they may undergo intramolecular nucleophilic attack. Reaction of the 2-amino-2-deoxy-D-aldohexonic acids with nitrous acid affords the 2,5-anhydro-D-hexonic acids of retained configuration at C-2 by double inversion.[58,59] Similar reactions of L-glutamic acid and L-glutamine result in the γ-lactone of L-α-hydroxyglutaric acid.[60,61] On the other hand, L-asparagine undergoes deamination with the replacement of only the α-amino group,[61] and there is no evidence for β-lactone formation in the careful work of Kuhn[49,51] on the chlorination of disodium maleate. It appears that in the dimethyl series ring closures are facilitated by alkyl substitution (the Thorpe–Ingold effect).[62]

From each of the bromination reactions we have also isolated, by fractional crystallisation, a crystalline bromohydrin, as reported



Scheme 2 The α-lactone interpretation of the results of Tarbell and Bartlett.

by Tarbell and Bartlett;[22] their structures have been determined by X-ray crystallography (Fig. 2). The *erythro* bromohydrin **7** was obtained from the maleate **1** and the *threo* bromohydrin **8** from the fumarate **2**. These correspond to *syn* addition to the alkene in each case, having the same configuration as the lactone from the same reaction. It was believed by the original authors[22] that the same bromohydrin was produced from maleate and fumarate and that it was not a primary reaction product but arose from hydrolysis of the individual lactone during isolation, by a unimolecular mechanism allowing a single product to be formed. We therefore treated each lactone under acidic conditions and found that a bromohydrin with the same configuration as the parent lactone was formed stereospecifically. This corresponds to a mechanism involving hydrolysis by acyl–oxygen cleavage of the lactone ring.[63] We shall discuss the origin of the bromohydrins again below.

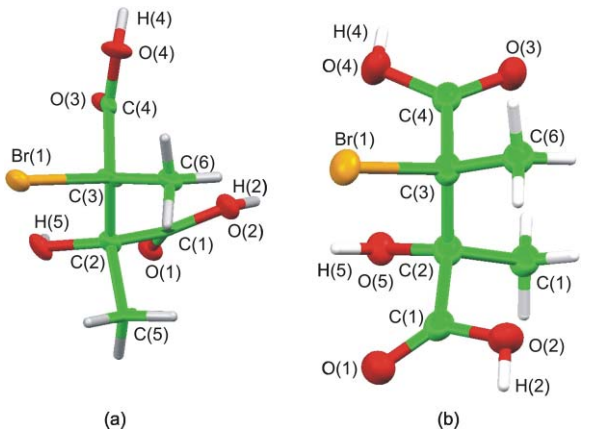
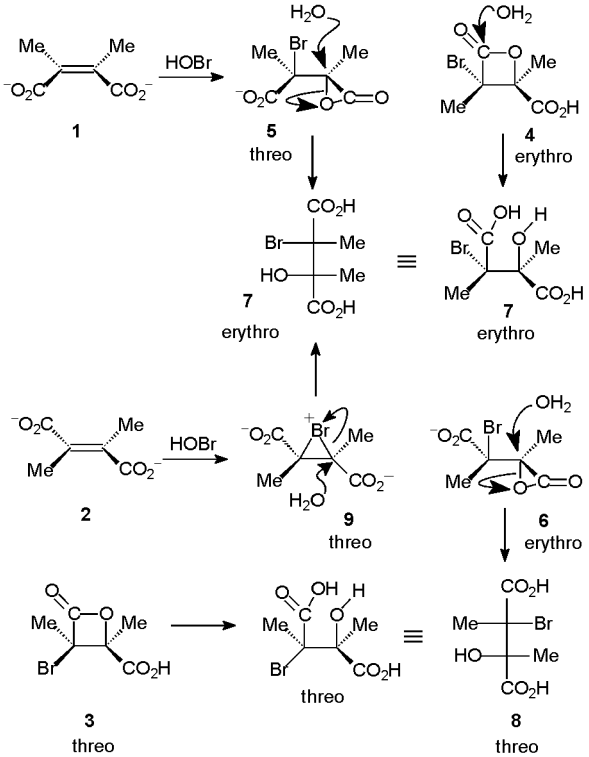


Fig. 2 X-Ray crystallographic structures for bromohydrins: (a) *erythro* compound **7** from 2,3-dimethylmaleate; (b) *threo* compound **8** from 2,3-dimethylfumarate.

The isolated yields in the brominations were not good. Having the NMR spectra of the expected components to hand, we were able to analyse in detail the crude ethyl acetate extracts of the acidified reaction mixtures. We confirmed that the maleate product contained 70% of the *erythro* lactone **4** together with 25% of *erythro* bromohydrin **7**. No other lactone or bromohydrin was present and only very small amounts of material not identified. In the products from the fumarate **2** there was 85% of the *threo* lactone **3** and 5% of each of the bromohydrins **7** and **8**. The presence of both bromohydrins in this case is of interest; the low bromohydrin yield is probably due to the extra care taken in isolating the products as rapidly as possible.

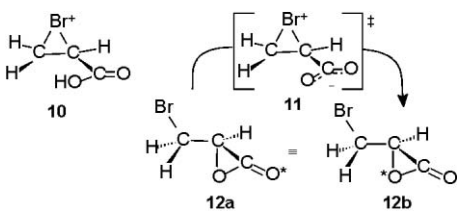
There is now the question of the origin of the bromohydrins **7** and **8** (Scheme 3). Although in the case of the reaction of the maleate the *erythro*-bromohydrin may arise from hydrolysis of the β-lactone **4**, there is also the possibility that the α-lactone intermediate **5** may be trapped by solvent water with the same stereochemical result (Scheme 3). As for the fumarate reaction, the same reasoning would apply to the *threo*-bromohydrin **8**; the most likely source of the *erythro* bromhydrin from the fumarate is direct attack by water on the original halonium ion **9**, and it should be remembered that in fumarate itself there is mainly *anti* addition of HOBr.[49–51]



Scheme 3 Formation of bromohydrins.

Computational results and discussion

We have previously demonstrated that the cyclic bromonium cation **10** derived formally by addition of Br^+ to acrylic acid is a true intermediate lying in a potential energy minimum, whereas the analogous neutral cyclic bromonium species **11** (Scheme 4) from acrylate anion possesses a single imaginary vibrational frequency and corresponds to a first-order saddle point on its potential energy surface at the B3LYP/6-31+G(d) level of density functional theory within the polarised continuum model (PCM) of aqueous solvation.[64] The reaction-coordinate vibrational mode (transition vector) shows a concerted motion of opening and closing the two three-membered rings, coupled with rotation about the C_α–CO_2^- bond. Following the intrinsic reaction coordinate (IRC) downhill in both directions from this species leads to a pair of equivalent bromomethyloxiranones **12a** and **12b**, according to which of the oxygen atoms of the carboxylate group forms a bond to C_α. These α-lactones are themselves energy minima and would differ only in the labelling of the oxygen atoms, O and O*; in all other respects they are identical. Thus the cyclic bromonium from acrylate is the transition structure (TS) for degenerate rearrangement of the



Scheme 4 Degenerate rearrangement of α-lactone.

α-lactone; this identity process (which retains the stereochemical configuration at C_α) has a barrier of 85 kJ mol^{-1}.[64]

The overall negatively-charged cyclic bromonium species **13** derived formally by addition of Br^+ to 2,3-dimethylmaleate dianion possesses a mirror plane of symmetry perpendicular to the C2–C3 bond and containing the Br atom (Fig. 3). It also possesses a single imaginary frequency of vibration associated with a transition vector for motion of the bromine between C2 and C3 coupled with opening and closing of three-membered α-lactone rings, one at C2 and the other at C3. This species is the TS for degenerate rearrangement of one α-lactone **15** into its enantiomer **15′**; this identity process (which inverts the stereochemical configurations at both C2 and C3) has a free-energy barrier in water of 30 kJ mol^{-1} (Table 1). Similarly, the overall negatively-charged cyclic bromonium species **14** derived formally by addition of Br^+ to 2,3-dimethylfumarate dianion possesses a two-fold axis of symmetry bisecting the C2–C3 bond and containing the Br atom. It also possesses a single imaginary frequency of vibration associated with a transition vector for motion of the bromine between C2 and C3 coupled with opening and closing of three-membered α-lactone rings, one at C2 and the other at C3. This species is also the TS for degenerate rearrangement of one α-lactone **16** into its enantiomer **16′**; this identity process (which inverts the stereochemical configurations at both C2 and C3) has a free-energy barrier in water of only 10 kJ mol^{-1}.

Isodesmic relations have been previously employed[64] to estimate the ring strain energies of ethene bromonium cation and unsubstituted oxiranone (the parent α-lactone) as about 67 and 150 kJ mol^{-1}, respectively, at the same level of theory as used in this work. It therefore seems odd that bromoalkyl oxiranones are calculated to be significantly lower in energy than bromonium carboxylates, whether they are derived from unsubstituted acrylate anion or from substituted maleate and fumarate dianions. This apparent paradox is resolved by recognition of the even greater instability of the acyclic zwitterions $BrC_\beta H_2–C_\alpha{}^+H–CO_2{}^-$ and $BrC_\beta Me(CO_2{}^-)–C_\alpha{}^+Me–CO_2{}^-$. Formation of a cyclic bromonium species serves to stabilise a carbocation centre at C_α, but not

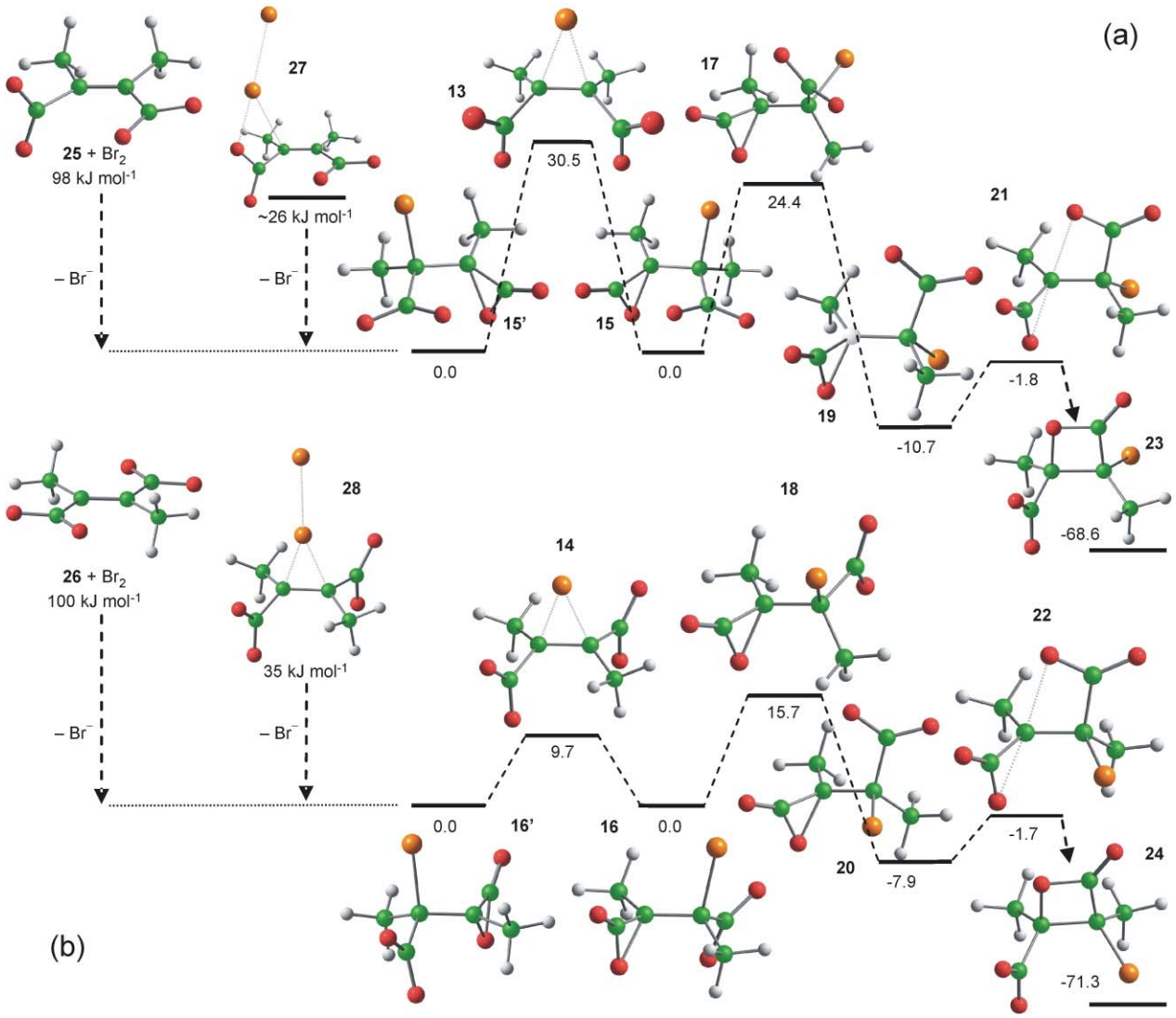


Fig. 3 PCM/B3LYP/6-31+G(d) optimised structures along the reaction coordinate for aqueous bromination of (a) 2,3-dimethylmaleate and (b) 2,3-dimethylfumarate.

Table 1 PCM/B3LYP/6-31+G(d) energies and free energies for optimised species in water

	Species	Type	$\nu^{\ddagger}$/cm^{-1}	E_{aq}/hartree	ΔE_{rel}/kJ mol^{-1}	G_{aq}/hartree	ΔG_{rel}/kJ mol^{-1}
13		[Bromonium]‡	201*i*	−3105.022397	35.9	−3104.947707	30.5
15		α-Lactone 1	Min	−3105.036053	0.0	−3104.959316	0.0
17		[Conformational]‡	62*i*	−3105.028058	21.0	−3104.950020	24.4
19		α-Lactone 2	Min	−3105.036238	−0.5	−3104.963395	−10.7
21		[Backside]‡	264*i*	−3105.034712	3.5	−3104.959990	−1.8
23		β-Lactone	Min	−3105.064542	−74.8	−3104.985429	−68.6
25		Me_2-maleate dianion	Min	−533.488924			
27		Asymmetric complex	Max	−5675.942021			
29		[Frontside]‡	126*i*	−3105.016491	51.3	−3104.942212	44.9
14		[Bromonium]‡	88*i*	−3105.029981	13.7	−3104.955462	9.7
16		α-Lactone 1	Min	−3105.035218	0.0	−3104.959172	0.0
18		[conformational]‡	50*i*	−3105.030137	13.3	−3104.953196	15.7
20		α-Lactone 2	Min	−3105.037660	−6.4	−3104.962180	−7.9
22		[Backside]‡	271*i*	−3105.034120	2.9	−3104.959828	−1.7
24		β-Lactone	Min	−3105.064413	−76.7	−3104.986344	−71.3
26		Me_2-fumarate dianion	Min	−533.487277			
28		Symmetric complex	Min	−5676.937899			
		Br_2	Min	−5143.425755			
		Br^+		−2571.268171			
		Br^-		−2571.915835			

as effectively as formation of a bromoalkyl oxiranone, since the former is still a zwitterion whereas the latter is formally a covalent species. The isodesmic relations previously considered neglected to take into account the energetic cost of charge separation; heterolytic opening of an α-lactone ring involves not only a favourable release of ring strain energy but also an unfavourable separation of positive and negative charges, even in solution as modelled by PCM.

The α-lactone **15** from 2,3-dimethylmaleate lies just 0.4 kJ mol^{-1} lower in free energy than its fumarate diastereomer **16** (Fig. 3). The endocyclic C_α–O_n bond is antiperiplanar to the C_β–Br bond in these anionic species, which each contain a C_α–C_β single bond between C2 and C3 and therefore may undergo internal rotation. Of particular interest is the rotamer in which the endocyclic C_α–O_n bond is antiperiplanar to the C_β–CO_2^- bond: conformational TS **17** leads from **15** *via* a 24 kJ mol^{-1} barrier to this α-lactone rotamer **19** which is 11 kJ mol^{-1} lower in free energy than **15** in the maleate-derived series. Correspondingly, conformational TS **18** leads from **16** *via* a 16 kJ mol^{-1} barrier to this α-lactone rotamer **20** which is 8 kJ mol^{-1} lower in free energy than **16** in the fumarate-derived series.

Intramolecular S_N2-like backside displacement may occur from **19** *via* TS **21** with a 9 kJ mol^{-1} barrier to β-lactone **23** which is 69 kJ mol^{-1} lower in free energy than **15**; similarly **20** may also undergo the analogous backside displacement, with inversion of configuration at C_α, *via* TS **22** with a 6 kJ mol^{-1} barrier to β-lactone **24** which is 71 kJ mol^{-1} lower in free energy than **16** (Fig. 3).

Fig. 4 shows overlays of PCM/B3LYP/6-31+G(d) optimized (colours) and crystallographic (blue) structures[30] for the neutral bromo-β-lactone products (the protonated forms of **23** and **24**): (a) (3*S*,4*S*)-3-bromo-4-carboxy-3,4-dimethyloxetan-2-one derived from 2,3-dimethylmaleate and (b) (3*R*,4*S*)-3-bromo-4-carboxy-3,4-dimethyloxetan-2-one derived from 2,3-dimethylfumarate. The numbers beside the non-hydrogen atoms are displacements in Ångström; these differences are largely due to crystal packing effects. The similarity between the calculated and crystallographic structures confirms PCM/B3LYP/6-31+G(d) as an acceptable theoretical method for these compounds.

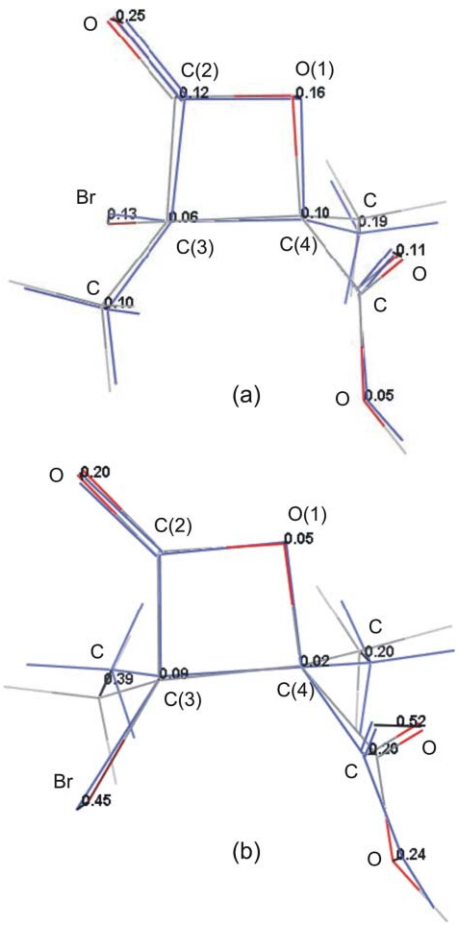


Fig. 4 Calculated (colours) and crystallographic (blue) structures for bromo-β-lactones from (a) 2,3-dimethylmaleate and (b) 2,3-dimethylfumarate.

The computational results clearly demonstrate the existence (at the level of theory employed) of smooth, continuous, and energetically feasible pathways leading stereospecifically *via*

the initially formed α-lactones to the experimentally observed bromo-β-lactones, in agreement with the proposed mechanism (Scheme 2, Fig. 3) for aqueous bromination of the dianions of 2,3-dimethylmaleate and 2,3-dimethylfumarate. But, if the cyclic bromonium species is neither an energy minimum nor a TS for electrophilic bromination, then how does bromination occur leading to an α-lactone as the first-formed intermediate?

Addition of Br_2 to 2,3-dimethylmaleate dianion **25** in water to give **15** and aqueous Br^- is exothermic by 98 kJ mol^{-1}; similarly, aqueous addition of Br_2 to 2,3-dimethylfumarate dianion **26** to give **16** and Br^- is exothermic by 100 kJ mol^{-1}. Unconstrained optimisation of Br_2 + 2,3-dimethylmaleate yielded an asymmetric structure **27** (Fig. 3) in which the proximal bromine was loosely associated with one of the carboxylate oxygens, but which possessed two imaginary frequencies and was 26 kJ mol^{-1} higher in energy than **15** and Br^-; deletion of the distal bromine (the incipient bromide anion) caused this species to collapse directly to the α-lactone **15**. Although we have been unable to locate it, we suspect that a first-order TS exists in which electrophilic attack by molecular bromine on C_β is coupled with nucleophilic attack by the carboxylate group on C_α. The two imaginary frequencies of **27** have low values and their associated normal modes are unrelated to the reaction coordinate for bromination; the asymmetric species **27** may therefore be considered as a quasi-intermediate on the pathway for electrophilic addition that avoids formation of the unfavourable symmetric species **13**. Unconstrained optimisation of Br_2 + 2,3-dimethylfumarate yielded a C_2-symmetric structure **28** (Fig. 3) in which the two bromine atoms are aligned perpendicularly to the plane of the fumarate moiety, but with a very elongated Br···Br distance of 2.99 Å as compared with 2.32 Å in Br_2; this intermediate is 35 kJ mol^{-1} higher in energy than **16** and Br^-. We suspect the existence of a TS in which electrophilic attack by molecular bromine on C_β is coupled with departure of the bromide leaving group and with nucleophilic attack by the carboxylate group on C_α. This species, and its maleate analogue, may be very difficult to locate and characterise within a PCM treatment of water, since an important component of the reaction coordinate is likely to be specific solvation of the incipient bromide anion.

Is there a pathway for overall *anti* addition to the C=C double bond that would allow formation of the experimentally unobserved diastereomers, *i.e.* **3** from **1** and **4** from **2** (Scheme 1) according to the original assumptions[22] of Tarbell and Bartlett? Firstly it should be stressed that there are no such paths leading downhill in energy from the cyclic bromonium TSs **13** and **14**: a first-order saddle point can only interconnect two adjacent energy minima,[65] which for these species are the pairs of enantiomeric α-lactones. Following extensive searching of the potential energy hypersurface between **15** and **24**, species **29** has been located and characterised as a genuine TS with a single imaginary frequency. Inspection of its transition vector reveals that the motion of the atoms in the TS corresponds to an unusual frontside intramolecular S_N2-like displacement in which the three-membered α-lactone ring opens by heterolytic cleavage of the C_α–O_n bond in concert with formation of the four-membered β-lactone ring by attack of the C_β–CO_2^- group upon the same face of C_α (Fig. 5). This TS lies 44 kJ mol^{-1} higher in free energy than α-lactone **15** from which it leads directly to the *cis* β-lactone **24**. The free energy difference between the competing TSs **13** and **29** corresponds to about four

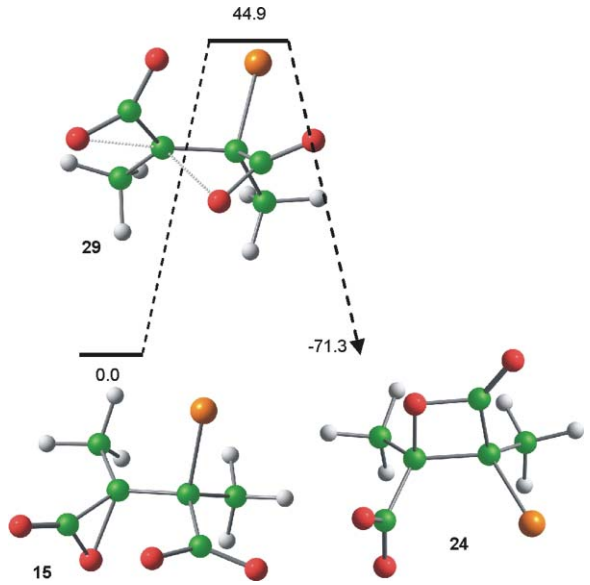


Fig. 5 PCM/B3LYP/6-31+G(d)-optimised structures for direct conversion of *cis* α-lactone **15** from 2,3-dimethylmaleate to *cis* β-lactone **24** *via* a frontside displacement TS **29**.

orders of magnitude in relative rate constants at 25 °C (more at the ambient temperature of the experimental work reported here!) and is more than enough to account for the failure to observe any signals corresponding to **24** in the NMR spectra for reaction of 2,3-dimethylmaleate with aqueous bromine. Despite our best efforts, we have been unable to locate any TS that would directly interconnect α-lactone **14** with β-lactone **23** for the corresponding reaction of 2,3-dimethylfumarate.

The frontside displacement TS **29** possesses carbocation character inasmuch as C_α is almost perfectly planar, but of course it has two negatively charged carboxylate substituents. Structurally it resembles an acyclic "zwitterion" (or cation/dianion), but it must be emphasised that no such species exists on the PCM/B3LYP/6-31+G(d) energy surface as an intermediate in a local energy minimum. The $^-O_2CC_\beta$–C_α^+–CO_2^- moiety is unstable with respect to lactone formation involving one or other of the two carboxylate groups. Interconversion between the α- and β-lactones occurs preferentially *via* the backside TS **21**, in which the positive charge at C_α is partially stabilised by interactions with negative carboxylates on opposite faces. Stabilisation of the carbocation centre by bridging interaction with the bromine atom is less effective; hence the cyclic bromonium species **13** is only a TS for interconversion of alternative α-lactones rather than a discrete intermediate. If both carboxylate groups are found on the same face of C_α in a particular conformation of the (unstable) acyclic "zwitterion", then simultaneous partial stabilisation of the carbocation by both of them (in TS **29**) is better than none at all. Finally we note that the non-existence of a discrete acyclic intermediate, that would allow stereochemical interconversion between the maleate and fumarate isomers by internal rotation about the C_β–C_α bond, obviates the need for Tarbell and Bartlett's requirement[22] for ring closure with the carbocationic centre to occur 'in the quickest possible succession' in order to form the β-lactone in a stereospecific manner.

Experimental

General remarks

NMR spectra were recorded on a Bruker DPX 400 (^{1}H: 400 MHz and ^{13}C: 100.6 MHz) or a Bruker AV 300 (^{1}H: 300.2 MHz and ^{13}C: 75.5 MHz) spectrometer in the deuterated solvent stated. 2,3-Dimethylmaleic anhydride was purchased from Aldrich and used without further purification. All other chemicals used were of analytical grade.

2,3-Dimethylfumaric acid

2,3-Dimethylmaleic anhydride (0.15 mol) was dissolved in 10% excess of NaOH in water (150 mL) and refluxed for 24 hours. The mixture was cooled in an ice-water bath and acidified with conc. hydrochloric acid to pH ~1. The precipitate was filtered, washed with dichloromethane and crystallised from ethyl acetate–toluene to give 2,3-methylfumaric acid in 20% yield. mp 246–248 °C (lit.,[22,66] 245 °C, 240–242 °C); δ_H [300 MHz, $(CD_3)_2SO$] 1.92 (s, 6H, 2Me); δ_C [75 MHz, $(CD_3)_2SO$] 17.9 (Me), 133.2 (C=C), 171.1 (COOH).

General procedure for bromination of sodium dimethylmaleate and sodium dimethylfumarate

To a solution of dimethylmaleic anhydride or fumaric acid (20 mmol) neutralised with sodium hydroxide (40 mmol) in 50 mL of water was added bromine (20 mmol) within 10 minutes. The solution was acidified with conc. sulfuric acid to pH ~1. The solution was extracted three times with ethyl acetate. The organic phase was dried ($MgSO_4$) and evaporated to give an oil (3.6 g for maleate and 3 g for fumarate), containing mainly of bromolactones. The lactones and bromohydrins were obtained by fractional crystallisation from toluene–petroleum ether and the bromohyrins recrystallised from ethyl acetate–toluene. The lactones have been described previously.[30]

***erythro*-2-Bromo-3-hydroxy-2,3-dimethylsuccinic acid (7).** Isolated from the maleate reaction, mp 180–181 °C (lit.,[22] 168–170 °C); δ_H [300 MHz, $(CD_3)_2CO$] 1.65 (s, 3H, Me), 2.05 (s, 3H, Me); δ_C [75 MHz, $(CD_3)_2CO$] 23.2 (Me), 27.0 (Me), 68.4 (C-3), 79.2 (C-2), 172.7 (C=O), 174.1 (C=O). {Found: MS-ES (+) *m/z* 257.9971; $C_6H_9{}^{79}BrO_5$ $[M + NH_4]^+$ requires 257.9972}.

Crystal data for $C_6H_9BrO_5$. M = 241.04, monoclinic, a = 11.4120(5), b = 5.8870(3), c = 12.3790(7) Å, β = 93.337(2)°, U = 830.24(7) Å^3, T = 30(2) K, space group = $P2_1/c$, Z = 4, μ(Mo-Kα) = 4.932 mm^{-1}, 1883 reflections (R_{int} = 0.0707), $R1$ = 0.0381 and $wR2$ = 0.0761 based on 1420 F^2 with $F_o \geq 4\sigma(F_o)$. Software used SHELXS,[67] SHELXL-97[68] and ORTEX.[69] CCDC reference number 652216. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b711538e

***threo*-2-Bromo-3-hydroxy-2,3-dimethylsuccinic acid (8).** Isolated from the fumarate reaction as a monohydrate, mp 168–170 °C (lit.,[22] 168–170 °C); δ_H [300 MHz, $(CD_3)_2CO$] 1.75 (s, 3H, Me), 2.02 (s, 3H, Me); δ_C [75 MHz, $(CD_3)_2CO$] 24.8 (Me), 26.6 (Me), 67.8 (C-3), 79.5 (C-2), 171.4 (C=O), 174.3 (C=O). {Found: MS-ES (−) *m/z* 238.9549; $C_6H_9{}^{79}BrO_5$ $[M - H]^-$ requires 238.9550}.

Crystal data for $C_6H_9BrO_5{\cdot}H_2O$. M = 259.06, triclinic, a = 6.2390(3), b = 7.2280(4), c = 11.1710(8) Å, α = 82.801(2), γ = 69.105(3)°, U = 466.56(5) Å^3, T = 150(2) K, space group = $P\bar{1}$ (no. 2), Z = 2, μ(Mo-Kα) = 4.403 mm^{-1}, 2075 reflections (R_{int} = 0.0683), $R1$ = 0.0378 and $wR2$ = 0.0758 based on 1623 F^2 with $F_o \geq 4\sigma(F_o)$. Software used SHELXS,[67] SHELXL-97[68] and ORTEX.[69] CCDC reference number 652217. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b711538e.

Acid-catalysed hydrolysis of lactones

The maleate lactone **4** or fumarate lactone **3** (0.25 g) was dissolved in 100 mL of 20% (v/v) sulfuric acid for 24 h. The solution was extracted twice with ethyl acetate, dried ($MgSO_4$) and evaporated, producing *only* one bromohydrin in each case together with some unreacted lactone. The bromohydrins were isolated in crystalline form and shown to be identical with those obtained from the reaction of aqueous bromine with dimethylmaleate and dimethylfumarate.

The course of hydrolysis was also followed by NMR measurements: ~50 mg of each lactone was dissolved in CD_3CN–D_2O [50% (v/v)] containing a few drops of conc. sulfuric acid and the reactions were followed by ^{13}C NMR for one week. The spectra of each lactone were also recorded in the same solvent mixture without added acid.

Maleate

Control. δ_C [75.5 MHz NMR, CD_3CN–D_2O] 22.0 (lactone-Me), 22.5 (lactone-Me), 63.7 (lactone-C-3), 83.8 (lactone-C-4), 167.2 (lactone-C=O), 169.1 (lactone-C=O).

First day. δ_C [75.5 MHz NMR, CD_3CN–D_2O containing H_2SO_4] 21.7 (lactone-Me), 21.8 (lactone-Me), 22.6 (bromohydrin-Me), 25.6 (bromohydrin-Me), 63.0 (lactone-C-3), 68.9 (bromohydrin-C-3), 77.9 (bromohydrin-C-2), 84.6 (lactone-C-4), 168.3 (lactone-C=O), 170.2 (lactone-C=O), 172.9 (bromohydrin-C=O), 174.8 (bromohydrin-C=O). Ratio of bromohydrin:lactone 0.4; after three days the ratio was 6.2.

One week later. δ_C [75.5 MHz NMR, CD_3CN–D_2O containing H_2SO_4] 21.7 (lactone-Me), 21.8 (lactone-Me), 22.2 (bromohydrin-Me), 25.6 (bromohydrin-Me), 63.0 (lactone-C-3), 68.9 (bromohydrin-C-3), 77.9 (bromohydrin-C-2), 84.6 (lactone-C-4), 168.4 (lactone-C=O), 170.2 (lactone-C=O), 172.9 (bromohydrin-C=O), 174.8 (bromohydrin-C=O). The amount of lactone was very small.

Fumarate

Control. δ_C [75.5 MHz NMR, CD_3CN–D_2O] 17.6 (lactone-Me), 20.1 (lactone-Me), 60.2 (lactone-C-3), 85.3 (lactone-C-4), 167.4 (lactone-C=O), 169.8 (lactone-C=O).

First day. δ_C [75.5 MHz NMR, CD_3CN–D_2O containing H_2SO_4] 17.3 (lactone-Me), 19.8 (lactone-Me), 22.7 (bromohydrin-Me), 24.7 (bromohydrin-Me), 59.9 (lactone-C-3), 66.4 (bromohydrin-C-3), 78.3 (bromohydrin-C-2), 85.8 (lactone-C-4), 168.1 (lactone-C=O), 170.7 (lactone-C=O), 172.2 (bromohydrin-C=O), 174.5 (bromohydrin-C=O). Ratio of bromohydrin:lactone: 0.3; after three days the ratio was 2.1.

One week later. δ_C [75.5 MHz NMR, CD_3CN–D_2O containing H_2SO_4] 17.3 (lactone-Me), 19.8 (lactone-Me), 22.7 (bromohydrin-Me), 24.7 (bromohydrin-Me), 59.8 (lactone-C-3), 66.4 (bromohydrin-C-3), 78.3 (bromohydrin-C-2), 85.8 (lactone-C-4), 168.2 (lactone-C=O), 170.8 (lactone-C=O), 172.2 (bromohydrin-C=O), 174.5 (bromohydrin-C=O). The amount of lactone was very small.

Computational methods

All calculations were performed by means of the GAUSSIAN98 program[70] using the B3LYP density functional method with the 6-31+G(d) basis (with six Cartesian d functions on non-hydrogen atoms), together with the PCM method for aqueous solvation using $\varepsilon = 78.4$ and default UAHF united-atom radii for the molecular cavity. Convergence in the SCF procedure was typically achieved using the "very tight" option; geometry optimisations used default convergence criteria. TSs were located by means of QTS2, QTS3 and EF methods as appropriate, and were characterised as possessing a single imaginary frequency corresponding to the transition vector (or reaction coordinate mode) for a particular chemical transformation, in contrast to energy minima with all-real vibrational frequencies. IRC calculations confirmed the identity of the energy minima adjacent to each saddle point. Energies reported (Table 1) as E_{aq} are what the Gaussian calls "total free energy in solution (with non-electrostatic terms)", *viz*. the total electronic energy polarised by the dielectric continuum together with the cavitation, dispersion and repulsive terms within PCM. Energies reported (Table 1) as G_{aq} are what the Gaussian calls "sum of electronic and thermal free energies" which includes zero-point, thermal and entropic terms at 298 K and 1 atm. The inappropriate standard state is of no consequence since all the reactions considered here are unimolecular, except for the Br_2 addition for which relative energies ΔE_{aq} are given in the text.

Overlay comparisons between calculated and crystallographic structures were performed by use of the rigid alignment method in the MOE2004.03 suite of programs.[71]

Conclusions

Aqueous bromination of the disodium salts of 2,3-dimethylmaleic and 2,3-dimethylfumaric acids yields bromo-β-lactones with stereochemistry that indicates overall *syn* addition: that is, *cis* alkene yields *erythro* lactone, and *trans* alkene yields *threo* lactone. These results, determined by X-ray crystallography, are contrary to what had been assumed by Tarbell and Bartlett in 1937, which has been quoted in textbooks since that time. Whereas Tarbell and Bartlett also reported that the same bromohydrin was produced by hydrolysis of both the maleate and fumarate derivatives, X-ray crystallography also now reveals stereospecific hydrolysis of each bromo-β-lactone to a different bromohydrin by acyl–oxygen cleavage of the lactone ring. B3LYP/6-31+G(d) calculations using a PCM description of aqueous solvation confirm the validity of our proposed mechanism, in which the first-formed intermediate in each case is an α-lactone. Electrophilic attack at one end of the C=C double bond occurs concertedly with ring-closure by the carboxylate group at the other end. The cyclic bromonium species is not an intermediate, but rather is the transition structure for interconversion of enantiomeric α-lactones. The unstable BrC_β–$C_\alpha{}^+$–$CO_2{}^-$ moiety is more effectively stabilised by bridging O^- than by bridging Br, since the resulting α-lactone is neutral whereas the bromonium is still zwitterionic. The initial α-lactone undergoes internal rotation about the central C–C bond to a conformer in which the carboxylate at C_β is suitably aligned for intramolecular backside nucleophilic displacement at C_α. An alternative pathway leading directly from *cis* alkene to *cis* β-lactone, *via* an unusual frontside displacement mechanism, is over 20 kJ mol^{-1} higher in free energy. No pathway leading directly from *trans* alkene to *trans* β-lactone could be found. Despite their ring strain energy, α-lactones may be formed in aqueous solution at room temperature—albeit transiently—and may be involved as reactive intermediates more widely than has generally been recognised. The experimental and computational evidence presented here correspond to Cinderella's slipper: α-lactones are more than a fantastical dream!

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