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Experimental and computational studies of α-lactones: Structure and bonding in the three-membered ring†

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ABSTRACT: 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 (**4** from **1**, and **3** from **2**) opposite to those originally assigned (**3** from **1**, and **4** from **2**). Specifically, the maleate leads to a bromo-β-lactone with the methyl groups in a *trans* relationship, whereas the fumarate leads to the corresponding *cis* isomer. To account for this observation, we suggest that the first-formed intermediate in each case is an α-lactone. B3LYP/6–31 + G(d) calculations in PCM water indicate that the cyclic chloronium and bromonium adducts of acrylate anion are not intermediates but transition structures for the degenerate rearrangement of halomethyl-α-lactones. Bader analysis of MP2/6–31 + G(d,p) electron density distributions indicates that oxiranone possesses considerable ionic character in the endocyclic C_α—O_n bond. In PCM water there is neither a ring critical point nor a bond critical point for C_α—O_n, although geometrically the molecule still possesses an acute-angled three-membered ring with a $C_\alpha CO_n$ angle of only 69°. Combined quantum/classical calculations for B3LYP/6–31 + G(d) oxiranone surrounded by about 600 explicit TIP3P water molecules indicate that the cyclic structure is an energy minimum in aqueous solution, and Bader analysis gives a result similar to that from the continuum model. Copyright © 2002 John Wiley & Sons, Ltd.

KEYWORDS: α-lactone; electrophilic addition; crystal structure; mechanism; computational modelling; *ab initio* MO; Bader analysis; QM/MM explicit solvation

INSTABILITY OF α-LACTONES

α-Lactones are cyclic esters containing a three-membered ring; they are highly reactive and readily polymerize.[1] The simplest of these, oxiranone, may be prepared by addition of carbene CH_2 to carbon dioxide in an inert matrix at low temperature,[2] but room-temperature isolable α-lactones possess electron-withdrawing and bulky substituents at C_α.[3] The instability of α-lactones may be due to facile ring opening to a zwitterion.[4] The intermediate implicated in hydrolysis of α-halocarboxylates with retention of configuration has been described as a zwitterion,[5] an α-lactone[6] or an α-lactone possessing much ionic character.[7] On the basis of MP2/6–311++G(d,p) calculations,[8] we concluded that the intermediate was best described as an α-lactone, but that the transition structure (for halide elimination from an α-halocarboxylate) leading to it possessed substantial charge separation and a significant degree of covalency in the bond between C_α and the endocyclic oxygen O_n. Calculations at the QCISD(T)/6–311G(2df,p)//MP2/6–311G(d,p) level of theory indicated that the exocyclic C=O bond raises the ring strain energy of oxiranone by 55 kJ mol^{-1} over that of oxirane.[9]

EXPERIMENTAL EVIDENCE FOR α-LACTONE INTERMEDIATES IN ADDITION OF AQUEOUS BROMINE TO DISODIUM DIMETHYL MALEATE AND FUMARATE

Addition of halogens to an alkene usually occurs in two stages and in an *anti* manner.[10] In 1937, Tarbell and Bartlett[11] found that the disodium salts of 2,3-dimethylmaleic acid and 2,3-dimethylfumaric acid (**1** and **2**, Fig. 1) reacted stereospecifically with aqueous bromine, each yielding a single crystalline bromo-β-lactone; the maleate and fumarate derivatives gave compounds with melting-points of 95–96 and 148–150 °C, respectively. The authors proposed that initial addition of bromine to give a carbocation was followed 'in the quickest possible

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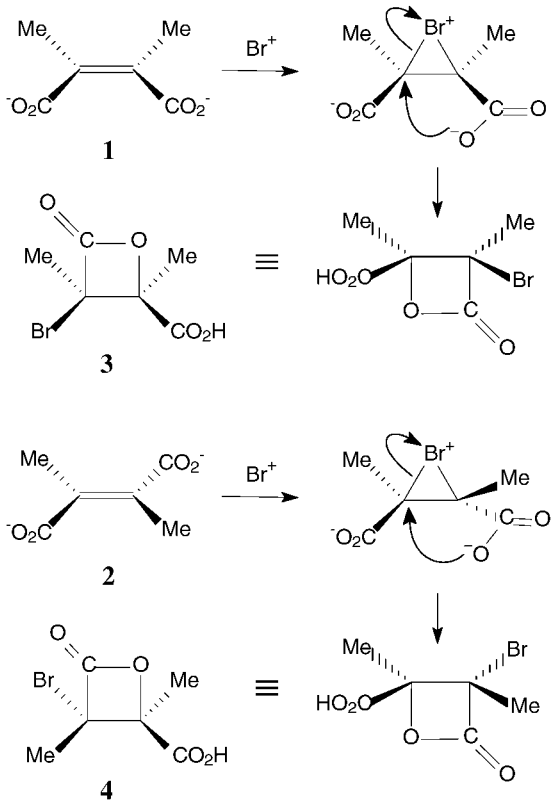

Figure 1. Winstein's interpretation of the results of Tarbell and Bartlett

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[12] proposing cyclic halonium ion intermediates for halogen addition to alkenes; Fig. 1 illustrates Winstein's subsequent interpretation.[13]

Suspecting that the reaction might be more complex than had been supposed, we prepared the two bromolactones from **1** and **2** by the published method[11] and established their structures by x-ray crystallography.[14] The disodium salt of 2,3-dimethylmaleic acid **1** yielded the bromo-*β*-lactone **4** (m.p. 92–94 °C) with the methyl groups in a *trans* relationship. Correspondingly, the disodium salt of 2,3-dimethylfumaric acid **2** yielded the bromo-*β*-lactone **3** (m.p. 148 °C). This unequivocal result corresponds to overall *syn* addition to the alkene and 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.[13,15] We believe that the most satisfactory explanation of our results (Fig. 2) involves formation of an α-lactone intermediate (**5** and **6**) as the first step in the decomposition of the bromonium ion. This α-lactone undergoes internal rotation about the central C—C bond. Subsequently the other carboxylate group attacks the α-lactone, with a second inversion of configuration, to give the *β*-

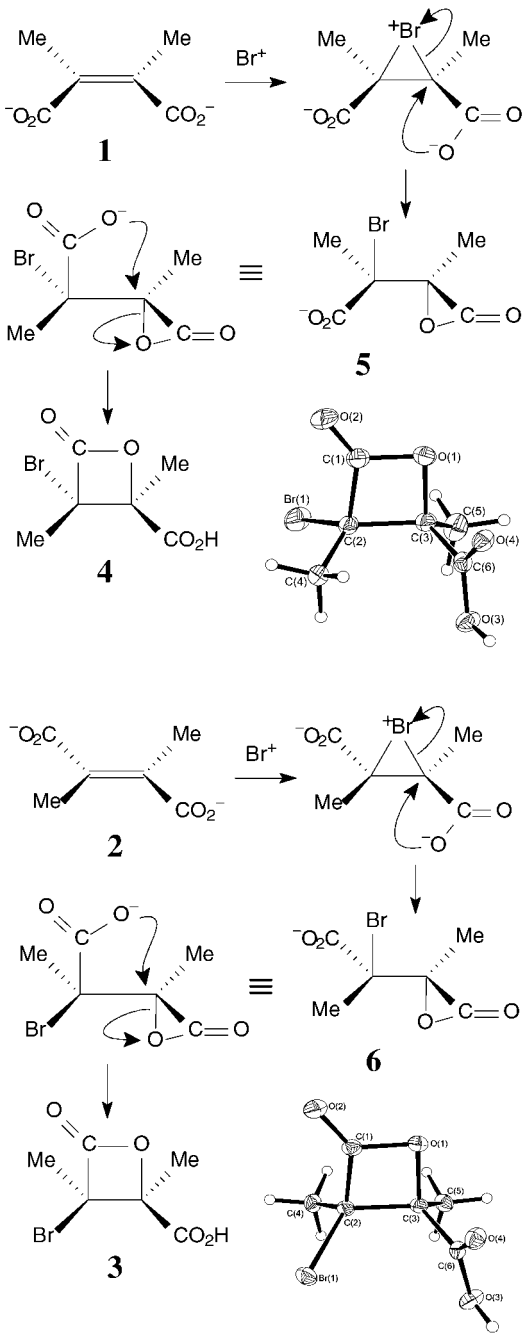

Figure 2. The α-lactone reinterpretation of the results of Tarbell and Bartlett, based on x-ray crystal structures for the bromo-*β*-lactones **4** (from maleate **1**) and **3** (from fumarate **2**)

lactone. This scheme accounts simply and satisfactorily for the overall stereochemical outcome.

COMPUTATIONAL EVIDENCE FOR α-LACTONE INTERMEDIATE IN ELECTROPHILIC HALOGENATION OF ACRYLATE ANION

Geometry optimization and frequency calculations using the B3LYP density functional with the 6–31 + G(d) basis

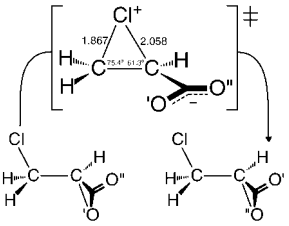

Figure 3. B3LYP/6–31 + G(d) calculations in PCM water predict the chloronium carboxylate from chlorination of acrylate anion to be a transition structure for degenerate rearrangement of equivalent chloromethyl oxiranones

and the PCM method for aqueous solvation ($\varepsilon = 78.4$) were carried out using the Gaussian98 program.[16] The positively charged cyclic chloronium and bromonium species formally derived by addition of Cl^+ or Br^+ across the C═C bond of acrylic acid are both found to be minimum-energy species; these would be capable of undergoing further reaction by attack of an external nucleophile. In contrast, the corresponding neutral species derived from acrylate anion are both found to be first-order saddle points. Determination of the transition vector, followed by intrinsic reaction-coordinate calculations in both directions from this transition structure, leads to a pair of equivalent α-lactones that would differ only in the labeling of the oxygen atoms (Fig. 3). Thus the cyclic halonium is the transition structure for degenerate rearrangement of the α-lactone; this process (which retains the stereochemical configuration at C_α) has a barrier of 71 kJ mol^{-1} for the chloromethyloxiranone and 85 kJ mol^{-1} for the bromomethyloxiranone. At first sight it is surprising that the α-lactones should be lower in energy than the cyclic haloniums. We estimate the ring strain energy of the parent ethene chloronium cation to be about 82 kJ mol^{-1} from a gas-phase isodesmic relation, whereas the ring strain energy of the parent oxiranone is about 169 kJ mol^{-1}, as noted above. Why is the chloromethyloxiranone about 70 kJ mol^{-1} lower in energy than the chloronium carboxylate species, despite possessing approximately twice as much ring strain energy? The answer lies with the extreme instability of the zwitterion $XCH_2C_\alpha{}^+CO_2{}^-$ (X = Cl or Br). Formation of the cyclic halonium carboxylate species serves to stabilize the carbocation centre at C_α, but not as effectively as formation of the α-lactone, since the former is still a zwitterion whereas the latter is formally a covalent species. A zwitterionic structure in which the methylene and carboxylate moieties of oxiranone are coplanar disintegrates spontaneously to CH_2 and CO_2.[9]

IS OXIRANONE AN α-LACTONE OR NOT?

Hughes and Ingold eschewed the term α-lactone;[5,17] Ingold considered that the α-carboxylate group established a 'rather long, somewhat weak, essentially electrostatic bond'[18] by interaction with the adjacent carbocationic centre. Winstein described the intermediate in hydrolysis of α-bromopropionate as an α-lactone,[13,19] but denied that this term implied a completely covalent species;[7a] instead, he reasoned that 'there is a very large ionic character to the new carbon-oxygen bond.'[7a]

Analysis of the electron density distributions for some three-membered rings was carried out at the SCI-PCM/MP2/6–31 + G(d,p)//HF/6–31 + G(d,p) level using the AIMPAC[20] suite of programs. As expected, oxirane in water shows a bond critical point (BCP) for each of the bonds of the ring, together with a ring critical point (RCP). However, although the C_α—O_n bond length of oxiranone in water (1.50 Å) is a reasonable value for an endocyclic bond, no BCP is found between these atoms.[21] The net charges on the O_nCO_x and $C_\alpha H_2$ groups are −0.63 and +0.63 respectively, which suggests zwitterionic character. However, the three interior angles of the ring are all ≤69°, so that the structure is not at all open, despite lacking an RCP and a C_α—O_n BCP according to the Bader analysis; geometrically the structure still resembles a cyclic species. The carboxylate group of oxiranone in water is able to approach closely to C_α, with the $C_\alpha CO_n$ angle distorting by about 50° from its value in α-chloroacetic acid.[8] Furthermore, analysis of the calculated vibrational Hessian indicates that there is a significant (although rather weak) restoring force for distortion of the C_α—O_n 'bond', consistent with there being no tendency for the 'ring' to spring open spontaneously. The theoretical results do seem to accord fairly well with Winstein's description of an α-lactone with considerable ionic character, and the Bader analysis certainly indicates that the C_α—O_n bond of oxiranone is different from the corresponding bond in oxirane.

CHARACTERIZATION OF EXPLICITLY SOLVATED OXIRANONE IN WATER

It may be argued that the analysis presented in the preceding section is flawed because the polarized continuum model for aqueous solvation does not take account of specific solvent interactions which might strongly stabilize the open, zwitterionic form of oxiranone relative to the cyclic α-lactone. In response to this suggestion (from a referee), we carried out a computational study of oxiranone in water using a combined quantum mechanical/molecular mechanical (QM/MM) approach.

Gas-phase geometry optimization of oxiranone was performed using the GAMESS-UK program[22] (the package is derived from the original GAMESS code due to M. Dupuis D. Spangler and J. Wendoloski) without any symmetry constraints, with the B3LYP/6–31 + G(d) method. QM/MM calculations in solution were carried out using the CHARMM27b2[23] (GAMESS-

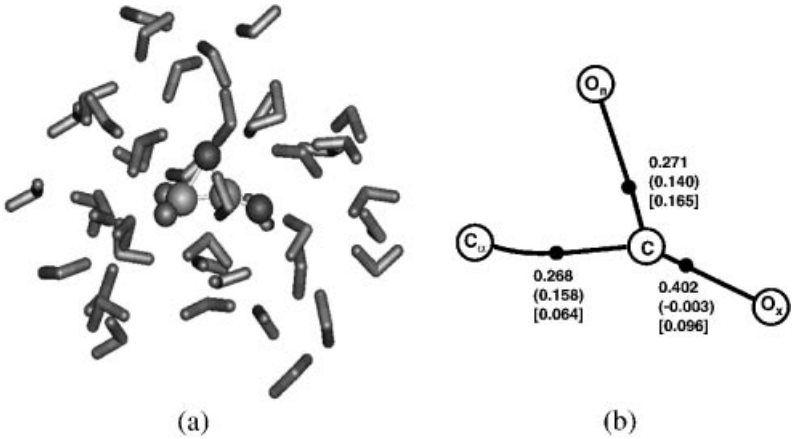

Figure 4. (a) Optimized structure for oxiranone in aqueous solution, showing specific solvent interactions, from a full QM/MM geometry optimization with B3LYP/6–31 + G(d) oxiranone surrounded by ~600 TIP3P water molecules. (b) Bond critical points (●) for oxiranone in aqueous solution (C_α—H bonds omitted), together with electron densities [ρ (e au^{-3})], Laplacians [$\nabla^2\rho$ (e a_0^{-5}, in parentheses)] and ellipticities (ε, in square brackets). 1 e au^{-3} = 1.081 × 10^{12} C m^{-3}; 1 e a_0^{-5} = 3.8611 × 10^{32} cm^{-5}

UK/CHARMM is a coupling of GAMESS-UK 6.2 and CHARMM c27b2 by P. Sherwood, E. Billings and B.R. Brooks, unpublished work) and GRACE[24] programs. The reacting system was placed in a cavity deleted from a 15 Å radius sphere of 605 water molecules as described by TIP3P empirical potentials. A sequence of initial energy minimization using the MM only energy function was performed in order to produce a reasonably well-packed arrangement of the solvating water molecules around the solute species.

Ab initio QM/MM stationary-point location and characterization were guided by means of GRACE, which uses a Newton–Raphson algorithm. In this method, the system was divided into two parts, the core and the environment. The Hessian matrix was calculated explicitly only for those atoms belonging to the core. Here the core represents QM oxiranone. Once this partitioning had been done, the stationary point, a minimum in this case, location was carried out in the degrees of freedom of the core. Before each energy and gradient evaluation step for the core, the degrees of freedom of the environment were relaxed to maintain an approximately zero gradient and to minimize the potential energy.

Starting from the B3LYP/6–31 + G(d)/PCM optimized structure for oxiranone, full geometry optimization within the QM/MM potential with ~600 explicit water molecules led to an energy minimized structure corresponding to the cyclic α-lactone. Figure 4(a) shows a selection of these solvent waters (rendered in licorice style) surrounding the oxiranone (rendered in ball and stick style); most of the water molecules have been omitted from this view for the sake of clarity. The C_α—O_n bond length (Table 1) is longer in the explicit QM/MM description (1.633 Å) than in the continuum treatment (1.560 Å), but the C_α—C—O_n angle is characteristic of a three-membered ring in both cases (69.1° explicit vs 68.4° continuum). Since attempts to elongate the C_α—O_n bond further reverted to the same cyclic structure, this geometry corresponds to a local energy minimum, indicating that the α-lactone is capable of (at least transient) existence in aqueous solution. It is certainly conceivable that there may also exist a separate energy minimum corresponding to an open, zwitterionic form for oxiranone in water, and that this might be of lower energy, but we cannot comment further upon this at present. The structure shown in Fig. 4(a) is only one of many possible configurations of solvent; a more complete description would involve averaging over many configurations in order to determine the free energy of the solvated oxiranone. This particular snapshot shows two water molecules acting as hydrogen-bond donors towards the endocyclic oxygen of oxiranone ($O_n\cdots$H distances of 1.88 and 1.93 Å) and one water molecules acting likewise towards the exocyclic oxgen ($O_x\cdots$H distance 1.798 Å).

The analysis of electron density distributions in a QM/MM environment was carried out by means of AIMPAC.[20] Figure 4(b) shows the values of the electron density ρ, its Laplacian $\nabla^2\rho$ and its ellipticity ε at the

Table 1. Selected bond lengths (Å) and angle (°) optimized for oxiranone in aqueous solution with the B3LYP/6–31 + G(d) method

Solvation method	C_α—O_n	C_α—C	C—O_n	C_α—C—O_n
Continuum: PCM (ε = 78.4)	1.560	1.442	1.327	68.4
Explicit QM/MM with ~600 TIP3P waters	1.633	1.466	1.413	69.1

BCPs for B3LYP/6–31 + G(d) oxiranone surrounded by ~600 TIP3P water molecules. The most noteworthy point is the non-existence of a BCP for the C_α—O_n bond, just as for the PCM treatment of this molecule.[21]

In conclusion, the picture of oxiranone in water that emerges from the explicit QM/MM description of solvation is qualitatively the same as found using the continuum PCM treatment.

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