The Walden cycle revisited: a computational study of competitive ring closure to α- and β-lactones

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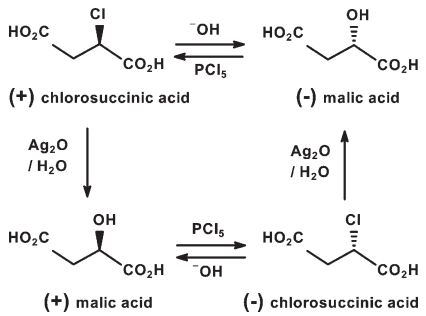
Received (in Cambridge, UK) 12th December 2005, Accepted 18th January 2006
First published as an Advance Article on the web 1st February 2006
DOI: 10.1039/b517461a

The text-book Walden cycle which interconverts the stereochemical configurations of chlorosuccinic and malic acids involves a β-lactone intermediate in preference to an α-lactone intermediate because the O_{nuc} C Cl angle in the transition structure for the former (174°) is more favourable than that for the latter (139°), as determined by PCM(ε = 78.4)/B3LYP/6-31+G* calculations; the smaller ring-strain energy of the β-lactone contributes little to the reactivity difference.

In 1896, Paul Walden discovered[1] the first example of an optical cycle (Scheme 1), later described[2] by Emil Fischer as 'the most surprising observation in the field of optically active substances since the fundamental investigations of Pasteur'. Having previously reported that (−)-malic acid could be converted into (+)-chlorosuccinic acid by the action of phosphorus pentachloride, Walden then demonstrated that (+)-chlorosuccinic acid treated with moist silver oxide gave (+)-malic acid. While this classic "Walden cycle" may be found in textbooks to illustrate the stereochemical principles with which we are now so familiar, it is not easy to find an explanation of the underlying chemistry that gives rise to the observed overall inversion of configuration of the malic acid.

It required many years of investigation, including the critical studies by Kenyon and Phillips[3] and by Hughes *et al.*,[4] in order to establish unequivocally that bimolecular nucleophilic substitution is accompanied by inversion of stereochemical configuration. In the light of this knowledge, it is clear that the conversion of (−)-chlorosuccinate to (+)-malate (and, equivalently, of (+)-chlorosuccinate to (−)-malate) upon treatment with potassium hydroxide (Scheme 1) involves inversion. Consequentially, the opposite conversion of malic acid to chlorosuccinic acid with PCl_5 must also involve inversion. Hence it is obvious that the Ag_2O/H_2O mediated hydrolysis of (−)-chlorosuccinate to (−)-malate (and of (+)-chlorosuccinate to (+)-malate) must proceed with retention of stereochemical configuration. Holmberg showed that under these reaction conditions a lactone was produced that contained no halogen,[5] but that no such product was obtained from chlorosuccinate esterified at the β-carboxyl group;[6] from this evidence it was concluded that a β-lactone was formed as a reaction intermediate in the hydrolysis with Ag_2O/H_2O.



Scheme 1 Walden cycle for stereochemical interconversion of chlorosuccinic and malic acids.

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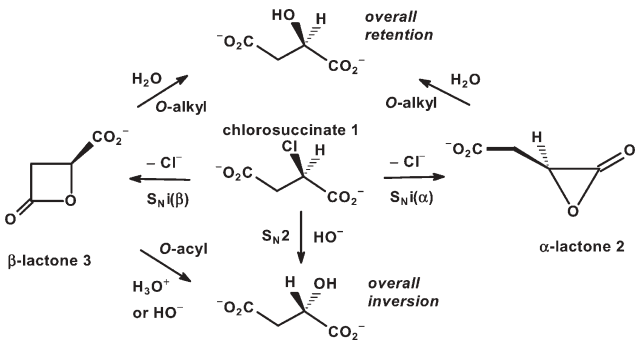
Another reaction found to proceed with overall retention of configuration was the hydrolysis of α-bromopropionate at low concentrations of hydroxide anion.[7] The proposed explanation was a two-step mechanism, with each step involving inversion. Although Hughes and Ingold disagreed,[8] Winstein described the reaction intermediate as an α-lactone.[9] This raises the following question: if hydrolysis of an α-halocarboxylate can produce an α-lactone by intramolecular nucleophilic substitution, why should hydrolysis of chlorosuccinate (**1**, Scheme 2) not also produce an α-lactone (**2**) rather than a β-lactone (**3**)? If this were to occur, the final stereochemical outcome of the Walden cycle (Scheme 1) would be unaffected.

According to Baldwin's rules for ring closure,[10] intramolecular nucleophilic attack by a carboxylate group in **1** is either a 3-*exo-tet* or a 4-*exo-tet* process, depending upon whether it leads to the α- or the β-lactone. Both possibilities are considered as 'favoured' since the qualitative and empirical nature of these rules does not allow a distinction to be made. However, Baldwin noted that the rules reflected the facility with which a given system could attain the required transition-state geometry to effect ring closure, following Ruzicka's hypothesis[11] that the ease of ring closure is determined by strain and probability factors. The relationship between the ring strain energy of the cyclic product of an intramolecular nucleophilic substitution and the ease of closure to a three- or



Scheme 2 α-Lactone and β-lactone as potentially alternative intermediates in the Walden cycle.

four-membered ring seems to depend upon the particular reaction under consideration. Thus for cyclisation of ω-bromoalkylmalonates, cyclopropanation is significantly faster than cyclobutanation despite similar ring strain energies for the products.[12,13] On the other hand, lactonisation of ω-bromo- and ω-chloroalkylcarboxylates is much slower for the reaction leading to the three- than to the four-membered ring product,[12,14] in line with the relative ring strain energies of α- and β-lactones. The greater reactivity of β-bromopropionic and β-bromocaproic acids towards lactonisation than the corresponding α-substituted isomers is predominantly due to the lower enthalpy of activation for reaction leading to the four-membered ring, not the entropy of activation.[15] Similarly, the enthalpies and entropies of activation for lactonisation of bromoacetate show clearly that the reactivity difference is enthalpic, not entropic, in origin.[14a,16]

We now present the results of PCM(ε = 78.4)/B3LYP/6-31+G* calculations† to investigate the competition between formation of the α-lactone **2** and β-lactone **3** from chlorosuccinate dianion **1**; in this reaction there is a choice of two carboxylate nucleophiles to attack a single carbon atom attached to a chloride leaving group. The alternative transition structures (TSs) are denoted as ‡$_\alpha$ **4** and ‡$_\beta$ **5**, respectively.

The minimum energy conformation of chlorosuccinate dianion **1** in PCM water is shown at the top of Fig. 1: this single reactant structure leads to two separate TSs for formation of both the α- and β-lactones. The energy barrier for α-lactone formation is 108 kJ mol^{-1}, and the angle $O_{nuc}C_\alpha Cl$ involving the nucleophile and leaving group atoms in ‡$_\alpha$ **4** is 139° in PCM water (Table 1). In contrast, the energy barrier for β-lactone formation in PCM water is only 85 kJ mol^{-1}, and the corresponding angle $O_{nuc}C_\beta Cl$ in ‡$_\beta$ **5** is, at 174°, much less distorted from collinearity. This result is in accord with the conventional view that the Ag_2O/H_2O mediated

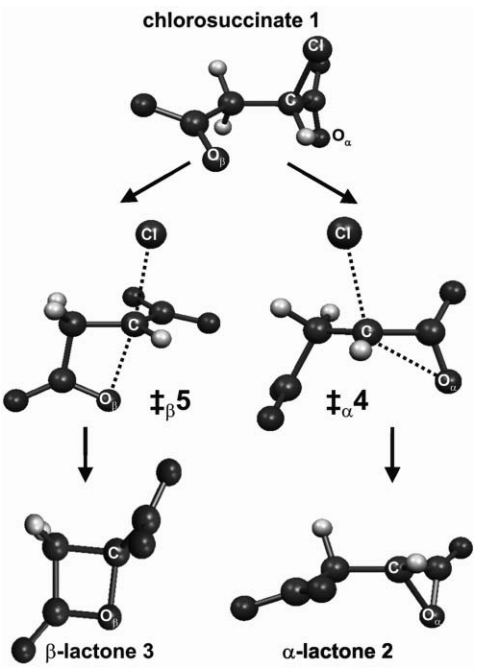


Fig. 1 B3LYP/6-31+G* optimised structures in PCM water for competitive formation of α-lactone and β-lactone from chlorosuccinate dianion. Selected bond lengths in Ångström and angles in degrees.

Table 1 B3LYP/6-31+G* relative energies Δ*E*/kJ mol^{-1} (total energies *E*/hartree), transition frequencies [$\nu^\ddagger$/cm^{-1}] and selected geometrical parameters (bond lengths/Å, angles/°) for optimised species under vacuum (*italics*) and in PCM water

Species	Rel. energy	CCl	$O_\alpha C$	$O_\beta C$	$O_\alpha CCl$	$O_\beta CCl$
1	*(−915.39497)*	*1.893*	*2.354*	*2.944*	*134.5*	*97.8*
	(−915.70891)	1.865	2.347	2.841	135.8	92.0
‡$_\alpha$ **4**	*43* [*90i*]	*2.785*	*2.216*	*2.990*	*132.8*	*116.6*
	108 [96*i*]	3.231	1.711	2.911	138.9	107.2
‡$_\beta$ **5**	*61* [*300i*]	*2.604*	*2.369*	*2.179*	*99.9*	*157.2*
	85 [407*i*]	2.456	2.367	2.006	92.5	173.8
2 + Cl$^-$	*−172*		*1.604*			
	64		1.576			
3 + Cl$^-$	*−242*			*1.507*		
	−22			1.506		

hydrolysis of chlorosuccinate proceeds by means of an intermediate β-lactone.

However, it is of interest to note that the respective energy barriers under vacuum are 43 and 61 kJ mol^{-1}: this implies that formation of the α-lactone would be the kinetically preferred channel for this reaction in the gaseous phase, despite β-lactone formation being more exothermic by 70 kJ mol^{-1}. In PCM water, α-lactone formation is predicted to be endothermic by 64 kJ mol^{-1} as compared with the exothermic (−22 kJ mol^{-1}) formation of the β-lactone. The dianionic reactant is solvated much more strongly than the two separate monoanionic products, lactone and chloride; thus solvation energy contributes endothermically to the overall energy change for the reaction, and serves to increase the reaction barriers relative to the gas phase.

We have estimated the ring strain energy of unsubstituted oxiranone, the parent α-lactone, at 150 kJ mol^{-1} by means of similar calculations applied to the same isodesmic reaction used previously to estimate the strain energy under vacuum.[20] Pauling bond orders $n = \exp[(r_1 - r_n)/0.6$ may be determined for the making and breaking of bonds in each TS, where r_n is the length of a bond with order n, based upon the C–Cl bond in the chlorosuccinate reactant and the C–O bond in the β-lactone product having unit bond order. For ‡$_\alpha$ **4** we obtain $n_{C–Cl} = 0.10$ and $n_{C–O} = 0.71$ in PCM water, whereas for ‡$_\beta$ **5** we obtain $n_{C–Cl} = 0.37$ and $n_{C–O} = 0.43$. Clearly the TS for endothermic α-lactone formation is more advanced along the reaction coordinate than the TS for exothermic β-lactone formation. The TS bond orders suggest that ‡$_\alpha$ **4** has progressed ~80% towards the product; the barrier height represents ~70% of the ring strain energy expected for an α-lactone. The difference in barrier heights for the two reactions (23 kJ mol^{-1}) is only 27% of the difference in strain energy between the α- and β-lactone products (86 kJ mol^{-1}) as determined by the difference in overall reaction energies in PCM water. Disparity between the ring-strain energies of small rings and of the TSs leading to them has been noted before.[12] Formation of the β-lactone also involves an increase in ring-strain energy, but in the present case this adverse energy change is more than compensated by the relief of Coulombic repulsion between the negative charges in the dianionic reactant, which provides the driving force for the intramolecular nucleophilic displacement of chloride anion. Lesser Coulombic repulsion between chloride and the slightly more distant "spectator" carboxylate is the probable reason for the lower gas-phase barrier for α-lactone formation; the differential effect is negligible in water due to screening.

It is clear from these computational results, combined with knowledge of the original experimental studies, that the intermediate in the moist silver-oxide mediated conversion of chlorosuccinic acid to malic acid with overall retention of stereochemical configuration[1] is the β-lactone identified by Holmberg.[5] (Note that moist Ag_2O seems to serve only as a source of hydroxide;[6,21] the silver ion itself apparently plays no role in the reaction.) However, the mechanism of the hydroxide-mediated reaction with inversion of configuration is less certain. It is known that, with appreciable concentrations of hydroxide, hydrolysis of α-bromopropionate occurs predominantly by intermolecular S_N2 attack of hydroxide,[7] since this is faster than intramolecular nucleophilic substitution leading to the α-lactone. It is also known that, when it is possible, β-lactone formation by means of intramolecular nucleophilic substitution is faster than α-lactone formation. Holmberg showed[5,21] that the disodium salt of bromosuccinnic acid formed the β-lactone with (what we may now interpret as) inversion; addition of excess hydroxide (or Ag_2O) would cause hydrolysis of the lactone with retention. Olson and Miller demonstrated that hydrolysis of the parent oxetanone (without the carboxyl substituent) proceeded with *O*-acyl cleavage in strongly acidic or basic solution, but with *O*-alkyl cleavage in neutral solution.[22] Summarising the earlier observations of both Holmberg[6] and Rørdam[23]—that the β-lactone from (−)-halosuccinnic acids gave (−)-malic acid in a first-order hydrolysis in dilute aqueous acid but yielded (+)-malic acid in stronger acid or basic solution—these authors commented that "interpretation of these results is complicated by the difficulty of determining the total concentration of lactone and also by the possible existence of an α-lactone as well as a β-lactone".[22] It is not known how the rates of intramolecular reaction (leading to a β-lactone intermediate) and direct intermolecular S_N2 attack by hydroxide compare under the conditions originally employed by Walden,[1] although both mechanisms would give the same stereochemical result, *i.e.* overall inversion. It is perhaps a mark of Walden's genius that he chose the particular experimental conditions that would cause overall inversion of configuration in the hydroxide mediated hydrolysis of chlorosuccinic acid but overall retention in the moist silver oxide mediated hydrolysis, even if *both* might involve a lactone intermediate! Chlorosuccinic acid hydrolysis with either overall retention or overall inversion may each occur by more than one mechanism (Scheme 2) as the pH is varied. There is more involved in the standard textbook illustration of the classic Walden cycle than meets the eye.

In conclusion, it is well known that bimolecular nucleophilic substitution prefers an essentially collinear arrangement between the nucleophile and the bond to the leaving group. Intramolecular nucleophilic substitution may incur an energetic penalty due to geometrical constraints preventing collinearity. The two internal nucleophiles in chlorosuccinate dianion lead to alternative TSs for substitution of chloride anion. Formation of the β-lactone product in water is kinetically favoured because it involves the TS with angle $O_{nuc}C_{\beta}Cl = 174^{\circ}$ closer to 180° than that for α-lactone formation with $O_{nuc}C_{\alpha}Cl = 139^{\circ}$, and therefore involving less angle strain. Thus the Walden cycle involves β-lactone as the intermediate involved in the double inversion. Although the β-lactone product is thermodynamically preferred over the α-lactone, owing to its smaller ring-strain energy, this factor contributes little to the reactivity difference. Solvation plays a crucial role in determining the observed preference.

We thank the EPSRC for a ROPA grant (GR/R94060/01) and the HEFCE/EPSRC JREI (GR/R55269) for computer equipment.

Notes and references

† The GAUSSIAN98 package of programs[17] was used with the B3LYP/6-31+G* level[18] of DFT and the polarized continuum model (PCM)[19] for aqueous solvation (ε = 78.4). TSs were located by means of the EF algorithm and characterized by frequency calculations, and by intrinsic reaction co-ordinate calculations to verify the adjacent local minima. The PCM energies given in Table 1 include both electrostatic and non-electrostatic (surface-area dependent cavity) contributions to the free energy of the solvated species.

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