Conformationally Restricted Criegee Intermediates: Evidence for Formation and Stereoelectronically Controlled Fragmentation

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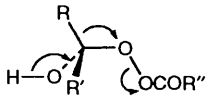
The Baeyer–Villiger reaction of 2-(2-oxocyclohexyl)acetic acid occurs *via* a bicyclic Criegee intermediate, which fragments with stereoelectronic control, as evidenced by product analysis; the reaction of the but-2-yl ester and of 2-(2-oxocyclopentyl)acetic acid also show evidence of such stereoelectronic control, but less convincingly.

Stereoelectronic theory requires that the Criegee intermediates of the Baeyer–Villiger reaction fragment with the cleaving C–C and O–O bonds mutually antiperiplanar (**1**).[1a] We have briefly



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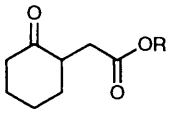
reported evidence for such stereoelectronic control,[2] and herein present a comprehensive study. This study is challenging as Criegee intermediates are not normally isolable, so that unmasking stereoelectronic effects needs a novel strategy. The one devised by us is a study of the intramolecular Baeyer–Villiger reaction, which produces a conformationally restricted Criegee intermediate whose mode of fragmentation may be traced by the nature of the final products. It is noteworthy that stereoelectronic theory has been vigorously debated,[1b] and that the present results are amongst the least ambiguous in support of it.

Results and Discussion

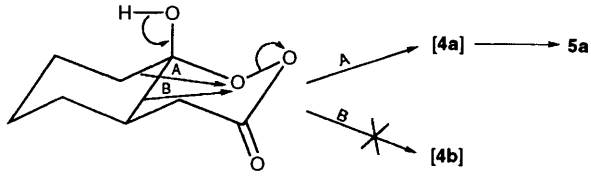
With the aim of producing Criegee intermediate **3** by cyclisation, ketoacid **2a** was oxidised with peroxyacetic acid in



2a R = H
b R = OH
c R = Bu^s

acetic acid, in order to produce keto-peroxy acid **2b**. The reaction produced 2-(4-acetoxybutyl)butanedioic acid (**5a**) in 62% yield (see Scheme 1); this could be hydrolysed to **5b**, or esterified to **5c** with diazomethane, both in good yield. Importantly, there was no trace of isomer **6a** in the oxidation; NMR of the product mixture showed no absorption at δ_H 4.3–5.5, as expected for AcOC*H* in **6a** and base treatment of the mixture did not form any octenedioic acid **7**. Apparently, a Baeyer–Villiger reaction takes place, but with the seven-membered ring lactone product (**4a**) cleaving further. Clearly, **5a** can form by stereoelectronically controlled fragmentation of **3**, by migration of a secondary centre (path A); the absence of **6a** suggests that migration of a tertiary centre (path **B**) is relatively disfavoured, *i.e.* the classical migratory preferences are overruled.

Evidence for the cyclisation of **2b** to **3** was obtained by treating but-2-yl ester **2c** with peroxyacetic acid, when both



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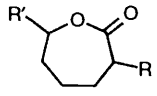
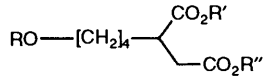


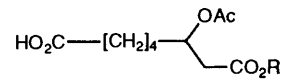
4	R	R′
a	CH_2CO_2H	H
b	H	CH_2CO_2H
c	$CH_2CO_2Bu^s$	H
d	H	$CH_2CO_2Bu^s$



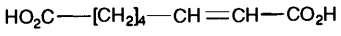
5	R	R′	R″
a	Ac	H	H
b	H	H	H
c	Ac	Me	Me
d	Ac	H	Bu^s

possible Baeyer–Villiger oxidation products, **5d** and **6b** (approx. 2:1 ratio), were formed—presumably *via* lactones **4c** and **4d** respectively (see Scheme 1). Clearly, only intermolecular attack of peroxy acid on ketone is possible, so evidence of stereoelectronic control is lost. However, the relatively higher yield of **5d** could well be due to intramolecular assistance for O–O cleavage by the ester carbonyl as in **8**: the stereoelectronic situation would be similar to that in the cleavage of **3**. Note that the formation of Criegee intermediates is thermodynamically controlled,[3] but intermediacy of **3** is not unequivocal *vis-à-vis* *cis*-fused epimer **9a**, **b** (different enantiomers are shown in **9a** and **9b** for convenience of representation): C-9-substituted decalins rather prefer *cis* ring fusion,[4] and **9a** has the requisite stereoelectronic features to give the observed products.

Interesting results were obtained when the above oxidation strategy was applied to 2-(2-oxocyclopentyl)acetic acid (**10a**) and its but-2-yl ester **10b**. Ketoacid **10a** produced six-membered lactones **11a** (10%) and **11b** (22%), and the cleavage product of **11a**, **12** (32%) (see Scheme 1). Thus, regioselectivity has been partially lost, suggesting the incursion of an intermolecular



6a R = H
b R = Bu^s



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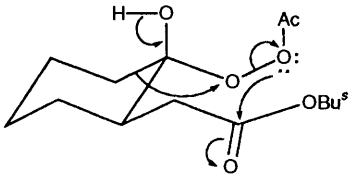

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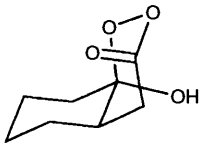
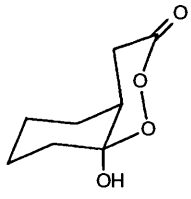
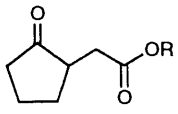


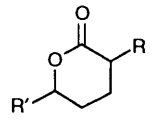
9a



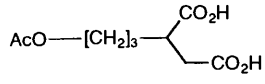
9b



10a R = H
b R = Bu^s



11	R	R′
a	CH_2CO_2H	H
b	H	CH_2CO_2H
c	$CH_2CO_2Bu^s$	H
d	H	$CH_2CO_2Bu^s$



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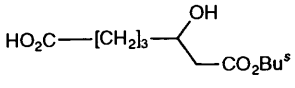

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pathway. Ester **10b** produced lactones **11c** (5%) and **11d** (35%), and the cleavage product of **11d**, **13** (20%), which constitutes nearly complete migratory aptitude control. All these results may be explained by invoking strain in the corresponding analogues of **3**, **8** and **9** (*i.e.* with the carbocyclic ring five-membered), without prejudice to stereoelectronic theory.

These results constitute evidence for stereoelectronic control in the fragmentation of Criegee intermediates. The study of stereoelectronic effects is almost always plagued by a fundamental problem, namely the impossibility of designing models

2a ⟶ [3] ⟶ [4a] ⟶ **5a** (62%)
2c ⟶ [4c] ⟶ **5d** (50%)
+
[4d] ⟶ **6b** (30%)
10a ⟶ **11a** + **11b** + **12**
(10%) (22%) (32%)
10b ⟶ **11c** + **11d** + **13**
(5%) (35%) (20%)

Scheme 1

which are conformationally rigid enough for stereoelectronic relationships to be well defined, and yet flexible enough to react. The above study is unique in being relatively free of this problem, apparently because of the structure of the cyclic peroxide **3**.

Experimental

IR spectra were recorded with a Perkin-Elmer 781 or Hitachi 270–50 spectrometer as thin films (liquids) or nujol mulls (solids). NMR spectra were recorded with a JEOL FX-90Q or a Varian T-60 spectrometer, at 90 MHz in $CDCl_3$ solution unless otherwise stated. EI mass spectra were recorded with a JEOL MS-DX 303 at 70 eV. Extracts of reaction mixtures were worked up by washing with H_2O, drying ($MgSO_4$ or Na_2SO_4) and evaporating the solvent *in vacuo*. Chromatography was carried out on silica gel columns. M.p.s are uncorrected. Ether refers to diethyl ether.

The methyl and ethyl esters of ketoacids **2a** and **10a** were easily hydrolysed under the reaction conditions, presumably by keto participation, but the but-2-yl esters were stable (but unstable to distillation, so did not provide satisfactory elemental analyses). Product mixtures were usually sensitive to chromatography and distillation, and were further derivatised; the yields shown are those of the isolated derivatives. Thus, mixture (**5d** + **6b**) gave, with alkali, hydroxydiacid **5b** (50%) and octenedioic acid **7** (30%), separated by crystallisation. This bears out the relative yields given in the Results and Discussion section, which are NMR estimates. Acid **7** was hydrogenated to octanedioic (suberic) acid. Neither elemental analysis nor high-resolution mass spectral data were obtained for lactone **11c**.

The products of the reaction of ketoacid **10a** were esterified with CH_2N_2 before resolution. In the reaction of ketoester **10b**, partial hydrolysis of the ester occurred, so the product mixture was heated with Bu^{s}OH/H$^+$ to re-esterify the CO_2H groups; the above hydrolysis presumably occurred after the Baeyer–Villiger reaction, as the reaction of ketoacid **10a** showed a different 'product spread'.

Preparation of Keto-esters **2c** *and* **10b**.—The keto-acid[5] (16 mmol) and conc. H_2SO_4 (0.07 cm^3) were heated in butan-2-ol (10 cm^3) for 7 h. After concentration, the mixture was extracted with $CHCl_3$, the extracts washed with aqueous $NaHCO_3$ and H_2O, and worked up. Chromatography (eluent: 0–1% EtOAc in hexane) gave the pure keto-esters (13.5 mmol, 85%) as liquids unstable to distillation.

Baeyer–Villiger Reactions: General Procedure.—A stirred solution of H_2O_2 (30%, 1.4 cm^3; 23 mmol), acetic acid (4.2 cm^3) and conc. H_2SO_4 (0.02 cm^3) was treated with the substrate (6 mmol) at 25 °C for 15 h and 70 °C for 3 h. After concentration, the mixture was extracted with CH_2Cl_2 (100 cm^3) and the extracts worked up.

The crude product of the reaction of keto-acid **2a** was

chromatographed (eluent: 5% MeOH in $CHCl_3$) to isolate **5a** as a viscous liquid (62%); attempted distillation seemed to form the anhydride, as shown by IR, so **5a** was hydrolysed to **5b** for characterisation, or esterified with CH_2N_2 (see below). In the case of keto-ester **2c**, the product mixture was also hydrolysed. In the case of keto-acid **10a**, the product mixture was esterified with CH_2N_2 in ether (as for **5a**), before chromatographic separation (eluent: 33% EtOAc in hexane) into the methyl esters of **11a** (10%), **11b** (22%) and **12** (32%). In the case of keto-ester **10b**, the product mixture was re-esterified with butan-2-ol and catalytic conc. H_2SO_4 (reflux 5 h); after work-up, the mixture was chromatographed (eluent: 33% EtOAc in hexane) to isolate **11c** (5%), **11d** (35%) and **13** (20%, as the dibut-2-yl ester).

Hydrolysis of **5a** *and* (**5d** + **6b**).—A solution of **5a** (0.334 g, 1.43 mmol) in 10% KOH in MeOH–H_2O (1:1, 8 cm^3) was refluxed for 2 h. After concentration, followed by acidification, the mixture was extracted into EtOAc and the extracts worked up to obtain **5b** (0.15 g, 0.79 mmol, 50%), m.p. 110–112 °C (EtOAc–hexane).

Similarly, (**5d** + **6b**) (2.1 g) in 10% KOH in MeOH–H_2O (1:1, 46 cm^3), at reflux for 5 h, and work-up as above, gave a mixture (1.44 g) separated by fractional crystallisation (EtOAc) into **5b** (0.74 g, 3.9 mmol, 50%) and oct-2-enedioic acid (**7**) (0.40 g, 2.3 mmol, 30%), m.p. 155–160 °C (from H_2O). Compound **7** (0.05 g, 0.29 mmol) was catalytically (5% Pd/C) hydrogenated in EtOH–H_2O (1:1) to octanedioic (suberic) acid (0.045 g, 0.25 mmol, 86%), spectrally identical with an authentic sample, m.p. 139–140 °C (acetone), mixed m.p. 140–141 °C (lit.,[6] 139–141 °C).

Esterification of **5a**.—The diacid (0.232 g, 1.0 mmol) in ether (3 cm^3) was slowly treated with diazomethane in ether[7] at 0–5 °C, till a yellow colour persisted. After evaporation of volatiles, the residue was chromatographed (eluent: 4% EtOAc in hexane) to obtain pure triester **5c** (0.222 g, 0.9 mmol, 90%) as a liquid, unstable to distillation.

Characterising Data.—Butyl ester **2c**. ν_{max}/cm^{-1} 1730 (ester CO) and 1710 (ketone CO); δ_H(60 MHz; CCl_4) 4.70 (1 H, sextet, *J* 7, OC*H*) and 3.00–0.66 (19 H, m, C*H*); *m/z* 212 (M^+), 156 ($M^+ - 56$) and 139 ($M^+ - 73$).

Acetate diacid **5a**. ν_{max}/cm^{-1} 3300–2300 (acid OH) and 1725 (CO); δ_H 11.20 (2 H, br s, CO_2H, D_2O exchangeable), 4.15 (2 H, m, AcOCH_2), 3.10–2.20 (3 H, m, COC*H*, COCH_2), 2.08 (3 H, s, CH_3) and 2.00–1.00 (6 H, m, CH_2); *m/z* 172 ($M^+ - 60$), 154 ($M^+ - 78$) and 136 ($M^+ - 96$).

Alcohol diacid **5b**. (Found: C, 50.8; H, 7.5. $C_8H_{14}O_5$ requires C, 50.5; H, 7.4%) ν_{max}/cm^{-1} 3500–2300 (OH) and 1725 (CO); δ_H[$(CD_3)_2CO$–$CDCl_3$] 5.56 (3 H, br s, COO*H* + O*H*), 4.05 (2 H, m, HOCH_2), 2.40 (3 H, m, COC*H*, COCH_2) and 2.00–1.40 (6 H, m, CH_2).

Triester **5c**. ν_{max}/cm^{-1} 1740 (CO); δ_H 4.05 (2 H, m, AcOCH_2), 3.72 (3 H, s, CO_2*Me*), 3.68 (3 H, s, CO_2*Me*), 2.98–3.10 (3 H, m, COC*H*, COCH_2), 2.07 (3 H, s, OCO*Me*) and 2.00–1.00 (6 H, m, CH_2).

Mixture (**5d** + **6b**). ν_{max}/cm^{-1} 3650–2350 (OH) and 1720 (CO); δ_H(60 MHz; CCl_4) 8.96 (br s, CO_2H), 5.33–4.50 (m, AcOC*H* and OC*H*), 4.20–3.80 (m, AcOCH_2) and 2.90–0.65 (m, COC*H* and C*H*).

Octenedioic acid **7**. (Found: C, 55.8; H, 7.3. $C_8H_{12}O_4$ requires C, 55.8; H, 7.0% ν_{max}/cm^{-1} 3350–2400 (OH), 1695 (CO) and 1650 (conj. CO); δ_H[$(CD_3)_2CO$–$CDCl_3$] 6.95 (1 H, m, C*H*=CCO$_2$H), 5.80 (1 H, d, *J* 15, C=C*H*CO$_2$H), 5.35 (2 H, br s, CO_2H), 2.60–2.00 (4 H, m, HO_2CC*H*, C=CC*H*) and 1.80–1.00 (4 H, m, CH).

Butyl ester **10b**. ν_{max}/cm^{-1} 1740 (ester CO) and 1730 (ketone CO); δ_H 4.90 (1 H, sextet, *J* 7, CO_2C*H*), 3.00–1.40 (11 H, m, COC*H* and *s*-C*H*), 1.20 (3 H, d, *J* 7, CH_3CEt) and 0.90 (3 H, t, *J* 7, CH_2CH_3).

Lactone **11a** (*Me ester*). ν_{max}/cm^{-1} 1740 (CO); δ_H 4.30 (2 H, m, CO_2C*H*), 3.76 (3 H, s, CO_2Me), 3.00–2.10 (3 H, m, COC*H*) and 2.10–1.00 (4 H, m, C*H*) (Found: M^+, 172.0738. $C_8H_{12}O_4$ requires *M*, 172.0736).

Lactone **11b** (*Me ester*). ν_{max}/cm^{-1} 1740 (CO); δ_H 4.80 (1 H, m, CO_2C*H*), 3.76 (3 H, s, CO_2Me), 2.70 (4 H, m, COC*H*) and 1.80 (4 H, m, C*H*) (Found: M^+, 172.0735. $C_8H_{12}O_4$ requires *M*, 172.0736).

Lactone-ester **11c**. ν_{max}/cm^{-1} 1740 (CO); δ_H 4.90 (1 H, sextet, *J* 7, CO_2C*H*), 4.30 (2 H, m, CO_2CH_2), 3.00–1.40 (9 H, m, COC*H*, C*H*), 1.20 (3 H, d, *J* 7, CH_3CEt) and 0.90 (3 H, t, *J* 7, CH_2CH_3).

Lactone-ester **11d**. ν_{max}/cm^{-1} 1740 (CO); δ_H 4.90 (2 H, m, CO_2C*H*), 2.60 (4 H, m, COC*H*), 2.10–1.40 (6H, m, C*H*), 1.20 (3 H, d, *J* 7, CHCH_3) and 0.90 (3 H, t, *J* 7, CH_2CH_3) (Found: M^+, 214.1205. $C_{11}H_{18}O_4$ requires *M*, 214.1205).

Acetate **12** (*dimethyl ester*). (Found: C, 53.55; H, 7.5. $C_{11}H_{18}O_6$ requires C, 53.7; H, 7.3%); ν_{max}/cm^{-1} 1740 (CO); δ_H(60 MHz; CCl_4) 3.95 (2 H, m, AcOC*H*), 3.78 (3 H, s, CO_2Me), 3.68 (3 H, s, CO_2Me), 2.80–2.00 (3 H, m, COC*H*), 2.07 (3 H, s, COMe) and 1.60 (4 H, m, C*H*); *m/z* 246 (M^+), 187 ($M^+ - 59$) and 173 ($M^+ - 73$).

Alcohol ester-acid **13** (*dibutyl ester*). (Found: C, 62.0; H, 9.8. $C_{15}H_{28}O_5$ requires C, 62.5; H, 9.7%) ν_{max}/cm^{-1} 3550 (OH) and 1740 (CO); δ_H 4.95 (2 H, m, CO_2C*H*), 4.03 (1 H, m, HOC*H*), 2.80 (1 H, s, O*H*, D_2O exchangeable), 2.40 (4 H, m, COC*H*), 2.00–1.40 (8 H, m, C*H*), 1.20 (6 H, 2 d, *J* 7, CH_3CEt) and 0.90 (6 H, t *J* 7, CH_2CH_3); *m/z* 288 (M^+), 159 ($M^+ - 129$), 141 ($M^+ - 147$) and 99 ($M^+ - 189$).

Acknowledgements

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