Theoretical Modelling of Pyrolysis Reactions. Thermal Retroaldol Reactions of β-Hydroxyesters

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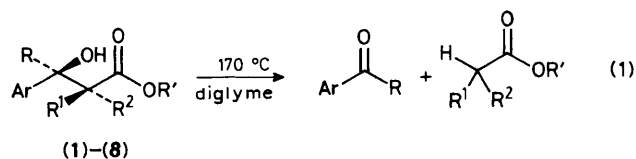[a] Philip Morris Research Center, Richmond, Virginia 23261, U.S.A.
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Reaction rate constants for the thermal retroaldol reaction of eight β-hydroxyesters were determined, and these were well correlated with MM2-derived steric energies.

In the last few years, empirical force field (EFF) calculations have successfully modelled a variety of reactions, most of which have incorporated a $C(sp^2) \longleftrightarrow C(sp^3)$ transformation.[1—3] The thermolysis of highly substituted ethanes, e.g. $R^1R^2R^3C–CR^4R^5R^6$, has been an additional example of the use of EFF strain–reactivity relationships to provide valuable structural and mechanistic information.[2] We now report the successful modelling of a system which incorporates heteroatoms and which participates in a more complex reaction than has previously been examined.

The thermolysis of β-hydroxyesters has been little studied, equation (1), although this functionality is a structural unit of considerable current interest.[4] A series of eight β-hydroxyesters (Table 1) were prepared, chosen to incorporate a wide substitution pattern and to demonstrate a large range in thermal stability.
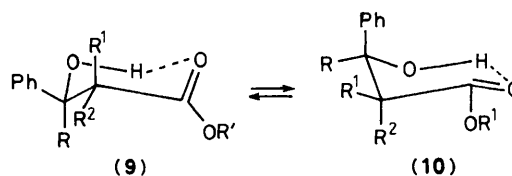
Table 1 lists the experimental first order pyrolysis (170 ± 0.8 °C) rate constants k_A for (1)—(8). A range in rates of almost four orders of magnitude is observed, with a continuously increasing rate with increased substitution. Careful examination of the i.r. spectra of (1)—(8) in CCl_4 reveals that these β-hydroxyesters exist primarily in their intramolecular hydrogen bonded conformations,† with hydrogen bonding to

the acyl oxygen predominating.[5] To quantify thermal stabilities, we performed geometry optimization of the hydrogen bonding models (9) and (10) of (1)—(8) using Allinger's MM2 force field.[6] In a number of cases, we varied the starting orientations of the phenyl group, the alkyl substituents, and the ester functionality so that the minimum energy for the hydrogen bonding models would be obtained. For example, we found a 0.9 kcal mol⁻¹‡ difference in steric energy between the 'equatorially' orientated phenyl group in (1) [c.f. (9)] and the conformation in which the phenyl substituent is 'axial'[c.f. (10)], the former being more stable. However conformation (10) appears to be preferred over (9) for (2) and (5)—(8). Importantly, the preferred conformation found[5] for these β-hydroxyesters was the hydrogen-bonded geometry, i.e., a pseudo-ring orientation was obtained for the contiguous atoms O=C–C–C–O–H, as illustrated by structures (9) and (10).

We base some of our analyses on the hypothesis, previously established in the literature for similar theoretical modelling, that $\Delta\Delta G^{\ddagger} = ca.\ \Delta\Delta G^{\circ}$.[1—3,7] According to the molecular mechanics model, for any molecule, $\Delta H_f^{\circ} = SE + H_{bond} + H_{str} + PFC$ where SE is the steric energy, H_{bond} is the sum of bond contributions, H_{str} is the sum of structural contributions, and PFC is the partition function contribution. The heat of reaction (ΔH_R°) can then be expressed as $\Delta H_R^{\circ} = \Delta SE +$

(1)—(8)

(1)

(9)   (10)

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† Additional, more refined EFF calculations with hydrogen bonding functions implemented are currently in progress. A complete discussion of the ground state geometries of these and other β-hydroxyesters will appear in the full paper.

‡ 1 kcal = 4.18 kJ.

Table 1. Experimental thermolysis rate constant (s^{-1}) and MM2-derived steric energies[a] (SE/kcal mol^{-1}).

Compound	β-Hydroxyester R	R^1	R^2	Ester	Exptl. k_Δ (rel.)	MM2 Parameters[b] $SE_{\beta-H/E}$	SE_E	$\Delta H_R{}^0$(rel.)
(1)	H	H	H	Me	1^c	6.0	4.9	0.8
(2)	Me	H	H	Me	9.6	8.0	4.9	3.1
(3)	H	Me	Me	Me	20	11.4	7.1	4.0
(4)	Me	Pr^i	H	Et	60	16.7	8.1	8.6
(5)	Me	H	Pr^i	Et	96	15.8	8.1	7.7
(6)	Me	Me	Me	Me	2100	17.2	7.1	10.1
(7)	Me	Et	Me	Et	4900	19.9	9.3	10.6
(8)	Me	Me	Et	Et	5700	19.7	9.3	10.4

^{a} For notations, see text. ^{b} $SE_{C=O}$(PhCHO) $-$ $SE_{C=O}$(PhCOMe) $= -2.40$ kcal mol^{-1}. ^{c} $k_\Delta = 5.4 \times 10^{-8}$ s^{-1}.

$\Delta H_{bond} + \Delta H_{str} + \Delta PFC$. Owing to cancellation effects, the relative $\Delta H_R{}^\circ$ for compounds studied here may be simply approximated as $\Delta H_R{}^\circ$(rel.) $= ca.$ $SE_{\beta-H/E} - (SE_E + SE_{C=O})$ $- \Delta H_C$, where $SE_{\beta-H/E}$ represents the steric energy of the β-hydroxyester; SE_E the product ester; and $SE_{C=O}$ for the product acetophenone or benzaldehyde; ΔH_C is the correction term to account for the two possibilities for R in equation (1); R = H or Me. The ΔH_C term is taken to be 2.7 for R = H and 0.0 kcal mol^{-1} for R = Me by considering the known[8] experimental $\Delta H_R{}^\circ$ for equation (2). A correlation between log(k_Δ) and $\Delta H_R{}^\circ$ is excellent, equation (3).

$$\text{MeC(R)(OH)Me} \rightleftharpoons \text{R(Me)C=O} + \text{CH}_4 \quad (R = H, Me) \quad (2)$$
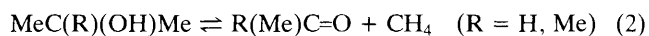
$$\log(k_\Delta) = 0.35\Delta H_R{}^\circ - 0.28 \quad (3)$$
$$(r = 0.95, n = 8, \text{ probability} = 0.00072)$$

Based on the above results, we conclude that: (a) the preferred ground state geometries of (1)—(8) are the hydrogen-bonded conformations; (b) steric strain release is the predominant controlling factor in the thermal retroaldol reaction, contrary to previous literature conclusions;[9] (c) the retroaldol pyrolysis occurs via a cyclic transition state (TS);[10] and (d) as the slope of equation (3) is small, the thermal retroaldol proceeds via an early TS.[3] We speculate that a knowledge of the rate accelerating features in the thermal retroaldol reaction will be related to the steric decelerating features in the aldol reaction, and that a knowledge of the former will lead to a better understanding of the stereoselectivities observed in the latter. Our successful modelling of the

kinetics of a pseudopericyclic reaction (which incorporates a wide rate range) offers encouragement for the use of the molecular mechanics approach for the study of other complex transformations.

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