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Experimental and computational (AM1, MNDO, PM3) studies on the hydrolysis rates of ethylene ketals in 1,3-cyclohexanediones

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Abstract. The relative hydrolysis rates of cyclohexanone ethylene ketals having different substituents at the β-carbon, such as H_2, $(OCH_2)_2$, $(SCH_2)_2$, =O, were determined at 20°C in aqueous H_2SO_4–silica gel–CH_2Cl_2 medium. The observed kinetic trend of $H_2 > (OCH_2)_2 > (SCH_2)_2 >$ =O is correlated with calculated ΔH values (AM1, MNDO and PM3) for the ionisation of β-substituted cyclohexanes to the corresponding cations.

Keywords. Ketal hydrolysis; carbocation stability; AM1 calculations; β- substituent effect.

1. Introduction

The synthesis of monoethylene ketal of 2-methyl-1,3-cyclopentanedione 1 via a two-step procedure, (1, chart 1), was reported some time ago (Volpe *et al* 1986). The controlled hydrolysis of diketal 2 affords monoketal 3 in 70% overall yield. Notwithstanding the synthetic utility of such a procedure, the reason for the acid catalysed hydrolysis stopping at the monoketal stage was not alluded to in the communication (Volpe *et al* 1986). Survey of extensive acetal hydrolysis rate studies (Cordes and Bull 1974; Lowry and Richardson 1981; Ali and Satchell 1993) did not lend a plausible explanation to the high degree of selectivity in the reaction. In order to probe the effects influencing the selective formation of monoketal, we carried out the hydrolysis of cyclohexanone-ketals with different substituents at the β-carbon. The objective was to understand the steric and/or electronic basis for the observed selectivity, since controlled hydrolysis of acetals usually affords mixtures of products.

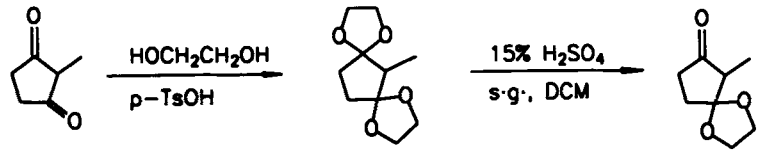
2. Experimental methods

Ketals 4a–d and 5a–d were synthesised according to published procedures (Mertes 1961; Greene 1981). The general procedure for hydrolysis of diketal 5 to monoketal 7 under heterogeneous conditions (Volpe *et al* 1986) is as follows.

To a solution of diketal 5 (0·1 mmol) in 200 μL of distilled CH_2Cl_2 at 20°C was added freshly activated silica gel† (60 mg, 100–200 mesh) and 6 μL of 15% aqueous H_2SO_4.

*For correspondence

†Silica gel (100–200 mesh) was heated on a bunsen burner flame in an RB flask for 20 min, cooled to ambient temperature, and stored in a dessicator under nitrogen.



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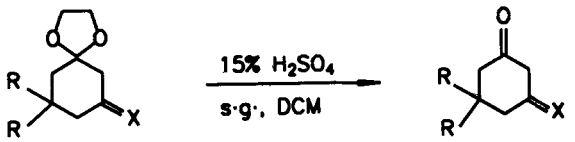
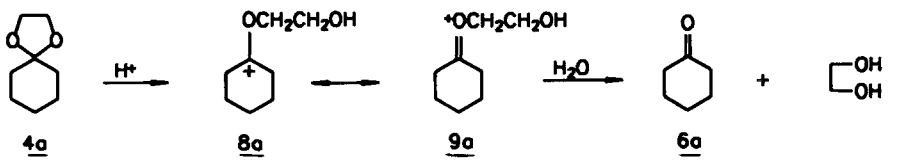
70% overall yield (1)



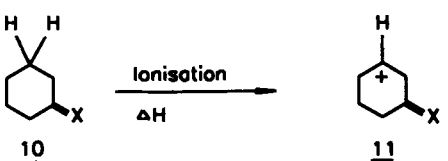
4: R=H
5: R=CH3

a: X=H2
b: X=OCH2CH2O
c: X=SCH2CH2S
d: X=O

6: R=H
7: R=CH3 (2)



4a 8a 9a 6a (3)



10 11

a: X=H2
b: X=OCH2CH2O
c: X=SCH2CH2S
d: X=O (4)

The reaction mixture was magnetically stirred at 20°C for the specified number of hours (table 1). The isolated yield of the crude residue was > 85%.

Aliquots were drawn from the reaction flask at regular intervals, filtered through celite and the solvent evaporated. The percentage conversion of diketal 5 to monoketal 7 was determined by ^{1}H NMR ($CDCl_3$, 200 MHz, Bruker ACF-200 instrument) integration of the 2H methylene resonance α to ketal or ketone. Additionally, the 4H signal due to the ketal protons was also integrated to monitor the disappearance of starting material. Details are provided as under:

5a → 7a: δ 3·84 (*s*, 4H, ketal) vs 2·25–2·15 (*t* and *s*, 2H each, α CH_2's).
5b → 7b: δ 1·91 (*s*, 2H, α CH_2) and 1·54 (*s*, 4H, $\alpha + \gamma$ CH_2's) vs 2·56 (*s*, 2H, α CH_2) and 2·23 (*s*, 2H, α CH_2).

Table 1. Reaction time (h) for hydrolysis of ketals 5 and time for 50% conversion ($t_{\frac{1}{2}}$, h) to ketones 7.

Ketal	Reaction time	$t_{\frac{1}{2}}$
5a	4	1·0
5b	6	2·3
5c	25	7·5
5d	130	56·0

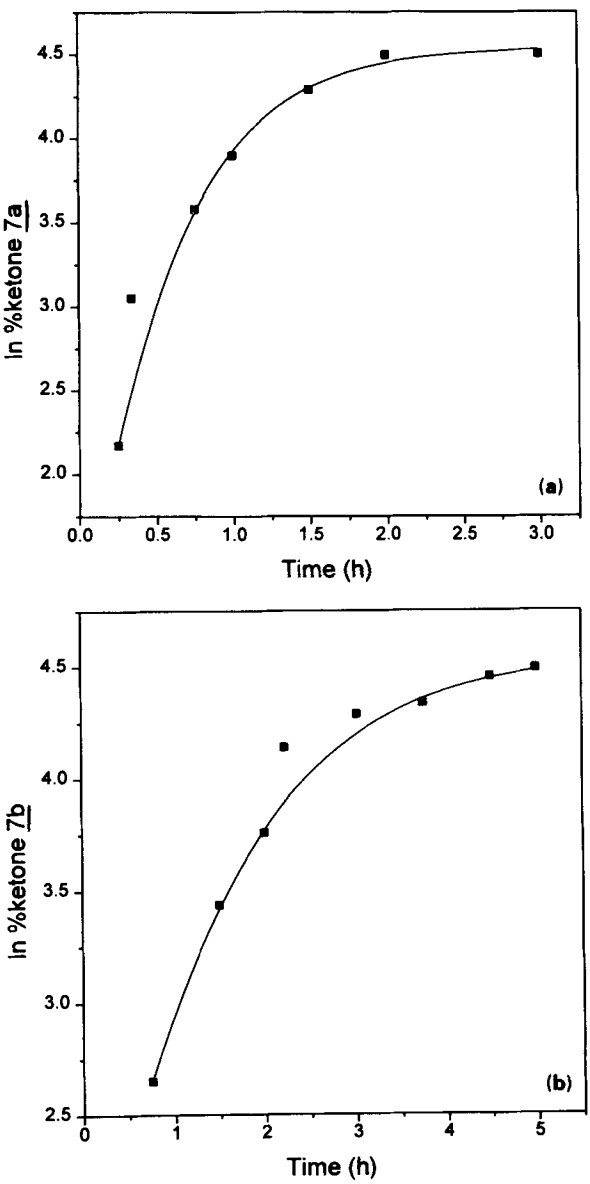


Figure 1. (**a**) and (**b**) Progress of hydrolysis of ketals 5a–b to ketones 7a–b.

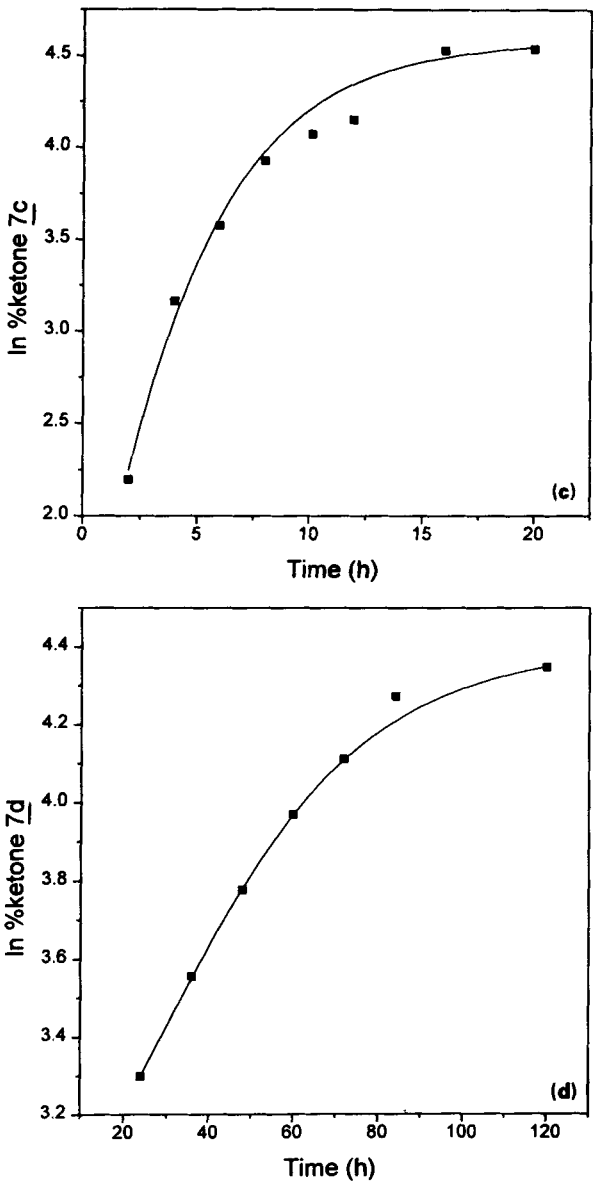


Figure 1. (c) and (d) Progress of hydrolysis of ketals 5c–d to ketones 7c–d.

5c → 7c: δ 3·96 (*s*, 4H, ketal) and 2·00 (*s*, 2H, α CH_2) vs 2·89 (*s*, 2H, α CH_2) and 2·41 (*s*, 2H, α CH_2).

5d → 7d: δ 3·86 (*s*, 4H, ketal) vs ~ 5·30 (*s*, 1H, vinyl of enol-form) and 3·26 (*s*, 2H, α CH_2 of keto-form).

3. Results and discussion

The reported selectivity in the acid-catalysed hydrolysis was verified to be general in nature by preparation of monoketals 6b and 7b from diketals 4b and 5b of 1,3-

cyclohexanedione (H2-CHD) and 3,3-dimethyl-1,3-cyclohexanedione (dimedone, Me2-CHD), respectively (2, chart 1). The relative hydrolysis rates of cyclohexanone-ketals with dimethyl at the 3-position and varying substitution at the 5-position to the ketal carbon were determined. The choice of 3,5-functionalised cyclohexanone ketals 5a–d is intentional because the three pairs of chemically distinct, non-equivalent and uncoupled proton singlets permit convenient monitoring of the reaction progress by ^{1}H NMR integration. The progress of acid-catalysed ketal hydrolysis for Me2-CHD substrates 5a–d was monitored up to 80–90% conversion at 20°C. Graphs of ln (%ketone 7) vs time were plotted and time required for 50% conversion ($t_{\frac{1}{2}}$) calculated using ln 50% = 3·9 (figures 1a–d, table 1). Based on these values the reaction of Me2-CHD ketals 5 follows the trend $X = H_2 > OCH_2CH_2O > SCH_2CH_2S > =O$. Because of the heterogeneous reaction medium, further processing of kinetic data for hydrolysis of 5 as rate laws and coefficients will not be reliable (Laidler 1987). Reactions of H2-CHD ketals 4a–d were similarly monitored and the trend was the same as that of the Me2-CHD ketals 5a–d except that reactions were slower. The faster rates of Me2-CHD ketals compared to H2-CHD substrates is due to the relief in 1,3-diaxial Me–O steric congestion (Sammakia and Smith 1992) upon hydrolysis to monoketals 7a–d. Therefore, based on steric considerations alone hydrolysis within a homologous series of ketals 5a–d should follow the trend: $X = OCH_2CH_2O$ faster than $X = O$.

Apart from the steric driving force to ketal hydrolysis, the electronegativity of the β-substituent X also controls the hydrolysis rate. The irreversible formation of cationic intermediate 8 by an A-1 mechanism is postulated as the rate-determining step (rds) of the reaction (3) (Cordes and Bull 1974; Lowry and Richardson 1981; Ali and Satchell 1993). Factors that stabilise the carbocationic intermediate relative to the ground state would also stabilise the developing transition state and accelerate the reaction. Stabilisation of the intermediate carbocation 8a and the oxonium ion 9a compared to the neutral ketal 4a will result in enhanced reaction rates. It may be reasonably assumed that the contribution of the oxonium ion 9a should be constant for different X's. The ability of X at stabilising the β-carbocation can, therefore, be estimated by calculating ΔH for the model reaction 10 → 11, (4), in which the dioxolane is omitted to simplify the calculation and reduce computer time. The formation of cation 8a from ketal 4a is equivalent to the ionisation of 10a to 11a, and so on.

The heats of formation of 10 and 11, and their differences (ΔH) calculated by three different semi-empirical methods (Turi and Dannenberg 1993), viz, AM1 (Dewar *et al* 1985), MNDO (Dewar and Thiel 1977), and PM3 (Stewart 1989) are summarised in table 2. The calculated ΔH's for the ionisation of 10 to 11 show excellent correlation with the observed trend in ketal hydrolysis rates of 5 to 7. There is a 7–9 kcal/mol

Table 2. Calculated ΔH for ionisation of 10 → 11 (kcal/mol).

	AM1			MNDO			PM3		
X	10	11	ΔH	10	11	ΔH	10	11	ΔH
a	−35·32	174·41	209·73	−32·35	186·96	219·31	−26·10	186·20	213·10
b	−112·79	99·61	212·40	−107·15	115·21	222·36	−101·12	115·75	216·87
c	−14·99	198·73	213·72	−29·16	194·70	223·86	−5·09	210·82	215·91
d	−63·29	158·53	221·82	−60·01	169·03	229·04	−60·13	165·25	225·38

energy difference between the $\Delta H'$s for the β-ionisation of cyclo-hexanone-ketal 10b vs cyclohexanone 10d. The difference in $\Delta H'$s accounts for the facile hydrolysis of diketal 5b compared to monoketal 5d. The remote carbonyl group strongly destabilises the formation of the β-carbocation 11d as compared to 11b. The ketal carbon ($q = 0{\cdot}20$) is less electron-withdrawing compared to the ketonic carbon ($q = 0{\cdot}23$) based on AM1 calculated charges in 10b,d respectively. The atomic charges on the corresponding carbon in 10a,c are $-0{\cdot}15$ and $-0{\cdot}26$ respectively, indicating that formation of β-carbocation should be favoured.

4. Conclusions

These results indicate that hydrolysis rates of ethylene ketals in cyclohexanones are influenced by the steric and electronic nature of the substituent at the remote β-carbon. The experimental observation that *bis*-dioxolanes undergo unusually facile hydrolysis to keto dioxolanes whereas further hydrolysis to diones is retarded is explained by the combined contribution of the following effects: (i) acceleration because of sterically bulky OCH_2CH_2O group, and (ii) deactivation by electron-withdrawing C=O group. Thus, the steric and electronic effects of β-substituent are significant enough to provide favourable selectivity to the hydrolysis step. This should find use in protection/deprotection protocols towards the synthesis of complex organic molecules.

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