

A Geminal Interaction in the Iodination of Methoxyacetone

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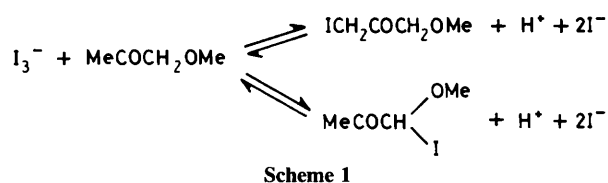
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Iodination of methoxyacetone yields initially 1-iodo-3-methoxypropanone, which then rearranges to its 1,1-isomer; the latter product is favoured thermodynamically by a factor of 2.9×10^5 as a result of a stabilising interaction between geminal iodine and oxygen atoms.

It is well known from quantum calculations and measurements of heats of formation that geminal oxygen atoms in acetals, hydrates, and ortho esters experience a mutually stabilising interaction of up to 10 kcal mol^{-1} , and that this interaction has a stereochemical component manifested in the anomeric effect.¹ Apart from the anomeric effect, however, direct experimental demonstrations of this stabilisation have been surprisingly few and confined mainly to resistance of 'clustered' oxygen or fluorine atoms to displacement as leaving groups in elimination or substitution reactions.² Recent calculations have stressed that interaction of oxygen with electronegative atoms beyond the first row of the periodic table, including phosphorus, sulphur and chlorine, are also stabilising.³ In this communication we describe the effect of an

interaction between iodine and oxygen atoms upon iodine-hydrogen exchange equilibria of methoxyacetone in aqueous solution (Scheme 1).

Halogenation is familiar as a method of measuring rates of enolisation of ketones.⁴ Perhaps less well known is that, for iodine, this reaction is reversible and that an equilibrium constant (K_I) for exchange of hydrogen with iodine, is easily measured.⁵ In practice this exchange usually involves the tri-iodide ion I_3^- , and the equilibrium depends sensitively upon the pH and the concentration of iodide ions, as shown for reaction at the methylene position of methoxyacetone in equation (1). Values of K_I may be measured spectrophotometrically from the change in absorbance of a solution of I_3^- ($\lambda_{\text{max}} 353 \text{ nm}$; $\epsilon 26 000$) accompanying (incomplete) iodination



of a known excess of ketone. In general, reversibility of iodination becomes detectable at low pH and a high concentration of iodide ions.

$$K_1 = \frac{[\text{MeCOCHIOMe}][\text{H}^+][\text{I}^-]^2}{[\text{MeCOCH}_2\text{OMe}][\text{I}_3^-]} \quad (1)$$

The iodination of methoxyacetone is unusual in that reaction occurs initially at the methyl group and is then followed by slower *deiodination* at this position and *reiodination* at the thermodynamically more favourable methylene position. Reaction of an excess of substrate in aqueous acetic acid buffer at 25°C shows a normal, linear, zero-order dependence of the concentration (and absorbance) of I_3^- upon time, with a rate constant consistent with iodination (enolisation) at both methyl and methylene positions, the former predominating. At lower pH values, however, in perchloric acid solution, the zero-order plots show curvature, implying that reaction at the methyl group has become reversible. Normally this curvature would be associated with incomplete consumption of iodine, but, as shown in Figure 1, for methoxyacetone a second phase of iodination takes place, considerably slower than the first, in which the iodine is completely consumed.

This second reaction may be interpreted as iodination at the methylene group of the substrate. However, the observed rate constant is smaller than expected for direct iodination at this position because prior iodination of the methyl group furnishes an 'invisible' source of iodine which replenishes that consumed from solution. In the course of the reaction the iodine in the methyl group becomes completely transferred to the methylene position, with the result that the observed uptake of iodine appears to be slowed. A rate constant for direct iodination of the methylene group is obtainable at lower pH values (or higher iodide concentrations) at which reaction of the methyl group is completely suppressed and zero-order kinetics again prevail. Under either set of conditions, bromination (which in contrast to iodination remains fully irreversible) yields the sum of rate constants for enolisation at both positions.

Finally, under extreme conditions of low pH and high iodide concentration (1.0 M HClO_4 and KI) zero-order iodination of the methylene group itself shows incomplete consumption of iodine, signalling the onset of reversibility.

Analysis of these kinetic and equilibrium data yields rate constants of 2.58×10^{-6} and $8.0 \times 10^{-7} \text{ M}^{-1} \text{ s}^{-1}$ and equilibrium constants (K_1) 1.1×10^{-2} and $3.16 \times 10^3 \text{ M}^2$ for iodination at the methyl and methylene groups of methoxyacetone, respectively. Thus reaction at the methylene group is disfavoured kinetically by a factor of 3.2 but favoured thermodynamically by a factor of 2.9×10^5 . The kinetic effect of the methoxy substituent reflects an adverse influence of this electron-withdrawing group upon acid-catalysed enolisation, and its thermodynamic effect a stabilising influence of geminal iodine and oxygen atoms. The magnitude of this geminal interaction is conveniently expressed as the equilibrium constant K_{gem} for the bond separation reaction (2). Combining equilibrium constants for iodination of methoxyacetone and acetone ($K_1 = 0.056$) one obtains $\text{p}K_{gem} (= -\log K_{gem}) =$

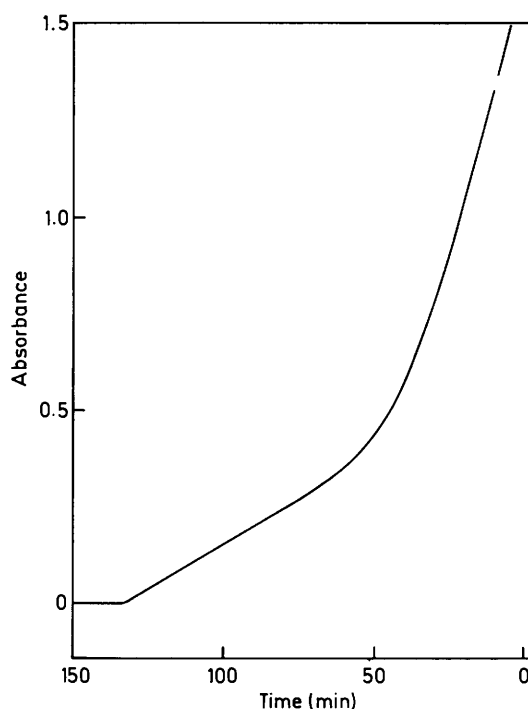
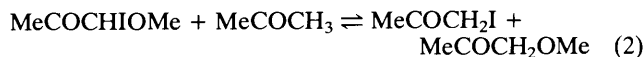


Figure 1. Iodination of 0.2 M methoxyacetone in 0.05 M perchloric acid and 0.2 M sodium iodide at 25°C (aqueous solution).

4.75, to be compared with values of 7.61 and 5.59 for carbon-oxygen bond separation equilibria in formaldehyde and acetaldehyde dimethyl acetals, respectively: ΔG° for reaction (2) is 6.48 kcal mol⁻¹.



The observed sequence of *deiodination* and *reiodination* of methoxyacetone recalls a report of the preparation of 1-bromo-3-methoxyacetone by Bell and Sondheimer⁶ which nicely illustrates the thermochemical stability of geminal halogen and oxygen atoms. The distilled product was found to 'boil spontaneously after some time on being allowed to stand (*sic*)' and to rearrange to its 1,1-isomer. Presumably the reaction was initiated photochemically.

Use of iodine exchange equilibria to measure geminal interactions of α -iodo ketones is quite general. Further examples relating to substituents associated with strong normal or reverse anomeric effects will be reported in a full paper.

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