Applications of Catalytic Thermometric Titrimetry to Studies of Molecular Structure and Reactivity. Part 2.[1] Condensation and Rearrangement Reactions of Carbonyl Compounds

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Aliphatic and aromatic carbonyl compounds and some binary mixtures of these compounds are used as indicator reagents in the catalytic thermometric titration of benzoic acid with potassium hydroxide in propan-1-ol. Comparison of titration curves obtained in blank titrations and in titrations of benzoic acid are used to evaluate the relative reactivities of the carbonyl compounds when they undergo inter- and intra-molecular condensation and rearrangement reactions, and to investigate reaction processes with the binary mixtures. Consideration of the relative reactivities is used to establish relationships between reactivity and molecular environment of the carbonyl group.

As discussed in Part 1,[1] catalytic thermometric titrimetry can be used to compare rates of reaction of different organic hydroxy compounds with acetic anhydride, and to establish a relationship between the relative reactivities and the molecular environment of the hydroxy groups.

In the present work, this analytical technique has been used to study the relative reactivities of various aliphatic, alicyclic, and aromatic carbonyl compounds when these compounds undergo inter- and intra-molecular condensation and rearrangement reactions catalysed by potassium hydroxide in propan-1-ol. This latter reagent is used as the titrant, and the carbonyl compound in the strongly ionising solvent dimethylformamide functions as the thermometric indicator in blank titrations and in the titration of benzoic acid dissolved in the indicator solution.

In general, the condensation and rearrangement reactions are initiated quickly by the catalyst/titrant and are terminated or reach equilibrium relatively quickly under the conditions of the titration. The temperature rise, ΔT, can be related to the heat of reaction Q by the equation:

$$Q = \Delta T \cdot C'_p \qquad (\mathrm{J})$$

where C'_p is the total heat capacity of the system (J K^{-1}).

The temperature rise, which usually occurs over a relatively short period of time (*e.g.* 2—5 min), can be used as a measure of the degree of conversion of the indicator reagent into a product, assuming the heat capacities to be approximately constant, and has been taken as a measure of the 'reactivity' of the carbonyl compound. Initial or overall reaction rates determined by the present technique in which equilibrium or termination of the reaction is achieved could be misleading as a measure of the ability of the compound to yield a product on treatment with a catalyst, and have not been determined.

Since ΔT values can vary slightly with changes in ambient temperature and with small variations in catalyst concentration (from batch to batch and on storage), a more useful value for comparing reactivities is the ratio of the ΔT values for equimolar solutions of the compound and of a standard carbonyl compound determined at the same time under the same titration conditions. Cyclohexanone has been chosen as the standard carbonyl compound for comparison purposes because it is readily available in a very pure form (99.8%) and gives ΔT values sufficiently large to be determined conveniently and accurately with the equipment employed.[2]

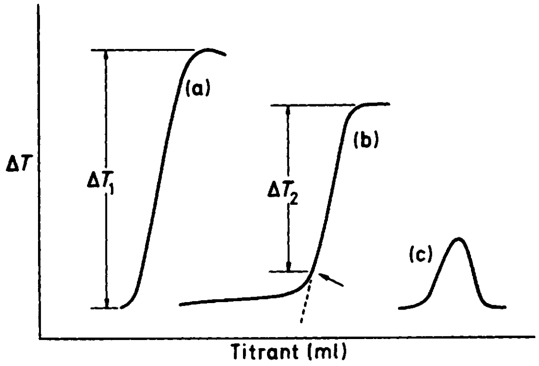

Figure 1. Catalytic thermometric titration curves: (a) blank titration curve; (b) sample titration curve; (c) first derivative of titration curve

Although blank titrations of the indicator solutions alone result in temperature changes greater than those obtained in titrations of solutions of benzoic acid, the latter titrations have the advantage of being much less affected by heats of mixing of the titrant and titrand solvents. Both types of titration have been carried out and their absolute and relative ΔT values have been tabulated. A brief comparison has been made also of the reactivities of aqueous solutions of formaldehyde, glyoxal, glutaraldehyde, and acetaldehyde, since the first three are available only as aqueous solutions.

In a study of the titration of binary mixtures of cyclohexanone and aldehydes it was found convenient to plot the first derivative of the titration curves. This makes it possible to measure rates of reaction and more easily to distinguish between the contributions of the two components of the mixture by accentuating the intermediate end-point region corresponding to the completion of the titration of the more reactive component.

A typical catalytic thermometric titration curve and its first derivative are shown in Figure 1. The rise in temperature after the end-point inflection, or the immediate rise in temperature in blank titrations, ΔT_2 and ΔT_1, respectively, are the values used to calculate the relative 'reactivities', which are more accurately designated 'pseudo relative reactivities', since they do not measure reaction rates.

Table. ΔT_1 and ΔT_2 values[a] and pseudo relative reactivities for different carbonyl reagents

		Blank titrations		Benzoic acid titrations[b]	
Reagent	M	ΔT_1	Relative reactivity	ΔT_2	Relative reactivity
Cyclohexanone[c]	1.0	0.75—0.95	1	0.68—0.78	1
Cyclohexanone	2.5	1.6—1.9	1	1.4	1
Cyclohexanone	5.0	2.4—2.9	1	2.5	1
Acetaldehyde	1.0	10.1	12.6	3.6	5.0
Propionaldehyde	1.0	9.4	11.8	3.4	4.7
Butyraldehyde	1.0	9.1	11.4	3.3	4.6
Isobutyraldehyde	1.0	7.5	9.4	2.9	4.0
Valeraldehyde	1.0	8.6	10.8	3.6	5.0
Hexanal	1.0	8.7	10.9	2.8	3.9
Heptanal	1.0	9.1	11.4	3.1	4.3
DL-2-Phenylpropionaldehyde	1.0	—		0.81	1.1
Aq. formaldehyde	5.0	0.7	—	0.5	—
Aq. acetaldehyde	5.0	10.7	—	4.8	—
Aq. glutaraldehyde	5.0	11.5	—	6.5	—
Aq. glyoxal	5.0	1.6	—	1.3	—
Acetone	1.0	0.34	0.45		
Acetone	5.0			1.10	0.44
4-Phenylbutan-2-one	1.0	0.27	0.36	0.20	0.3
Butane-2,3-dione	1.0	6.6	8.8	5.1	7.5
Hexane-2,5-dione	1.0	3.4	4.5	1.1	1.6
1-Phenylpropane-1,2-dione	1.0	11.0	14.7	5.3	7.8
Benzil	1.0	4.1	5.5	1.6	2.4
Cyclohexanone	1.0	0.95	1		
Cyclohexanone	5.0			2.5	1
Cyclopentanone	1.0	2.5	2.6		
Cyclopentanone	5.0			6.63	2.65
Cyclobutanone	1.0	8.4	8.9		
Cyclohexane-1,2-dione	2.5	9.5	5.9	6.3	4.5[d]
Cyclohexane-1,4-dione	2.5	22.6	14.1	15.2	10.9[d]

[a] To the nearest 0.1 °C for temperatures of 1 °C and above; to the nearest 0.01 °C for temperatures below 1 °C. [b] 0.5 Milliequivalent. [c] ΔT Values for cyclohexanone are given as the range for titrations carried out at different ambient temperatures and with titrants of molarity differing slightly from the nominal 0.5M value. [d] 0.25 Milliequivalent.

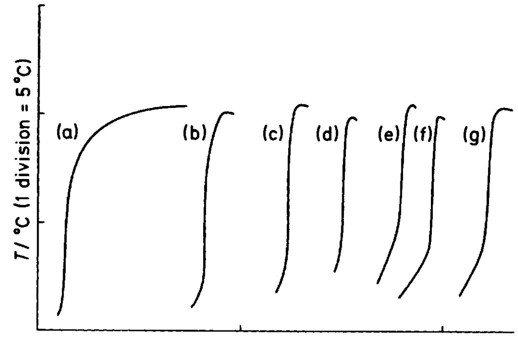

Figure 2. Thermometric titrations with 1M aliphatic aldehydes as indicator reagents (blank titrations): (a) acetaldehyde; (b) propionaldehyde; (c) butyraldehyde; (d) isobutyraldehyde; (e) valeraldehyde; (f) hexanal; (g) heptanal

Results and Discussion

Titration curves for indicator reagent solutions alone and solutions containing 0.5 milliequivalent of benzoic acid are shown in Figures 2—8. Relative reactivities and ΔT values are given in the Table. In all titrations 0.5M potassium hydroxide in propan-1-ol was used as the titrant. Procedures for locating the end point of a catalytic thermometric titration are discussed in Part 1.[1] Three concentrations of carbonyl compounds in dimethylformamide, 1, 2.5, and 5M, have been evaluated as indicator reagents. The higher concentrations were used for carbonyl compounds with lower heats of reaction in order to obtain more reliable values for the rise in temperature.

Aliphatic Aldehydes.—Figure 2 shows the blank titration curves for 1M solutions of the C_2—C_7 normal aldehydes and isobutyraldehyde in dimethylformamide. Figure 3 shows the tiration curves for the same aldehyde solutions containing benzoic acid. Figure 3 also includes the titration curve for DL-2-phenylpropionaldehyde, an α-arylalkyl aldehyde, for comparison.

It can be seen from the titration curves that the ΔT values for all the C_2—C_7 aldehydes are similar, except that with acetaldehyde the temperature continues to rise, although at a slower rate, after the initial sharp rise. With acetaldehyde, under the conditions of the titration, the initial intermolecular aldol condensation proceeds further to yield a polymeric product which, ultimately, undergoes dehydration to a coloured polyene—as noted in an earlier paper.[3] The other aldehydes examined do not appear to condense further under these conditions of titration, and the temperature rise terminates rather abruptly.

It can be seen in Figure 3 that in titrations of benzoic acid there is a significant rise in temperature before the end-point inflection occurs. This initial temperature rise results, presumably, from the addition of the titrant solvent, propan-1-ol, to the aldehyde to yield the hemiacetal. The temperature rise after the end point, which is used to calculate the relative reactivity, results, in part at least, from the intermolecular condensation of the hemiacetals.

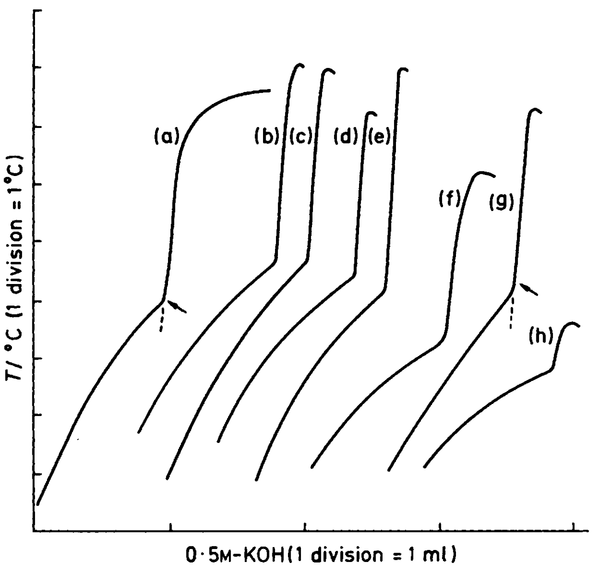

Figure 3. Thermometric titrations with 1M aliphatic aldehydes as indicator reagents (titrations of benzoic acid): (a) acetaldehyde; (b) propionaldehyde; (c) butyraldehyde; (d) isobutyraldehyde; (e) valeraldehyde; (f) hexanal; (g) heptanal; (h) DL-2-phenylpropionaldehyde. Arrows indicate location of end points

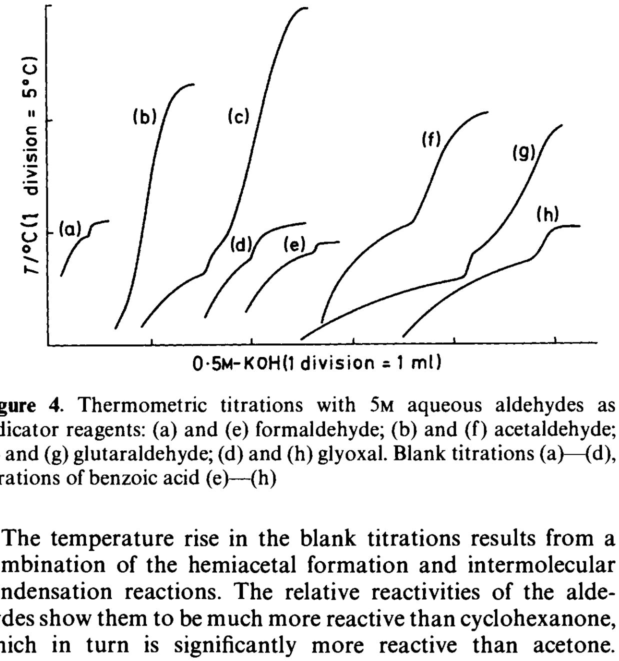

Figure 4. Thermometric titrations with 5M aqueous aldehydes as indicator reagents: (a) and (e) formaldehyde; (b) and (f) acetaldehyde; (c) and (g) glutaraldehyde; (d) and (h) glyoxal. Blank titrations (a)—(d), titrations of benzoic acid (e)—(h)

The temperature rise in the blank titrations results from a combination of the hemiacetal formation and intermolecular condensation reactions. The relative reactivities of the aldehydes show them to be much more reactive than cyclohexanone, which in turn is significantly more reactive than acetone. Substitution of a phenyl group in the α-position of propionaldehyde is seen to reduce the reactivity by a factor of about 4.2.

The titration curves for 5M aqueous solutions of formaldehyde, acetaldehyde, glyoxal, and glutaraldehyde are shown in Figure 4. It can be seen that the formaldehyde is the least reactive of these aldehydes. Aqueous formaldehyde, glyoxal, and glutaraldehyde contain some free acid, consequently true blank titrations are difficult to obtain. The content of free acids can be determined from the titration curves. Gaál *et al.*[4] have shown that aqueous formaldehyde is a suitable indicator reagent for the catalytic thermometric titration of acids. In aqueous solution the aldehydes are already in their equilibrium hydrated form so that significant rises in temperature caused by hemiacetal formation on addition of the titrant would not be expected.

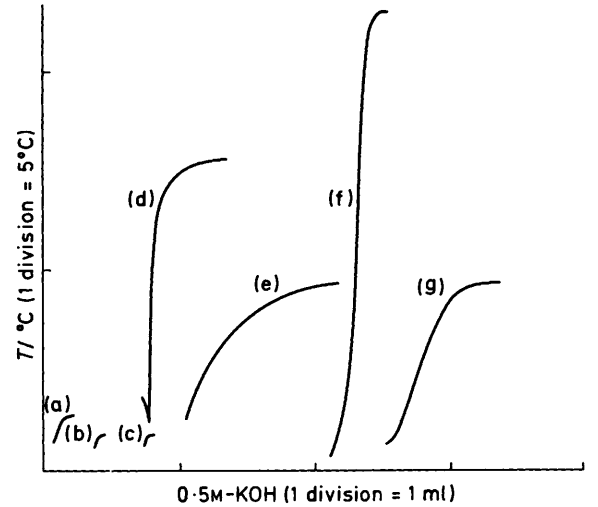

Figure 5. Thermometric titrations with 1M dialkyl, arylalkyl, and diaryl ketones and diketones as indicator reagents (bank titrations): (a) cyclohexanone (for comparison); (b) acetone; (c) 4-phenylbutan-2-one; (d) butane-2,3-dione; (e) hexane-2,5-dione; (f) 1-phenylpropane-1,2-dione; (g) benzil

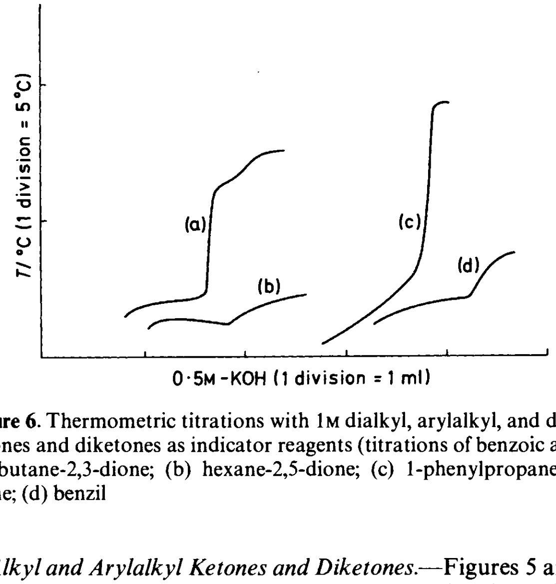

Figure 6. Thermometric titrations with 1M dialkyl, arylalkyl, and diaryl ketones and diketones as indicator reagents (titrations of benzoic acid): (a) butane-2,3-dione; (b) hexane-2,5-dione; (c) 1-phenylpropane-1,2-dione; (d) benzil

Alkyl and Arylalkyl Ketones and Diketones.—Figures 5 and 6 show the titration curves obtained by the titration of 1M solutions of a range of alkyl and arylalkyl ketones and diketones, alone and containing 0.5 milliequivalent of benzoic acid, respectively.

Vaughan and Swithenbank,[5] who first reported on the use of acetone as an indicator in the catalytic thermometric titration of weak acids in acetone solution, examined a number of other aliphatic ketones but found that none of these gave a useful temperature rise at the end point of the titration. This was confirmed for diethyl ketone, methyl ethyl ketone, methyl isobutyl ketone, and methyl isopropyl ketone in the present work. Acetone as a lower heat of condensation than cyclohexanone when treated with 0.5M potassium hydroxide reagent, the relative reactivity being 0.41 for 5M solutions of the ketones in dimethylformamide.

Some aliphatic diketones have been titrated. The 1,2-diketone, butane-2,3-dione, undergoes a rapid intermolecular condensation reaction on addition of the potassium hydroxide titrant. This is followed by ring closure to form 2,5-dimethyl-1,4-benzoquinone.[6] The temperature rise was 6.6 °C in the blank titration of a 1M solution compared with 0.75 °C for the same

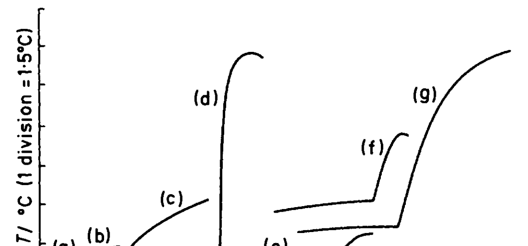

Figure 7. Thermometric titrations with alicyclic ketones as indicator reagents: (a) and (e) acetone (for comparison); (b) and (f) cyclohexanone; (c) and (g) cyclopentanone; (d) cyclobutanone. Blank titrations of 1M solutions (a)—(d), titrations of 5M solutions containing benzoic acid (e)—(g)

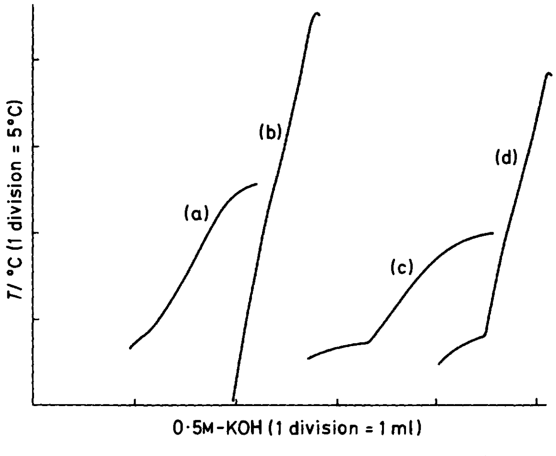

Figure 8. Thermometric titrations with 2.5M alicyclic diketones as indicator reagents: (a) and (c) cyclohexane-1,2-dione; (b) and (d) cyclohexane-1,4-dione. Blank titrations (a), (b); titrations of benzoic acid (c), (d)

concentration of cyclohexanone. The 1,3-diketone pentane-2,4-dione does not undergo an alkali-catalysed condensation reaction but, as its acidic enolic form, is neutralised by the titrant to yield a potassium salt. In contrast, the 1,4-diketone hexane-2,5-dione undergoes an intramolecular condensation reaction followed by ring closure to form 3-methylcyclopent-2-enone[7] and has a relative reactivity of 4.5, when compared with cyclohexanone using 1M solutions of the ketones.

Three arylalkyl ketones have been investigated. Propiophenone previously has been shown to undergo an alkali-catalysed reaction which resulted in a rise in temperature of less than 1 °C, when the undiluted ketone is titrated with M potassium hydroxide in propan-2-ol.[2] There was a possibility that this reaction was not characteristic of the ketone because purified, *i.e.*, redistilled, samples did not show a temperature rise when titrated. The corresponding diketone, 1-phenylpropane-1,2-dione, however, proved to be highly reactive, a 1M solution giving a temperature rise of 11.0 °C when titrated. This corresponds to a relative reactivity of 14.7. It was possible that the original sample of propiophenone contains a small amount of the diketone, which could be formed by oxidation on storage, but this could be confirmed by gas chromatography.

In contrast to propiophenone, 4-phenylbutan-2-one gave a temperature rise only slightly less than that obtained with acetone, when titrated as a 1M solution, suggesting that the position of the carbonyl group with respect to the phenyl group is critical.

Diaryl Ketones.—Benzil, a diaryl 1,2-diketone which undergoes an alkali-catalysed rearrangement to benzilic acid, was investigated as a possible thermometric indicator. The temperature rise in the titration of a 1M solution of benzil was 4.1 °C compared with 6.6 °C for butane-2,3-dione determined under the same conditions. In the titration of benzil with the 0.5M potassium hydroxide reagent an intense blue intermediate product was formed. This has been shown to be the benzil radical anion by e.s.r. spectroscopy.[8] It is apparent that the diaryl diketone is slightly less reactive than the dialkyl diketone and considerably less reactive than the aryl alkyl diketone, 1-phenylpropane-1,2-dione. The titration curves obtained using the benzil reagent are shown in Figures 5 and 6.

Alicyclic Ketones.—In Figure 7 it can be seen that the reactivities of cyclic ketones vary with increase in the ring size in the order four > five > six, both when the indicator solution alone is titrated and when the reagent is used for the titration of benzoic acid. The ΔT values for 1M solutions of cyclobutanone, cyclopentanone, and cyclohexanone were 8.4, 2.5, and 0.95, respectively. When cycloheptanone solutions were titrated there was a slight decrease in temperature, suggesting an endothermic heat of mixing of the solvents and a negligible heat of reaction. The ΔT values in the titrations of benzoic acid followed the same order for the four-, five-, and six-membered ring compounds. There was no end-point inflection with cycloheptanone as the indicator reagent.

Alicyclic Diketones.—Titration curves obtained using cyclohexane-1,2- and -1,4-dione as the indicator reagents are shown in Figure 8.When solutions of the 1,3 isomer are titrated the temperature rise occurs only slowly and in titrations of benzoic acid there is no discernable end-point inflection. The compound is similar to the pentane-2,3-dione already discussed in that it forms an acidic stabilised enolic form which is neutralised by the titrant, yielding an insoluble potassium salt which does not react further. The 1,2- and 1,4- isomers undergo rapid condensation reactions when treated with the potassium hydroxide solution. Unlike the 1,2 and 1,4 linear diketones, butane-2,3-dione and hexane-2,5-dione, the 1,4 isomer is much more reactive than the 1,2 the relative reactivities being 14.1 and 5.9, respectively.

The 2-methyl and 2-chloro derivatives of cyclohexanone are less reactive than cyclohexanone and show only gradual rises in temperature when titrated as 5M solutions in dimethylformamide.

Mixtures of Cyclohexanone with Propionaldehyde and Butyraldehyde.—The effect of using binary mixtures of cyclohexanone and aldehydes as thermometric indicators has been examined in a semi-quantitative manner. Mixtures of cyclohexanone with acetaldehyde, propionaldehyde, butyraldehyde, isobutyraldehyde, and benzaldehyde were examined. All the mixtures were effective as end-point indicators in the titration of benzoic acid, and in all instances a cross-aldol condensation was the main indicator reaction.

The reaction products obtained with aliphatic aldehydes as the second component were analysed by gas chromatography–mass spectrometry and were found to comprise a mixture of the *cis*- and *trans*-forms of the 2-alkylidene- and 2,6-dialkylidenecyclohexanone together with the unsaturated self-condensate of the aldehyde [$RCH{=}CH(R^1)CHO$]. The cylohexanone–benzaldehyde mixture gave a precipitate identified as 2,6-benzylidenecyclohexanone. With equimolecular mixtures the temperature rise was significantly higher than that obtained with cyclohexanone alone.

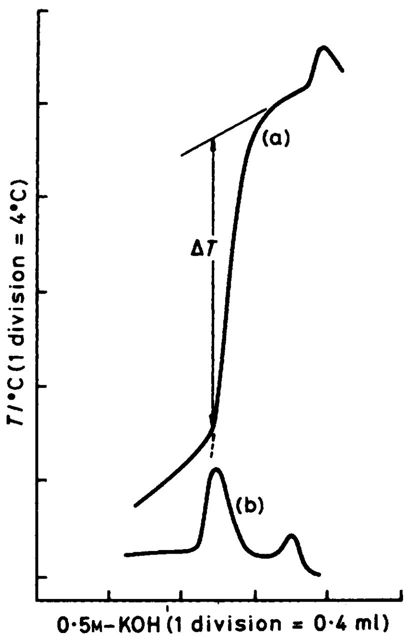

Figure 9. Thermometric titration of an equimolar mixture of cyclohexanone and butyraldehyde (3.7 ml sample): (a) titration curve; (b) first derivative of titration curve

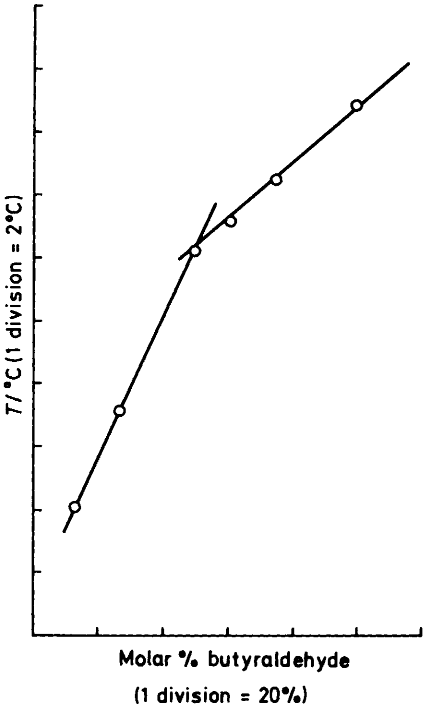

Figure 10. Relationship between temperature rise and butyraldehyde content in the catalytic thermometric titration of cyclohexanone–butyraldehyde mixtures

The mixture of cyclohexanone with butyraldehyde was investigated further. A typical titration curve is shown in Figure 9. The curve shows that the indicator reaction is complex, and the first derivative of the curve suggests that two consecutive reactions occur. Seven mixtures of the two components, each mixture with a total volume of 2 ml, and ranging from 2 ml cyclohexanone + 0 ml aldehyde to 0 ml cyclohexanone + 2 ml aldehyde, in aliquots of 0.25 ml, were titrated. The heats of reaction were found to increase with the aldehyde content. On plotting the overall temperature rise against the aldehyde content, as shown in Figure 10, it can be seen that the graph represents two intersecting straight lines. The point of intersection corresponds to a mixture with a molar ratio of approximately 1:1. The reaction products formed up to the point of intersection were found to contain mainly the monobutylidenecyclohexanone.

The first-derivative curves in Figure 9 enable the relative reaction rates for the two stages of the reaction to be measured. The rates suggest that formation of the monobutylidenecyclohexanone occurs much faster than formation of the dibutylidene derivative.

General Considerations

The temperature rise during the titration depends on the heat capacity of the solution, *i.e.*, of the mixture of the carbonyl compound and its reaction products, dimethylformamide, propan-1-ol and small amounts of potassium hydroxide and potassium salts. With indicator solutions of the same molarity, the ratio of dimethylformamide to carbonyl compound (w/w) will depend on the relative molecular mass of the latter. Thus, measurement of the temperature rise only will not lead to an accurate comparison of the reactivities of the carbonyl compounds, but it is useful for a semi-quantitative comparison, and this is the intention of the present work. Knowing the heat capacities of dimethylformamide, propan-1-ol- and the carbonyl compounds, it would be possible to calculate approximate values for the heats of reaction. However, this calculation would not take account of the heat capacities of reaction products.

When evaluating relative reactivities, titrations of the cyclohexanone standard of the appropriate molarity were carried out at the same time and under the same conditions as the titration of the carbonyl compound under investigation. In the Table, the ΔT values for the cyclohexanone titrations cover a range; the variations result from determinations carried out at different times, not necessarily with the same batch of titrant and probably at different ambient temperatures.

Measurements of relative reactivity would be expected to be more reliable for reactions that occur rapidly than those occurring over a long period of time and which involve the addition of larger amounts of titrant, when comparisons of the temperature rise with that of the standard compound, cyclohexanone, would be less meaningful. However, the shape of the titration curves will give some indication of the kinetics of these alkali-catalysed reactions.

The relative reactivities for the aliphatic aldehyde indicator reagents are much higher for the blank titrations than when they are calculated from the results of benzoic acid titrations because, as noted above, acetal formation is also involved in the former titrations.

In the titrations with the aqueous aldehydes as indicator reagents, significantly different reactivity values would be expected for formaldehyde and glyoxal compared with acetaldehyde and glutaraldehyde, because different reactions occur—the Cannizzaro reaction with the former compounds and the aldol condensation with the latter. Relative reactivities with respect to cyclohexanone are not given in the Table for aqueous aldehydes because the comparison standard is not water soluble.

In the Cannizzaro reactions and the alkali-catalysed rearrangement of benzil, acids are formed and it might be expected that the end point in the titration of benzoic acid using formaldehyde, glyoxal, or benzil as the indicator reagent would not correspond to the neutralisation of the benzoic acid only. However, under the conditions used, the end point does correspond to the benzoic acid content, if one allows for free acid initially present in the formaldehyde and glyoxal.

Allinger *et al.*[9] have compared the strain energies of cyclic ketones and hydrocarbons, and find for cyclobutanone, cyclopentanone, and cyclohexanone that the ketone is more strained than the corresponding cycloalkane. In cyclobutanone and cyclopentanone there is serious bending at the trigonal carbon which tends to raise the energy of the ketone relative to that of the hydrocarbon. The explanation for the high reactivity of cyclohexanone compared with that of acetone is not obvious. With the higher alicyclic ketones (C_7 and above) a combination of residual van der Waals and torsional energies makes the compounds more stable in the ketone than in the hydrocarbon form. Thus, the difference in the reactivities of the C_4—C_7 cyclic ketones examined in the present study can be attributed to ring strain and steric effects.

Experimental

Reagents.—Benzoic acid, propan-1-ol, and dimethylformamide were of analytical reagent grade. All other reagents were of laboratory reagent grade. The 0.5M potassium hydroxide titrant was prepared by dissolving analytical reagent grade KOH in propan-1-ol.

Apparatus.—The automatic titration apparatus was as described in Part 1.[1]

Titration Procedure.—The 0.5M potassium hydroxide reagent was added at a rate of 0.2 ml min^{-1} to 5 ml amounts of 1, 2.5, or 5M solutions of the carbonyl compounds in dimethylformamide, alone or containing 0.5 milliequivalent (61 mg) of benzoic acid, in a 14 ml Dewar beaker, while the solution was stirred with a magnetic stirrer. The temperature, measured with a thermistor immersed in the titrand, was recorded during the course of the titration. The two-open recorder had one pen connected through a first-derivative converter.

Acknowledgements

We thank Professor A. G. Davies, University College, London, for discussions and for providing the e.s.r. spectra.

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Received 2nd September 1987; *Paper* 7/1602