Applications of Catalytic Thermometric Titrimetry to Studies of Molecular Structure and Reactivity. Part 1. Organic Hydroxy Groups

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Solutions of organic hydroxy compounds in acetic anhydride are used as indicator reagents in the catalytic thermometric titration of the weak base, quinoline, and the very weak base, caffeine, with perchloric acid in acetic acid. Comparisons of the titration curves are used to evaluate the relative reactivities of the hydroxy reagents. Consideration of these relative reactivities for hydroxy compounds of similar structure is used to establish relationships between reactivity and molecular environment of the hydroxy group.

In catalytic thermometric titrimetry,[1] the rise in temperature marking the end point is caused by an exothermic reaction catalysed by the titrant; the reagents for this indicator reaction are included in the sample solution.

Ideally, the sample (titrand) should inhibit the indicator reaction until the titrand–titrant (derminative) reaction is virtually complete, and a small surplus of titrant should initiate the indicator reaction immediately. If such a situation were possible, the thermometric end point would be seen as a sharp inflection in the graph relating temperature and titrant volume (Figure 1, curve a), and the volume of titrant corresponding to this inflection would be that required to satisfy the stoicheiometry of the determinative reaction.

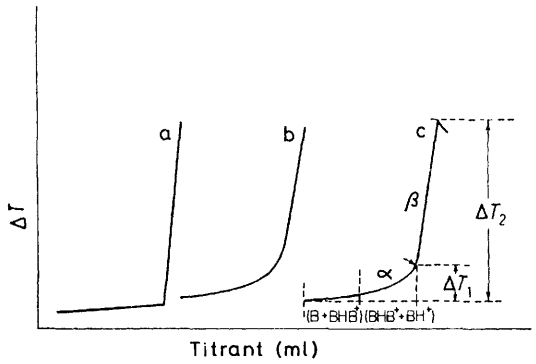

Figure 1 Catalytic thermometric titration curves: a, ideal curve; b, typical curve; c, segmented theoretical curve. Arrow indicates end-point

In practice, the determinative and indicator reactions do not occur consecutively but overlap; consequently in most instances the end point of the titration is marked by a gradual change in the slope of the titration curve instead of a sharp inflection (Figure 1, curve b). The shape of the titration curve can give an indication of the efficiencies of the titrand and titrant as inhibitor and initiator, respectively, for the indicator reaction.

Usually, the temperature rise caused by the determinative reaction is almost negligible when compared to that arising from the indicator reaction because the indicator reagents are major constituents of the sample solution (they are often used as the solvent), whereas the sample is a minor constituent. For example, in a typical catalytic thermometric titration of a weak acid, in which acrylonitrile is used as the indicator reagent, *ca.* 10 mg of the acid dissolved in 5 ml of acrylonitrile is titrated with 0.1M-strong alkali in non-aqueous solution.[2]

Temperature changes occurring during the determinative step of the titration can often be attributed largely to the heat of mixing of the titrant solvent with the sample solvent and other dilution effects. These changes can be assigned without ambiguity when the heats of mixing and dilution are endothermic. Figures 8, 10, 11, 18, and 21—23 of ref. 1 show such changes, which can exceed 4 °C in extreme cases.

When several reagents or combinations of reagents are suitable as thermometric indicators for the same determinative reaction, the possibility arises of using catalytic thermometric titrimetry to compare the reactivities of the indicator reagents. For example, the marked difference between the response of acetone and acetaldehyde to the action of potassium hydroxide in both aqueous and alcoholic solution is obvious from the titration curves obtained when these compounds are used as indicator reagents in the catalytic thermometric titration of weak acids with the potassium hydroxide solutions.[3]

Recently,[4] it has been shown that when the perchloric acid-catalysed acetylation of hydroxy compounds with acetic anhydride is used to indicate the end point in the non-aqueous titration of bases with perchloric acid, the

[1] E. J. Greenhow, *Chem. Rev.*, 1977, **77**, 835.
[2] E. J. Greenhow and L. E. Spencer, *Analyst*, 1973, **98**, 90.
[3] E. J. Greenhow and L. E. Spencer, *Talanta*, 1977, **24**, 201.
[4] E. J. Greenhow, *Analyst*, 1977, **102**, 584.

shape of the titration curves is influenced by the nature of the hydroxy compound. In the present investigation, this indicator reaction is used to compare the rates of reaction of different organic hydroxy compounds with acetic anhydride, and an attempt is made to establish a relationship between the relative reactivities, measured in this way, and the molecular environment of the hydroxy groups.

RESULTS AND DISCUSSION

Titration curves obtained when the weak base, quinoline (pK_b 8.94), and the very weak base, caffeine (pK_b 13.39), are determined by the catalytic thermometric method, using different hydroxy compounds mixed with acetic anhydride as the indicator reagent are shown in Figures 2—10.

Procedures for locating the position of the end point in catalytic thermometric titrimetry are discussed in ref. 1. In the present experiments, it has been found that the theoretical end point occurs on addition of a volume of titrant corresponding to the inflection in the titration curve (shown by an arrow in Figure 1c) or, when the inflection is not clearly discernible, to the point where a tangent drawn to the main temperature rise (β in Figure 1c) leaves the titration curve at its lower temperature end. Vaughan and Swithenbank [5] have justified the latter procedure in the determination of very weak acids by assuming that the rate of the indicator reaction increases sharply when the determinative reaction is virtually complete.

With nearly all the indicator mixtures, it can be seen that the temperature rise before the end-point inflection is significantly greater in titrations of the weaker base, caffeine, than it is in the corresponding titrations of quinoline. Such a rise in temperature can be attributed to acetylation occurring at a measurable rate before the catalyst (perchloric acid) is, theoretically, present in the solution in the free form, since it may be assumed that the determinative reaction proceeds virtually to completion at a rate faster than that at which the perchloric acid reagent is added. Most acid–base reactions occur at rates far exceeding that at which the syringe burette operates; however, the protonated bases formed in the titrations under consideration are themselves acidic, and the pK_a value of protonated caffeine (0.61) is much less than that of protonated quinoline (5.06). One would expect, therefore, that 'uncatalysed' acetylation, catalysed in fact by the protonated base, would be more likely to occur in the titration of caffeine than of quinoline. The catalytic effect of the protonated base should be more noticeable after the half-neutralisation stage than before, because virtually all protonated base (BH^+) will be associated with unprotonated base (B) as a homoconjugated ion (BH^+B) until half the base is protonated. The acidity of this conjugate ion will be significantly lower than that of BH^+, which would be expected to appear, in its unconjugated form and in increasing concentration, after the half-neutralisation stage.

In many of the titrations, tangents drawn to the titration curve before the end-point inflection reveal that the temperature increases at almost a constant rate before the half-neutralisation point and at an increasing rate after it, until the end-point inflection is reached. The sharp rise in temperature after the end point is almost linear in the majority of the titration curves. Figure 1c is an 'ideal' titration curve of this type in which temperature changes caused by heats of dilution and mixing are negligible compared with those arising from catalysed and 'uncatalysed' acetylation reactions. The slopes of the segments α and β of this idealised curve should be characteristic of the reactivity of the hydroxy component of the indicator reagent. The overall temperature rise and the temperature rise before the end point are also characteristic of the reactivities of the indicator reagents because they are measures of the heats of reaction of the overall and 'uncatalysed' processes. The fall in temperature following the final temperature rise can be attributed to the cooling effect of titrant added in excess of that required by the determinative and indicator reactions.

If the reaction rates immediately before and after the end point are to be used to characterise the reactivity of the hydroxy component of the indicator mixture, it will be necessary to establish standard conditions for their measurement, *e.g.*, to bring the apparatus and reagents to a constant, preselected temperature before commencing the titration. It will also be necessary to assume that heats of mixing and dilution will either be negligible for all the indicator systems evaluated or independent of the hydroxy reagent when the latter is present in the sample solution in constant molar concentration. The latter assumption is unlikely to be valid because heat changes caused by mixing and dilution will be influenced by the molecular size and complexity of the hydroxy component. These molecular effects will not be insignificant because, in most instances, the hydroxy component is present in a relatively high concentration.

In view of the exacting experimental requirements and the intrinsic difficulties associated with the determination of reaction rates from the slopes of the segments α and β of the titration curve, it was decided in the present investigation to use a simpler comparison procedure for the evaluation of the reactivities of the hydroxy reagents. The titration curves obtained by using hydroxy reagents of similar structure and, where possible, of the same molecular weight, are collected together in each of Figures 2—10. Differences in the reactivities of the hydroxy groups in these compounds have been established by comparing the shapes of the titration curves and their ΔT_1 and ΔT_2 values (Figure 1c).

The Table gives the ranges of ΔT_1 and ΔT_2 values obtained in titrations in which different classes of organic hydroxy compounds were used as reagents.

Butanols and 4-*Hydroxy*-4-*methylpentan*-2-*one*.—In Figure 2 it can be seen that the reactivities of normal, iso, secondary, and tertiary butanols are not very different

[5] G. A. Vaughan and J. J. Swithenbank, *Analyst*, 1970, **95**, 890.

when these are used as indicator reagents in the titrations of the same nitrogenous base, but for each alkanol there is a marked difference between the shapes of the titration curves obtained with quinoline and caffeine as

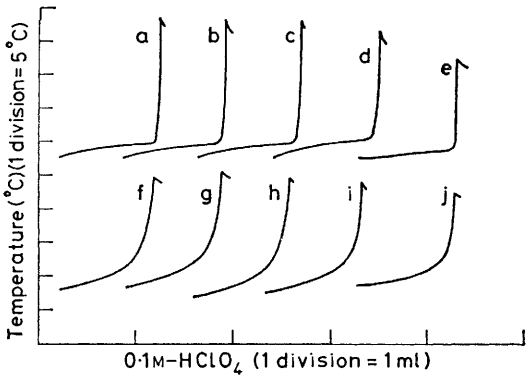

FIGURE 2 Thermometric titrations with alkanols and 4-hydroxy-4-methylpentan-2-one as indicator reagents. Hydroxy reagents: a, butan-1-ol; b, 2-methylpropan-1-ol; c, 1-methylpropan-1-ol; d, 2-methylpropan-2-ol; e, 4-hydroxy-4-methylpentan-2-one; f—j, as a—e, respectively. Conditions: quinoline (a—e) or caffeine (f—j) (0.1 mequiv.) and hydroxy reagent (4 mequiv.) dissolved in acetic anhydride (5 ml) and titrated with 0.1M-$HClO_4$ reagent

the titrands. As already observed,[4] there is a marginal improvement in the sharpness of the end-point inflection in the titration of quinoline when 4-hydroxy-4-methylpentan-2-one is used instead of the alkanols as the hydroxy component of the indicator reagent. In addition, the ΔT_2 values for the keto-alkanol are significantly less than those of the alkanols in titrations of both bases. The ΔT_1 value is also lower in the titration of quinoline, and marginally lower in the titration of caffeine. These results could be attributed to the lower reactivity of the hydroxy group in the keto-alkanol, which results from its intramolecular hydrogen bonding with the carbonyl group. Such bonding might be expected to reduce the extent of ' uncatalysed ' acetylation before the end-point of the titration, thereby causing a sharpening of the end point inflection. The keto-alkanol acquires a transient lilac colour at the end-point of the titration, suggesting the formation of an intermediate more complex than any that may occur in the acetylation of the simple alkanols.

Hydroxyalkanoic Acids and Esters.—Titration curves obtained with hydroxyalkanoic acids and esters as indicator reagents are shown in Figure 3. The curves differ markedly in shape and in the magnitude of the ΔT_1 and ΔT_2 values. 2-Hydroxypropanoic acid (lactic acid) gives rise to sharper end-points than do hydroxyacetic and 2-hydroxy-2-methylpropanoic acids, and the ΔT_2 value is greater than those obtained in titrations with the last two acids. The differences in the shapes of the curves obtained with these three reagents, which are representative of primary, secondary, and tertiary hydroxy-acids, are much greater than those seen in the curves obtained by using the corresponding primary, secondary, and tertiary butanols as indicator reagents. There is evidence from these results that, in the solvent system employed, hydrogen bonding is stronger in lactic acid than in the other two acids, since with lactic acid the temperature rise before the end-point inflection is much smaller. The end-point inflection is sharp and the temperature rise before the inflection is almost negligible

ΔT_1 and ΔT_2 values [a] obtained with different organic hydroxy reagents

	Quinoline titrations		Caffeine titrations	
Reagent	ΔT_1	ΔT_2	ΔT_1	ΔT_2
Butanols	3—4	19—21	9—10	16—17
4-Hydroxy-4-methylpentan-2-one	2	15	7	14
Hydroxyacetic acid	7	12	6	12
2-Hydroxypropanoic acid	2	25	8	22
Ethyl 2-hydroxypropanoate	2	22	6	20
2-Hydroxy-2-methylpropanoic acid	6	17	8	17
Methyl 2-hydroxy-2-methylpropanoate	9	15	8	15
Phenylmethanol	8	19	7	17
Diphenylmethanol	9	19	9	17
Triphenylmethanol	−1	0.6 [b]	0	1
2-Hydroxyphenylacetic acid	9	17	9	14
2,2-Diphenylhydroxyacetic acid	2	12	2	11
Phenols and monoalkylphenols	1—6	9—13	—5	9—12
2,4-Di-t-butylphenol	2	11	3	11
2,6-Di-t-butylphenol	2	8	2	8
1- and 2-Naphthol	1, 2	9, 10	3, 3	11, 12
4-Hydroxybiphenyl	2	9	3	10
2,2'-Dihydroxybiphenyl	1	9	3	11
1,2-, 1,3-, and 1,4-Dihydroxybenzenes	4, 4, 5	11, 11, 11	4, 4, 6	11, 11, 12
3-Nitrophenol	2	9	2	9
4-Nitrophenol	1	7	1	7
2-, 3-, and 4-Monohydroxybenzoic acids	0, 0, −1	5, 8, 6 [b]	−1, 1, −1	6,[b] 8, 6 [b]
3-Hydroxy-2-naphthoic acid	0	4	0	4
2-, 3-, and 4-Monohydroxybenzaldehydes	4, 9, 8	16, 18, 15	7, 12, 10	17, 20, 18
2-Hydroxy-1-naphthaldehyde	4	13	5	17
2- and 3-Hydroxyacetophenones	1,3	5, 9	0, 4	5, 9
Dialkyl ketones		0—2		0—2
Alkyl aryl ketones		0—1		1
Diketones		1—3		1—3

[a] In °C to the nearest degree. [b] $\Delta T_2 - \Delta T_1$.

when 2-hydroxybutanedioic acid (malic acid) is used as a reagent. Malic acid resembles lactic acid in being a secondary alcohol and the similarities in end-point sharpness when these reagents are used in the titration of quinoline is perhaps to be expected. However, malic acid gives rise to a sharper end-point in the titration of caffeine. This difference, and the slower rise in temperature after the end-point when malic acid is used, can be attributed to the much lower solubility of the acid in acetic anhydride. The acid is not completely dissolved when the end-point is indicated but goes into solution on addition of a further 0.5 ml of titrant. Titration curves obtained with tartaric acid as the hydroxy reagent are similar to those for malic acid, but show the former reagent to be less soluble in the sample solution (Figure 3, curves e and l).

The esters of lactic and 2-hydroxy-2-methylpropanoic acids are very similar to the parent acids with respect to the reactivity of their hydroxy groups towards the acetylating agent (Figure 3, curves b, c, f, and g, and i, j, m, and n).

Arylalkanols and Hydroxyarylacetic Acids.—The effect of aromatic substituents on the reactivities of hydroxy groups in alcohols and hydroxyacetic acids can be deduced from the shapes of the titration curves shown in Figure 4. Phenyl- and diphenyl-methanol are seen to undergo a significant degree of acetylation before the titrant-catalyst appears in excess, in both the titrations of quinoline and caffeine. In contrast, triphenylmethanol does not appear to be acetylated to any real extent under the conditions obtaining. When it is used as a reagent in the titration of quinoline the end-point is marked by a small rise in temperature and the appearance

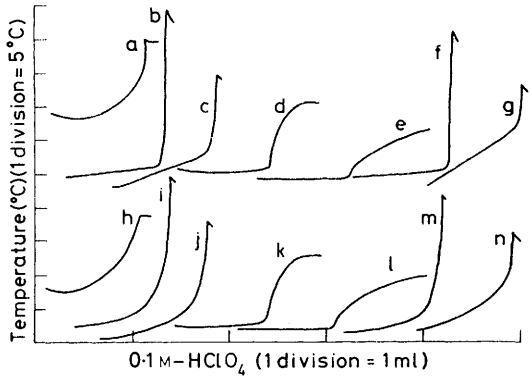

FIGURE 3 Thermometric titrations with hydroxyalkanoic acids and esters as indicator reagents. Hydroxy reagents: a, hydroxyacetic acid; b, 2-hydroxypropanoic acid; c, 2-hydroxy-2-methylpropanoic acid; d, DL-2-hydroxybutane-1,4-dioic acid; e, DL-2,3-dihydroxybutane-1,4-dioic acid; f, ethyl 2-hydroxypropanoate; g, methyl 2-hydroxy-2-methylpropanoate. h—n, as a—g, respectively. Conditions: as Figure 2; quinoline titrations a—g, caffeine titrations h—n

of a yellow colour, but in the titration of caffeine the colour appears gradually. The use of triphenylmethanol as an end-point indicator in titrations in which perchloric acid is the titrant has already been noted; and the colour developed at the end point has been identified as that of the triphenylmethyl carbonium ion.[6]

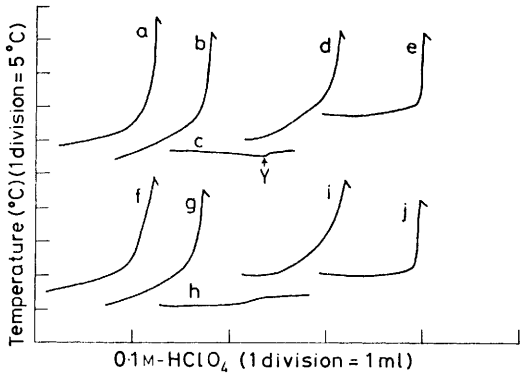

FIGURE 4 Thermometric titrations with arylalkanols and hydroxyarylacetic acids as indicator reagents. Hydroxy reagents: a, phenylmethanol; b, diphenylmethanol; c, triphenylmethanol; d, 2-hydroxy-2-phenylacetic acid; e, 2,2-diphenyl-2-hydroxyacetic acid. f—j, as a—e, respectively. Conditions: as Figure 2; quinoline titrations a—e, caffeine titrations f—j. Y indicates colour change from colourless to yellow

The titration curves obtained for quinoline by using the phenyl- and diphenyl-hydroxyacetic acid reagents (Figures 4d and e) differ significantly from those obtained with the corresponding methyl- and dimethyl-hydroxyacetic acids (Figures 3b and c). Thus, while Figure 3b has a sharp inflection to mark the end-point and a small temperature rise before the inflection, Figure 4d has a rounded end-point 'inflection' following a marked temperature rise. An opposite effect results when two methyl groups in the reagent are replaced by two phenyl groups; Figures 3c and 4e reveal that the end-point inflection is sharpened and the temperature rise before the end-point is reduced. Similar effects are seen in the comparison of the titration curves for caffeine. The marked difference in the influence of the methyl and phenyl substituents on the reactivity of the hydroxy group can probably be explained in terms of combinations of inductive, mesomeric, and steric factors.

Phenols, Naphthols, and Hydroxybiphenyls.—It can be see from Figures 5 and 6 that many of the phenols evaluated as thermometric indicators give rise to quite sharp end-point inflections. The most effective, in terms of end-point sharpness, are the phenols with t-butyl or s-butyl substituents in one of the *ortho*-positions (Figure 5, curves b, e, f, j, m, and n), the 1- and 2-naphthols (Figure 6, curves a, b, i, and j), 4-hydroxybiphenyl (Figure 6, curves c and k), and 2,2′-dihydroxybiphenyl (Figure 6, curves h and p).

The steric effects of the t-butyl and s-butyl groups substituted in the *ortho*-position might be expected to reduce the extent of acetylation before the end-point, and this would explain the improvement in the sharpness of the end-point inflection over that achieved with phenol itself. Steric effects are unlikely to influence the reactivities of the hydroxy groups in the naphthols, and the lower reactivities of the latter compared with that of

[6] S. H. Harper, in 'Rodd's Chemistry of Carbon Compounds,' ed. S. Coffey, Elsevier, Amsterdam, Oxford, and New York, 1974, 2nd. edn., vol. III, part F, p. 124.

phenol must be attributed to other factors. The relatively lower reactivity of the 4-hydroxybiphenyl will, presumably, be attributed to the same factors, which

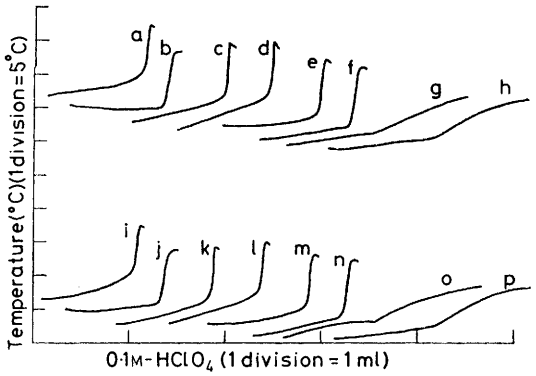

FIGURE 5 Thermometric titrations with phenol and alkyl phenols as indicator reagents. Hydroxy reagents: a, phenol; b, 2-t-butylphenol; c, 3-t-butylphenol; d, 4-t-butylphenol; e, 2-s-butylphenol; f, 2,4-di-t-butylphenol; g, 2,6-di-t-butylphenol; h, 2,6-di-t-butyl-4-methylphenol. i—p, as a—h, respectively. Conditions: as Figure 2; quinoline titrations a—h, caffeine titrations i—p

will include differences in electron density in the region of the hydroxy group. The unusually sharp end-point inflection when 2,2′-dihydroxybiphenyl is the reagent results from the low reactivity of the hydroxy groups in the absence of the acid catalyst, caused by the intramolecular hydrogen bonding, and the high reactivity when the catalyst appears in excess after the end-point.

As would be expected, phenols substituted with t-butyl groups in the *meta*- and *para*-positions, but not in the *ortho*-position, undergo considerably more acetylation in the absence of acid catalyst than do the *ortho*-substituted isomers (Figure 5, curves, c, d, l, and m). In contrast, when both positions *ortho* to the hydroxy group are occupied by t-butyl groups the steric effect is to reduce

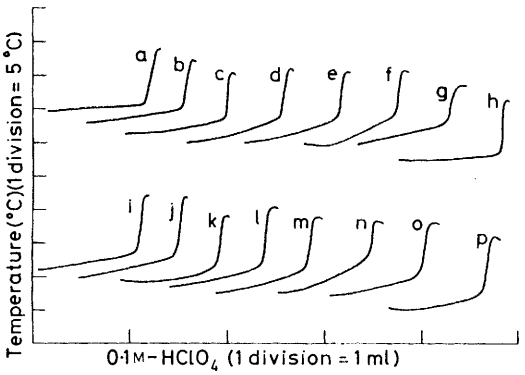

FIGURE 6 Thermometric titrations with naphthols, hydroxybiphenyls, and dihydric phenols as indicator reagents. Hydroxy reagents: a, 1-naphthol; b, 2-naphthol; c, 4-hydroxybiphenyl; d, pyrocatechol; e, resorcinol; f, quinol; g, 1,2,3-trihydroxybenzene; h, 2,2′-dihydroxybiphenyl; i—p, as a—h, respectively. Conditions: as Figure 2; quinoline titrations a—n, caffeine titrations i—p

the reactivity of the former group towards acetic anhydride both before and after the end-point inflection (Figure 5, curves g, h, o, and p) and, as a consequence of this, the inflection is less sharp than those obtained with the mono *ortho*-substituted phenols as reagents, and the values for ΔT_2 are lower.

The effect of intramolecular hydrogen bonding on the reactivity of the phenolic hydroxy group is shown dramatically in titrations in which nitrophenols are the reagents (Figure 7). With *o*-nitrophenol no end-point inflection is observed. Apparently, hydrogen bonding effectively prevents acetylation under the conditions of the titration. In contrast, a sharp inflection marks the end-point when *m*-nitrophenol is the reagent. The titration curve obtained with *p*-nitrophenol again shows a distinct inflection but the reaction rate after the end-point is significantly less than that achieved by using the *meta*-isomer. The electron-withdrawing property of the nitro group reduces the reactivity of phenolic hydroxy towards acetic anhydride and will, of course, reinforce the

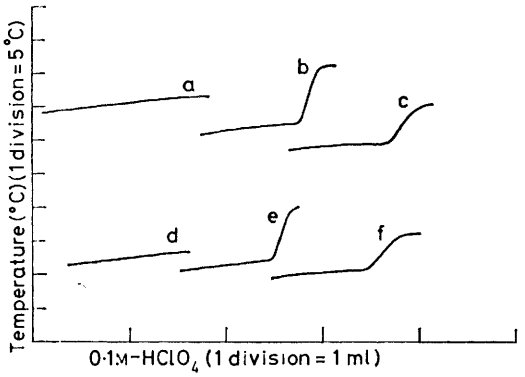

FIGURE 7 Thermometric titrations with nitrophenols as indicator reagents. Hydroxy reagents: a, 2-nitrophenol; b, 3-nitrophenol; c, 4-nitrophenol; d—f, as a—c, respectively. Conditions: as Figure 2: quinoline titrations a—c, caffeine titrations d—f

hydrogen bonding effect in the *ortho*-isomer in preventing acetylation.

The reactivity of the hydroxy groups of the three dihydroxybenzenes depends on the relative positions of the groups, as can be seen in Figure 6 (curves d—f and l—n). All three compounds give rise to titration curves that show a significant degree of acetylation under the ' non-catalytic ' conditions, but quinol is acetylated more readily than are pyrocatechol and resorcinol. The lower reactivity of the *meta*-isomer can be explained in terms of the weaker directing properties of *meta*-substituents, and that of pyrocatechol can be explained by the intramolecular hydrogen bonding opposing the effect of the *ortho*-directing properties of adjacent hydroxy groups on the reactivities of the groups. The titration curves obtained by using 1,2,3-trihydroxybenzene as the reagent (Figure 6, curves g and o) are similar to those obtained with pyrocatechol and resorcinol, as might be expected.

Hydroxybenzoic and Naphthoic Acids and Esters.—Carboxy groups do not have so great an adverse effect as nitro groups on the reactivity of phenolic hydroxy towards acetic anhydride. Titration curves obtained

with hydroxyarylcarboxylic acids as indicator reagents are shown in Figure 8. The intramolecular hydrogen bonding in 2-hydroxybenzoic acid combines with the electron-withdrawing effect of the carboxy group to reduce the rate of acetylation of the hydroxy group during the titration, both before and after the end-point inflection (Figure 8, curves a and g). The end-point

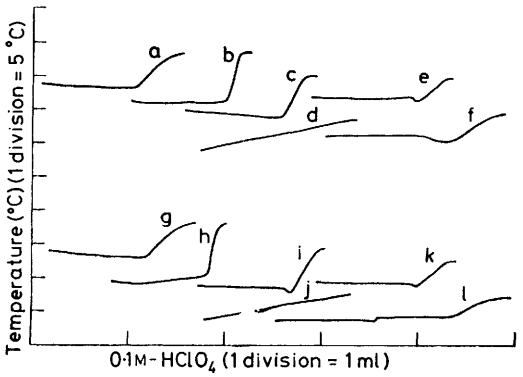

FIGURE 8 Thermometric titrations with hydroxybenzoic and naphthoic acids as indicator reagents. Hydroxy reagents: a, 2-hydroxybenzoic acid; b, 3-hydroxybenzoic acid; c, 4-hydroxybenzoic acid; d, 2,6-dihydroxybenzoic acid; e, 3-hydroxy-2-naphthoic acid; f, 2-hydroxy-1-naphthoic acid. g—l, as a—f, respectively. Conditions: as Figure 2; quinoline titrations a—f, caffeine titrations g—l

inflections observed with *m*- and *p*-hydroxybenzoic acids are markedly sharper, that with the *meta*-isomer being the sharpest. Presumably, the electron-withdrawing power of the *meta*-substituted carboxy group is less effective than that of the *para*-substituted one. The difference between the titration curves obtained with the *ortho*- and *para*-isomers is clearly due to intramolecular hydrogen bonding in the former.

There is no evidence of acetylation in titrations in which 2,6-dihydroxybenzoic acid is used as the hydroxy reagent. This lack of reactivity can clearly be attributed to powerful intramolecular hydrogen bonding in the symmetrical 2,6-hydroxybenzoate ion, the stability of which is indicated by the lower pK_a value of the acid (2.30).

o-Hydroxynaphthoic acids give rise to titration curves similar to those obtained with 2-hydroxybenzoic acid as the reagent (Figure 8, curves e, f, k, and l), although the low solubility of 2-hydroxy-1-naphthoic acid in acetic anhydride delays the onset of the rise in temperature after the expected end-point, and thus a simple comparison is not possible.

The titration curves obtained by using methyl and n-butyl 2-hydroxybenzoates as reagents closely resemble the corresponding curves obtained with the free acid reagent (Figure 8, curves a and g). The curves obtained with 2-hydroxy-2-phenylacetic acid (Figure 4, curves d and i) and its methyl ester are also similar. It has been noted that esters of hydroxyalkanoic acids give rise to titration curves similar to those obtained by using the parent acids as reagents (Figure 3), and it is reasonable to assume that, under the reaction conditions, the ester and carboxy groups influence the reactivity of hydroxy groups on the same molecule to about the same extent.

Hydroxyaryl Aldehydes and Ketones.—A comparison of Figures 8 and 9 reveals that hydroxybenzaldehydes are significantly more reactive, before and after the end-point inflection, than the corresponding hydroxybenzoic acids. However, the temperature rise before the end-point inflection is lower with the 2-hydroxybenzaldehyde than with the 3- and 4-isomers as reagents, and it may be assumed that intramolecular hydrogen bonding of the hydroxy and aldehyde groups is influencing the reactivity of the former group. Similarly, 2-hydroxy-1-naphthaldehyde reagent is more reactive than the corresponding hydroxynaphthoic acids towards acetic anhydride under both 'uncatalysed' and catalysed conditions. The end-point is sharper with the hydroxynaphthaldehyde than with the 2-hydroxybenzaldehyde reagent, as may be expected, since the naphthoic acids give rise to sharper end-points than does the phenol reagent.

While the titration curves obtained with 2-hydroxyacetophenone as the reagent are sharper than those achieved with 2-hydroxybenzoic acid, the curves for the 4-hydroxyacetophenone reagent are much less sharp than those for the 4-hydroxybenzoic acid. A comparison of Figure 8, curves a, c, g, and i, and Figure 9, curves e, f, k, and l, suggests that the acetyl substituent is not as effective as the carboxy group in reducing the reactivity of phenolic hydroxy towards the acylating agent.

The difference between the shapes of the curves for 2- and 4-hydroxyacetophenone must be attributed to the

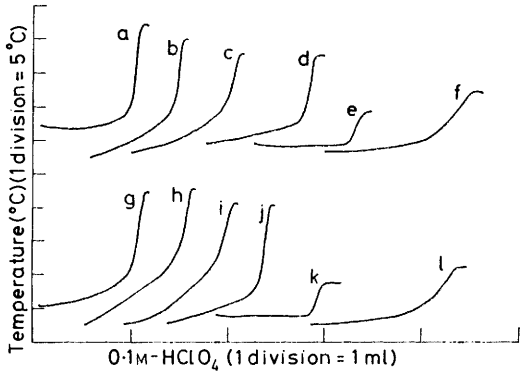

FIGURE 9 Thermometric titrations with hydroxyaryl aldehydes and ketones as indicator reagents. Hydroxy reagents: a, 2-hydroxybenzaldehyde; b, 3-hydroxybenzaldehyde; c, 4-hydroxybenzaldehyde; d, 2-hydroxy-1-naphthaldehyde; e, 2-hydroxyacetophenone; f, 4-hydroxyacetophenone. g—l, as a—f, respectively. Conditions: as Figure 2; quinoline titrations a—f, caffeine titrations g—l

strong intramolecular hydrogen bonding in the former compound.

Alkyl and Aralkyl Ketones.—Alkyl and aralkyl ketones and especially diketones can exist in enolic forms which might be expected to undergo acetylation under the conditions obtaining in catalytic thermometric titrations of the type being studied. Figure 10 shows that there is no evidence for more than a small amount of acetylation

when representative ketones and diketones are used as hydroxy reagents in titrations of quinoline and caffeine. The titration curves show small inflections corresponding to the end-point, and these are less distinct in the titrations of caffeine. The inflections obtained with diketones as reagents are no more distinct than those obtained with monoketones. The least distinct inflection was obtained with 1,3-diphenylpropan-2-one (curve f), and ethyl acetoacetate gave an inflection similar to those obtained with simple ketones.

Blank Titrations.—During the titrations of quinoline and caffeine a significant volume of acetic acid, the titrant solvent, is added to the sample solution. It is known [4] that acetic acid influences adversely the sharpness of the end-point inflection in these non-aqueous titrations, and in order to assess the importance of this effect in the present investigation some titrations of indicator solutions alone have been carried out (Figure 11). In most of the titrations the rise in temperature occurs on addition of the first drops of titrant, when the content of acetic acid will be minimal. The shapes of the titration curves follow a similar pattern to those obtained in the titrations of the bases. Thus, a greater temperature rise occurs with butan-1-ol than with 4-hydroxy-4-methylpentan-2-one as the hydroxy reagent, triphenylmethanol and 2,6-dihydroxybenzoic acid do not give end-point inflections, and the delay before the temperature rise with 2-hydroxy-1-naphthoic acid as a reagent still persists. The titration curves obtained with 2-, 3-, and 4-nitrophenols show a similar trend to those in Figure 7, but the temperature rise with 2-nitrophenol is greater although with no inflection. In the titrations involving phenol and 2,6-di-t-butyl-4-methylphenol the rise in temperature occurs more rapidly than in the corresponding titrations of bases shown in Figure

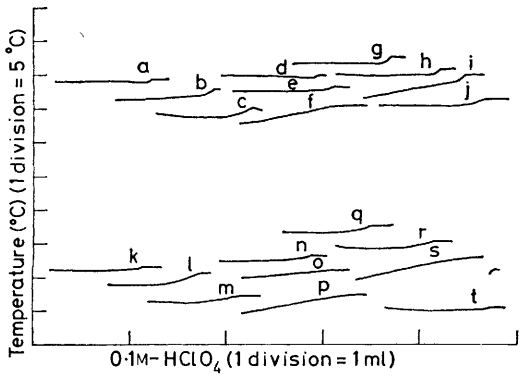

FIGURE 10 Thermometric titrations with ketones as indicator reagents. Reagents: a, butan-2-one; b, 3,3-dimethylbutan-2-one; c, acetophenone; d, 1-phenylpropan-2-one; e, valerophenone; f, 1,3-diphenylpropan-2-one; g, 4-methylpent-3-en-2-one; h, pentane-2,4-dione; i, 1-phenylbutane-1,3-dione; j, ethyl 3-oxobutanoate; k—t, as a—j, respectively. Conditions: as Figure 2; quinoline titrations a—j, caffeine titrations k—t

5, curves a and i, and h, and p, respectively. The rise in temperature with 2-hydroxybenzoic acid and 3-hydroxy-2-naphthoic acid is similar to that observed when the same reagents are used in the base titrations. A rather greater temperature rise occurs in the titration of the ketone, 3,3-dimethylbutan-2-one than in the

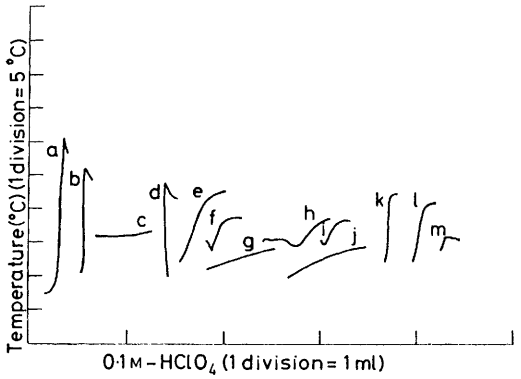

FIGURE 11 Thermometric titrations of indicator solutions only. Hydroxy reagents: a, butan-1-ol; b, 4-hydroxy-4-methylpentan-2-one; c, triphenylmethanol; d, phenol; e, 2,6-di-t-butyl-4-methylphenol; f, 2-hydroxybenzoic acid; g, 2,6-dihydroxybenzoic acid; h, 2-hydroxy-1-naphthoic acid; i, 3-hydroxy-2-naphthoic acid; j, 2-nitrophenol; k, 3-nitrophenol; l, 4-nitrophenol; m, 3,3-dimethylbutan-2-one. Conditions: hydroxy reagent (4 mequiv.) + acetic anhydride (5 ml) are titrated with 0.1M-$HClO_4$ reagent

corresponding titration shown in Figure 10 (curve b), but the rise is still small compared with that obtained in the titration with butan-1-ol as the reagent.

General Considerations.—The effect of different *non*-hydroxylic solvents on end-point sharpness in this catalytic thermometric titration system has been investigated [4] and it has been shown that the sharpness can be improved by including nitromethane or dichloromethane in the sample solution. Clearly, variation of the type and amount of solvent in the titrant and titrand solutions could be used to obtain further insight into the reactivity of the hydroxy reagent.

According to Satchell,[7] direct acetylation in the presence of acid catalysts, with acylating agents such as acetic anhydride, is an electrophilic process, and the substrate atom acylated acts as a nucleophile. The evidence obtained with the different hydroxy compounds examined in the present study is in accord with this view, since electron-donating groups are seen to increase the reactivity of the oxygen atom of the hydroxy group, and electron-withdrawing groups to decrease it. Satchell points out that the acid catalyst operates by assisting the decomposition of the acylating compound RCOX to yield the electrophilic reactive ionic species RCO^+. He suggests that an alternative mechanism, involving a non-ionic displacement reaction (1) where SH is the

$$RCOX + SH \longrightarrow RCOS + HX \qquad (1)$$

substrate, is less likely to proceed by way of a carbonyl addition intermediate when the reaction is acid catalysed than when it is uncatalysed. Since only mild catalysis occurs before the end-point inflection in the titrations investigated in the present work, it is possible that car-

[7] D. P. N. Satchell, *Chem. and Ind.*, 1974, 683; *Quart. Rev.*, 1963, **17**, 160.

bonyl addition is taking place in the period of the titration corresponding to section α of Figure 1c. A reaction requiring carbonyl addition as the first step would be more likely to be inhibited by hydrogen bonding or steric hindrance of one of the reactive centres than would a direct reaction involving the ionic acylating agent. Hydrogen bonding and steric hindrance do appear to have had a significant effect in many of the titrations and in particular on the acetylation occurring before the end-point inflection.

It can be seen in the Table that the ΔT_2 values differ widely and are dependent on the nature of the organic hydroxy compound used as a reagent. Small differences in ΔT_2 values may be accounted for by differences in specific heats of hydroxy compounds and their acetylation products but, because the content of hydroxy compound in the sample solution rarely exceeds 15% w/w, it will be necessary to find other causes for major differences in the ΔT_2 values. The molar ratio of acetic anhydride to hydroxy compound is 13.26 : 1, and it can be assumed, therefore, that when equilibrium is attained acetylation will have proceeded virtually to completion. Differences in ΔT_2 values must be accounted for mainly by differences in the kinetics of the acetylation reactions and the heats of reaction. The cooling effect of added titrant solvent is more or less constant, consequently when reaction rates are slow the ' downturn ' at the end of the titration curves will occur sooner than when the rates are fast.

EXPERIMENTAL

Reagents.—Acetic anhydride was of AnalaR grade. Hydroxy compounds were of laboratory-reagent grade; solids were dried in a vacuum desiccator and liquids were dried over molecular sieve 4A before use. Perchloric acid, 0.1M in acetic acid, was prepared by adding to a solution of AnalaR grade $HClO_4$ (aqueous, 71.0—73.0%) in glacial acetic acid, 10% more acetic anhydride than was required theoretically to convert the water content into acetic acid.

Apparatus.—The automatic titration apparatus, comprising a motor-driven syringe burette, an unsilvered Dewar beaker (14 ml) with a magnetic stirrer, and a thermistor connected through a bridge circuit to a potentiometric recorder, has been described elsewhere.[8]

Titration Procedure.—Perchloric acid reagent is added at a rate of 0.2 ml min^{-1} to a stirred solution of quinoline or caffeine (0.1 mequiv.) and hydroxy reagent (4 mequiv.) in acetic anhydride (5 ml), and the temperature is recorded during the course of the titration. Colour changes and the extent of the dissolution of solid hydroxy reagents during the course of the titration are noted.

The University of London Central Research Fund Committee is thanked for a grant to purchase apparatus.

[8/077 *Received*, 17*th January*, 1978]

[8] E. J. Greenhow and L. E. Spencer, *Analyst*, 1973, **98**, 98.