

## Chemistry of Quinones. Part 6.<sup>1</sup> The Selective Hydrolysis of $\alpha$ -Acetoxy-anthraquinones and Related Compounds by Trifluoroacetic Acid Containing Small Amounts of Water

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Acetoxy- or benzoyloxy-substituents adjacent to the carbonyl groups of anthraquinone, 1,4-naphthoquinone, naphthacene-5,12-quinone, benzophenone, and methyl benzoate are selectively converted into hydroxy-groups by treatment with trifluoroacetic acid containing small amounts of water. In the absence of water a reversible acidolysis occurs. Water reacts with the acylating agent, thus preventing the reverse reaction. Evidence is presented that the hydrolyses are of the  $A_{AC1}$  type.

RECENTLY we treated an anthraquinone derivative with hot trifluoroacetic acid (TFA) and found that after a few minutes the  $\alpha$ -acetoxy-groups originally present had been quantitatively converted into hydroxy-groups. We have investigated the generality and mechanism of this reaction and now report the results.

### RESULTS AND DISCUSSION

A range of  $\alpha$ -acetoxyanthraquinones and related compounds were treated with TFA. Although many

substituents adjacent to the carbonyl groups of anthraquinone, 1,4-naphthoquinone, naphthacene-5,12-quinone, benzophenone, and methyl benzoate are readily converted into hydroxy-substituents using the above reagent. In favourable cases a reaction time of 5 min is adequate. Other ester groups react much less readily or not at all, and selective reactions can be carried out without difficulty. The two amide substrates investigated reacted extremely slowly even though in one case the acetamido-group was adjacent to a carbonyl group.

TABLE 1  
Action of TFA on various esters and amides

Substrate	Reaction conditions <sup>b</sup>		Product	Yield <sup>c</sup> (%)	
	Water <sup>a</sup> in TFA (%)	Temperature (°C)			
<i>(a) 9,10-Anthraquinones</i>					
1-Acetoxy	5	65	0.5	1-hydroxy	96
2-Acetoxy	2.5	65	2	2-hydroxy	43 <sup>d</sup>
1,2-Diacetoxy	5	72	0.5	1-hydroxy-2-acetoxy	99
		65	4	1,2-dihydroxy	89 <sup>d</sup>
1,2-Dibenzoyloxy	C	72	5 min	1-hydroxy-2-benzoyloxy	94
1,4-Diacetoxy	C	72	5 min	1,4-dihydroxy	96
1,4-Dibenzoyloxy	C	72	5 min	1,4-dihydroxy	99
1,5-Diacetoxy	C	72	2	1,5-dihydroxy	96
1,8-Diacetoxy	5	65	1	1,8-dihydroxy	100
1,4,5-Triacetoxy	C	72	24	1,4,5-trihydroxy	98
1,4,5,8-Tetra-acetoxy	5	65	1	1,4,5,8-tetrahydroxy	100
1,6,8-Triacetoxy-3-methyl	C	72	5 min	1,8-dihydroxy-6-acetoxy-3-methyl	93
		72	20	1,6,8-trihydroxy-3-methyl	42
1-Acetamido	5	65	18	1-amino	18 <sup>d</sup>
2-Acetamido	5	65	18	2-amino	21 <sup>d</sup>
<i>(b) Other substrates</i>					
5-Acetoxy-1,4-naphthoquinone	C	72	0.75	5-hydroxynaphthoquinone	95
4,11-Diacetoxynaphthacene-5,12-quinone	C	72	5 min	4,11-dihydroxynaphthacene-5,12-quinone	97
2,4-Diacetoxybenzophenone	5	65	5 min	2-hydroxy-4-acetoxybenzophenone	98 <sup>d</sup>
		65	2	2,4-dihydroxybenzophenone	54 <sup>d</sup>
Acetylsalicylic acid	5	65	0.5	salicylic acid	95
Methyl acetylsalicylate	5	65	1	methyl salicylate	90
1,4-Diacetoxyanthracene	5	65	1	1,4-dihydroxyanthracene	46

<sup>a</sup> C = Commercial TFA with a water content of *ca.* 0.5%. <sup>b</sup> The reactions were monitored spectroscopically (i.r. or <sup>1</sup>H n.m.r.) and were generally worked up either when reaction was complete or after the reaction had been left overnight. <sup>c</sup> Unless indicated otherwise the yield is that of isolated material with m.p. in good agreement with literature values and satisfactory spectral data (i.r. and/or <sup>1</sup>H n.m.r.). <sup>d</sup> <sup>1</sup>H N.m.r. analysis.

substrates reacted smoothly and completely with commercial TFA, others, particularly polyacetoxy-compounds, reacted only very slowly after an initial fast reaction. In these cases addition of a small amount of water gave rapid and complete reaction. It is clear from the results (Table 1) that acetoxy- and benzoyloxy-

In order to gain insight into the reaction mechanism, the reaction of 1-acetoxyanthraquinone was studied more closely. The reactions were carried out with 0.2M solutions of substrate in TFA and were followed by observing the various acetyl signals in the <sup>1</sup>H n.m.r. spectrum. Treatment of 1-acetoxyanthraquinone for

2 h at 65 °C with TFA dried by the addition of 10% TFA anhydride gave 1-hydroxyanthraquinone and TFA-acetic acid mixed anhydride in 52% yield. Prolonged reaction times did not raise the yield. Conversely, addition of TFA anhydride to a completely hydrolysed reaction mixture regenerated 1-acetoxyanthraquinone in 40% yield. It is clear that in the absence of water the reversible reaction (E1) occurs and that water allows complete reaction by removing the acylating agent. With dilute solutions commercial TFA contains sufficient water (*ca.* 0.5%) for complete reaction, but for more concentrated solutions or with polyacetoxy-compounds more water is usually needed.

TABLE 2

Reactions of 1-acetoxyanthraquinone with water in TFA <sup>a</sup>

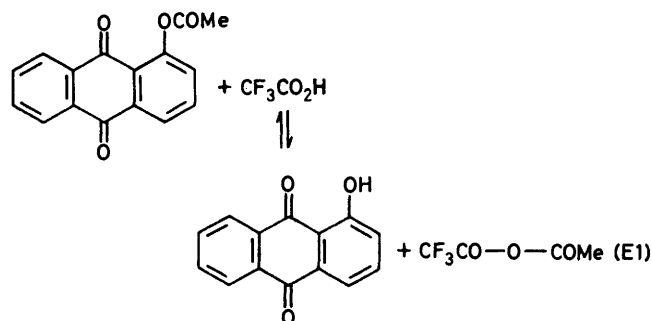
Added water (%)	Temperature (°C)	Observed first-order rate constant/10 <sup>3</sup> s <sup>-1</sup>
0.5	45	9.1
1.0	45	8.6
1.5	45	7.2
2.5	45	7.0
3.5	45	6.1
4.5	45	5.7
2.5	40	4.5
2.5	50	9.7
2.5	55	14.8
2.5	60	20.5
2.5	65	28.0
0.9 <sup>b</sup>	45	3.2
2.5 <sup>c</sup>	45	2.4
2.5 <sup>c</sup>	55	4.7
2.5 <sup>c</sup>	65	11.0

<sup>a</sup> Unless indicated otherwise, 0.2M solutions of substrate in commercial TFA were used with water added as indicated.

<sup>b</sup> Potassium trifluoroacetate (2.5 mol) added. <sup>c</sup> Reagent was 2.5% D<sub>2</sub>O in CF<sub>3</sub>CO<sub>2</sub>D.

A few substrates were selected for kinetic study. In every case the reactions were found to be cleanly first-order in substrate. The results are summarised in Tables 2 and 3. In the reaction of 1-acetoxyanthraquinone increasing the amount of added water from 0.5% to 4.5% slightly decreased the reaction rate, indicating that water is not directly involved in the rate-determining step. An Arrhenius plot for the reaction of the same

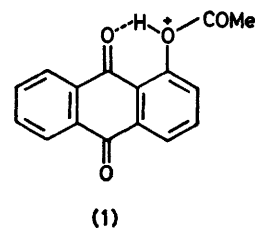
is not involved as a nucleophile in, or prior to, the rate-determining step. Changing the reagent to D<sub>2</sub>O (2.5%) in CF<sub>3</sub>CO<sub>2</sub>D slowed the reaction down by a factor of 0.4 at 65 °C (activation energy 69 kJ mol<sup>-1</sup>). *N*-Methylaniline can be used in place of water to ensure complete



reaction but here the reaction rate is much slower (*ca.* 1.5 h for complete reaction at 65 °C).

The results obtained with the other substrates (Table 3) quantify the observations made in the preparative experiments: in the anthraquinone series  $\alpha$ -acetoxy-groups react over 100 times faster than  $\beta$ -acetoxy-groups, and with 2,4-diacetoxybenzophenone the difference is 42-fold.

When TFA transfers a proton to another species tri-



fluoroacetate ion is formed. There must, therefore, be a significant concentration of this ion present in the reaction mixture, and it would be expected to be a stronger nucleophile than TFA itself. However, the kinetic study shows that neither trifluoroacetate nor

TABLE 3

Rate of reaction of various substrates with water-TFA <sup>a</sup>

Substrate	Observed first-order rate constants/s <sup>-1</sup>		Ratio of rate constants (adjacent/non-adjacent)
	Acyl group adjacent to carbonyl	Acyl group not adjacent to carbonyl	
1-Acetoxyanthraquinone	2.8 × 10 <sup>-2</sup>	7.4 × 10 <sup>-5</sup>	378
2-Acetoxyanthraquinone			
1,2-Diacetoxyanthraquinone	1.2 × 10 <sup>-2</sup>	1.0 × 10 <sup>-4</sup>	120
2,4-Diacetoxybenzophenone	2.2 × 10 <sup>-3</sup>	5.2 × 10 <sup>-5</sup>	42
1,4-Diacetoxyanthracene <sup>b</sup>		1.5 × 10 <sup>-4</sup>	

<sup>a</sup> Unless indicated otherwise, 0.2M solutions of substrate in TFA plus 2.5% water at 65 °C. <sup>b</sup> 0.3M Solution of substrate in TFA plus 5% water at 65 °C.

substrate in the temperature range 40–65 °C gave an activation energy of 64 kJ mol<sup>-1</sup>. The addition of a 2.5-fold excess of trifluoroacetate ion slowed down the reaction by a factor of *ca.* 0.4. Thus, this species also

water is involved as a nucleophile prior to or during the rate determining step. We suggest, therefore, that *the rate-determining step in the process is breakdown of the protonated substrate to hydroxy-compound and acylium*

*ion*.<sup>2</sup> The latter can react with TFA or trifluoroacetate to give mixed anhydride or with water to give acetic acid. This mechanism would also explain why acyl groups adjacent to carbonyl groups react more rapidly. In these cases the appropriate protonated form of the substrate, for example (1), is stabilized by H-bonding. The slight decreases in rate with the increase in water concentration and with added trifluoroacetate, and the considerable decrease in rate with addition of *N*-methyl-aniline can reasonably be ascribed to buffering and/or medium effects. The lower rate with the deuterio-system probably reflects the decreased acidity of the acid.

#### EXPERIMENTAL

Trifluoroacetic acid was purchased from Aldrich.

*Reactions summarised in Table 1.*—These were carried out under the conditions indicated in the Table using *ca.* 500 mg of substrate in 5 ml of trifluoroacetic acid. At the end of the reaction period the mixture was cooled, then added to an excess of water or, in the reactions of benzoates, to dilute

aqueous sodium carbonate. The precipitate was collected, washed, dried and, if necessary, recrystallised. The products had m.p.s in good agreement with literature values and satisfactory spectral data (i.r. and/or <sup>1</sup>H n.m.r.).

*Kinetic Studies.*—The reactions were carried out in n.m.r. tubes and the spectra were measured on a Varian A60 machine equipped with a variable-temperature probe. The reactions were followed by observing the various acetyl signals.

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#### REFERENCES

<sup>1</sup> Part 5, D. G. Davies, and P. Hodge, *J.C.S. Perkin I*, 1974, 2403.

<sup>2</sup> For other examples of *A*<sub>AC1</sub> ester hydrolysis see E. S. Gould, 'Mechanism and Structure in Organic Chemistry,' Holt, Reinhart, and Winston, London, 1959, p. 325; and R. W. Alder, R. Baker, and J. M. Brown, 'Mechanism in Organic Chemistry,' Wiley-Interscience, London, 1971, p. 333