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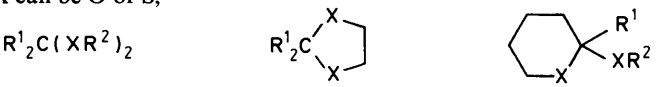
Mechanisms of Hydrolysis of Thioacetals

Derek P. N. Satchell and Rosemary S. Satchell
DEPARTMENT OF CHEMISTRY, KING'S COLLEGE LONDON, STRAND, LONDON WC2R 2LS

1 Introduction

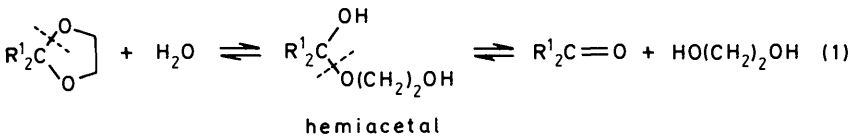
A. Systems.—This Review classifies acetals as either O,O-, O,S-, or S,S-compounds, and uses the name acetal to subsume ketals. Acetals take three general forms: open-chain [*e.g.* (1)], cyclic [*e.g.* (2)], and open-chain/cyclic [*e.g.* (3)]. In (1)—(3) X can be O or S,



(1) (2) (3)

R^1 can be H, alkyl or aryl, and R^2 can by alkyl or aryl. We exclude the structurally-related orthoesters [$R^1C(OR^2)_3$], ketene acetals [$R^1_2C{=}C(OR^2)_2$], and their thio-derivatives, and deal only cursorily with thio-sugars.

On hydrolysis an acetal is converted into an aldehyde or ketone, the bonds between the pro-carbonyl carbon atom and the O (or S) atoms being broken successively (*e.g.*, equation 1).



hemiacetal (1)

In the presence of a large excess of water the hydrolytic equilibrium usually lies well to the right. In homogeneous solution the hydrolyses of O,O-acetals are not catalysed by bases, but are catalysed by Brønsted acids, and sometimes by metal ions. Some O,O-acetals have significant spontaneous rates of hydrolysis at ordinary temperatures. A voluminous literature concerns the kinetics and mechanisms of hydrolysis of O,O-acetals.[1–4]

By comparison S,S-acetals have been little studied kinetically. They appear to hydrolyse relatively very slowly (especially the cyclic variety) and are much less affected by the catalysts useful with the O,O-compounds. As a result of their

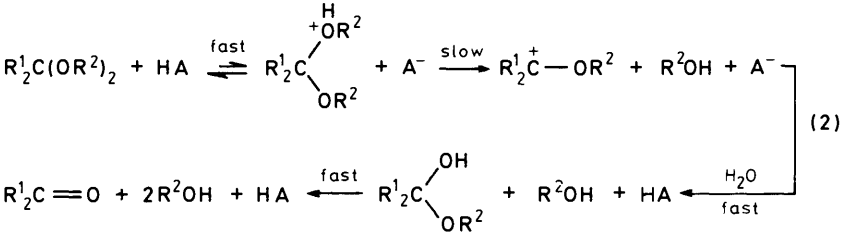
[1] E. H. Cordes and H. G. Bull, *Chem. Rev.*, 1974, **74**, 581.
[2] R. G. Bergstrom in 'The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues', ed. S. Patai, John Wiley, New York, 1980, Part 2, Ch. 20.
[3] T. H. Fife, *Acc. Chem. Res.*, 1972, **5**, 264.
[4] A. V. Willi in 'Comprehensive Chemical Kinetics', ed. C. H. Bamford and C. F. H. Tipper, Elsevier, Oxford, 1977, Vol. 8, Ch. 1.

resistance to hard acid and base catalysis, S,S-acetals have been used as protecting groups in a variety of organic syntheses and special reagents have been developed to hydrolyse them readily when required. These (powerful) reagents exploit soft–soft acid–base behaviour, but quantitative mechanistic studies involving them are comparatively recent. We shall discuss them. O,S-acetals occupy an intermediate position; their hydrolyses sometimes have significant spontaneous rates, and are catalysed by both Brønsted acids (weakly) and soft acids (strongly). Kinetic and mechanistic studies are again mostly recent, and will be compared with findings for the O,O- and S,S-compounds.

Typical relative reactivities of different types of acetal towards hydrogen ion catalysis are in Table 1.

B. O,O-Acetal Hydrolysis.—The past 15 to 20 years has seen a resurgence of interest in O,O-acetal hydrolysis, and something of a revolution in our understanding of it. We shall briefly summarize important aspects of the present position because it is the background against which the behaviour of the O,S- and S,S-compounds must be seen.

In the 1950s and 60s the Brønsted acid-catalysed hydrolysis was (as now) the main focus of interest, and seemed to be understood rather completely:[5] an *A*1 mechanism (equation 2) appeared to be almost universal and, except for a few special compounds whose (usually strained) structure greatly facilitated carboca-



(2)

tion formation, the hydrolysis of the hemiacetal intermediate was considered to be fast in comparison to its rate of formation. Among other facts,[1,4] the *A*1 mechanism was compatible with the common observation of (i) specific acid catalysis, (ii) solvent isotope effects $k_{D_2O}/k_{H_2O} > 1$, (iii) $\Delta S^{\ddagger}$ values near zero or positive, and (iv) powerful acceleration of the reaction by increasing the electron-releasing power of all the substituents R^1 and R^2. Since then there have been two principal discoveries: (a) the observation of numerous cases of general acid catalysis,[1–3] a kinetic form incompatible with the *A*1 mechanism, and (b) the finding that significantly slow hydrolysis of the hemiacetal is more widespread than previously realized.[2,6] Another new area of interest is the application of the ideas of stereoelectronic control, developed first for orthoesters,[7] to acetals.[8] This

[5] E. H. Cordes, *Prog. Phys. Org. Chem.*, 1967, **4**, 1.
[6] J. L. Jensen and P. A. Lenz, *J. Am. Chem. Soc.*, 1978, **100**, 1291.
[7] P. Deslongchamps, *Tetrahedron*, 1975, **31**, 2463.
[8] A. J. Kirby, *Acc. Chem. Res.*, 1984, **17**, 305.

Table 1 *Approximate rate constants for the hydrogen ion-catalysed hydrolysis of acetals in water*

k_{H^+} (l.mol^{-1} s^{-1} at 25—30 °C) has sometimes been estimated from values obtained under slightly different conditions.

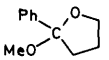
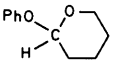
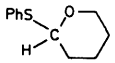
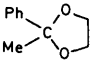
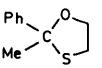
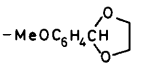
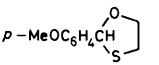
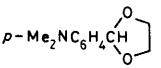
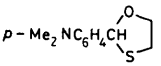
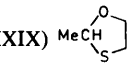
No.	*Acetal*	k_{H^+}	*Ref.*
(I)	$PhCH(OEt)_2$	160	24
(II)	PhCH(OEt)SEt	1.3	24
(III)	$PhCH(SEt)_2$	3.5×10^{-4}	24
(IV)	PhCH(OMe)OPh	41	*a*
(V)	PhCH(OMe)SPh	*ca.* 0.06	24
(VI)	$Ph(Me)C(OEt)_2$	*ca.* 6×10^3	*b*
(VII)	$CH_2(OEt)_2$	1.5×10^{-4}	*c*
(VIII)	$MeCH(OEt)_2$	1.6	*d*
(IX)	$Ph(Me)C(OMe)_2$	1.6×10^3	17
(X)		1.4×10^4	19
(XI)		0.16	*e*
(XII)		2.7×10^{-4}	34
(XIII)		*ca.* 5×10^{-2}	*b*
(XIV)		*ca.* 5	*f*
(XV)		*ca.* 1.2	*b*
(XVI)		2.4×10^{-4}	39
(XVII)		5×10^{-3}	45
(XVIII)		8×10^{-3}	32
(XIX)	p-$MeOC_6H_4CH(OEt)_2$	5×10^3	29
(XX)		130	29
(XXI)		0.1	29
(XXII)	p-$Me_2NC_6H_4CH(OPr)_2$	7×10^4	13
(XXIII)		3×10^3	13
(XXIV)		*ca.* 3	13
(XXV)		2.6×10^{-6}	*g*
(XXVI)		13×10^{-3}	*g*
(XXVII)		13×10^{-2}	*g*
(XXVIII)		*ca.* 2×10^{-7}	*h*

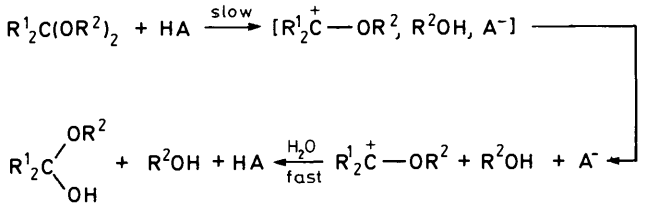
Table 1—*continued*

No.	*Acetal*	k_{H^+}	*Ref*	*No*	*Acetal*	k_{H^+}	*Ref*
(XXIX)		*ca* 6×10^{-4}	*h*	(XXX)		*ca* 6×10^{3}	*h*
				(XXXI)		*ca* 3×10^{7}	*h*

[a] B Capon and K Nimmo, *J Chem Soc, Perkin Trans 2*, 1975, 1113, [b] T H Fife and L Hagopian, *J Org Chem*, 1966, **31**, 1772, [c] P Salomaa, *Ann Acad Sci Fenn Ser A2*, 1961, No 103, [d] J L Jensen, A B Martinez, and C L Shimazu, *J Org Chem*, 1983, **48**, 4175, [e] T H Fife and L K Jao, *J Am Chem Soc*, 1968, **90**, 4081, [f] T H Fife and L K Jao, *J Org Chem*, 1965, **30**, 1492, [g] P Salomaa and A Kankannpera, *Acta Chem Scand*, 1961, **15**, 871, [h] K Pihlaja, *J Am Chem Soc*, 1972, **94**, 3330

is mainly relevant to rather rigid structures where, if the C–O bond which is breaking is not anti-periplanar to a lone pair of electrons on the other acetal oxygen atom, then the hydrolysis is unusually slow. An interesting correlation has also been discovered[9] between the rate of hydrolysis and the (ground state) length of the C–O bond being broken. These discoveries have fuelled the renewed activity in the field; this has mainly focused on (i) the interpretation of the general acid catalysis as an $A\text{-}S_E2$ mechanism (equation 3), and on deductions[3,10] about the structural features that favour this slow proton transfer mechanism relative to the more common pre-equilibrium ($A1$) mechanism, (ii) discussion of the details of the step involving proton transfer,[11] (iii) speculation as to the exact mechanistic significance of the value of the Brønsted exponent α obtained from studies of the general acid catalysis,[11,12] and (iv) other alternatives to the $A1$ mechanism that may occur in special circumstances.[3,4,13,14]

The essential difference between the $A1$ and the $A\text{-}S_E2$ mechanisms is that the first two stages of the former are amalgamated in the latter. The structural



(3)

[9] A J Kirby and P G Jones, *J Am Chem Soc*, 1984, **106**, 6207, A J Kirby and P G Jones, *J Chem Soc, Chem Commun*, 1986, 444

[10] J L Jensen, A B Martinez, and C L Chimazu, *J Org Chem*, 1983, **48**, 4175, J L Jensen and W B Wuhrman, *J Org Chem*, 1983, **48**, 4686

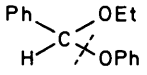
[11] G Lamarty and C Menut, *Pure Appl Chem*, 1982, **54**, 1837

[12] J L Jensen, L R Herold, P A Lenz, S Trusty, V Sergi, K Bell, and P Rogers, *J Am Chem Soc*, 1979, **101**, 4672, J L Jensen and K S Yamaguchi, *J Org Chem*, 1984, **49**, 2613

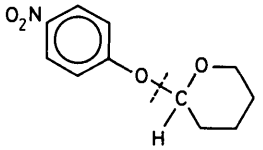
[13] T H Fife and R Natarjan, *J Am Chem Soc*, 1986, **108**, 2425, 8050

[14] A J Kresge and D P Weeks, *J Am Chem Soc*, 1984, **106**, 7140

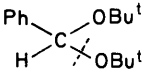
features of the acetal that favour the $A\text{-}S_E2$ mechanism have been identified[3,10,15,16] as (a) a leaving group with strong electron withdrawal or subject to steric strain, (b) a weakly basic leaving group, and (c) other groups in the acetal which stabilize the carbocation and aid the rapid departure of the leaving group. There is some debate as to the relative importance of features (a) and (b), but in most, although not all, cases they amount to much the same thing. Examples of acetals exhibiting general acid catalysis are (4), (5), and (6). Thus



(4)



(5)



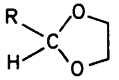
(6)

whereas increasing electron release by all the substituents R^1 and R^2 (including the leaving group) in (1)—(3) favour the $A1$ mechanism, the $A\text{-}S_E2$ scheme is favoured by poor release in the leaving group.[1] This result is understandable: in the $A1$ mechanism protonation is complete in the transition state; for $A\text{-}S_E2$ it is only partial and leaving ability has enhanced relative importance. In reality there will, of course, be a whole spectrum of transition states.[12]

Because acetals that react *via* the $A\text{-}S_E2$ mechanism have leaving groups that are readily lost, these acetals sometimes also possess a conveniently measurable spontaneous hydrolysis. The mechanism of this spontaneous hydrolysis, has, however, been little studied since for most acetals the reactions are relatively very slow. It has been suggested[3,17] that it involves a unimolecular (S_N1-like) ionization, followed by rate-determining separation of the ion pair formed (equation 4).

$$R^1_2C(OR^2)_2 \rightleftharpoons [R^1_2\overset{+}{C}-OR^2,\ \bar{O}R^2] \rightleftharpoons R^1_2\overset{+}{C}-OR^2 + R^2O^- \xrightarrow{H_2O} R^1_2C\begin{matrix}OH\\OR^2\end{matrix} + R^2OH \quad (4)$$

Cyclic, O,O-acetals [*e.g.*, 1,3-dioxolanes, (2) X = O] possess features that may lead them to depart from the simple $A1$ and $A\text{-}S_E2$ patterns outlined above.[4] Although they may exhibit specific or general acid catalysis, they usually react significantly (typically 20 to 10^3-fold) more slowly than their open-chain analogues, and their speeds are not increased nearly as much as would be those of open-chain compounds by, for example, making the structural change



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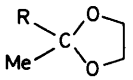
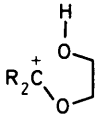
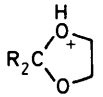


(8)

[15] B. Capon, *Pure Appl. Chem.*, 1977, **49**, 1001.
[16] A. Kankannpera and M. Lahti, *Acta Chem. Scand.*, 1969, **23**, 3266.
[17] W. P. Jencks and P. R. Young, *J. Am. Chem. Soc.*, 1977, **99**, 8238.

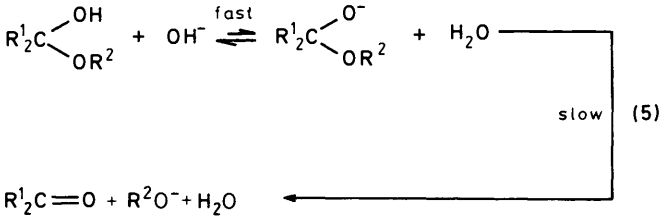


(9)



(10)

(7) ⟶ (8) when R = Ph or Me (Table 1). These effects may be related both to stereoelectronic control (ring geometry), and to the ease with which the carbocation (9) can re-cyclize in these systems so that, except at high pH [when OH^- ions rapidly capture (9)], the slow step may involve attack by water on (9) [or even on (10)] rather than ring-opening.[13] These cyclic compounds may therefore display *A*2-like mechanisms with the attack of water general base-



catalysed, and it may be significant that their $\Delta S^{\ddagger}$ values are normally more negative (by 20—40 J K^{-1} mol^{-1}) than those of their open-chain analogues. Another (rather similar) situation for which *A*2 mechanisms have been suggested even for open-chain O,O-acetals is where the carbocation is so reactive (short-lived) that C–O bond cleavage and attack by water become concerted.[14,17] This may occur for simple aliphatic acetals in low dielectric constant solvents.

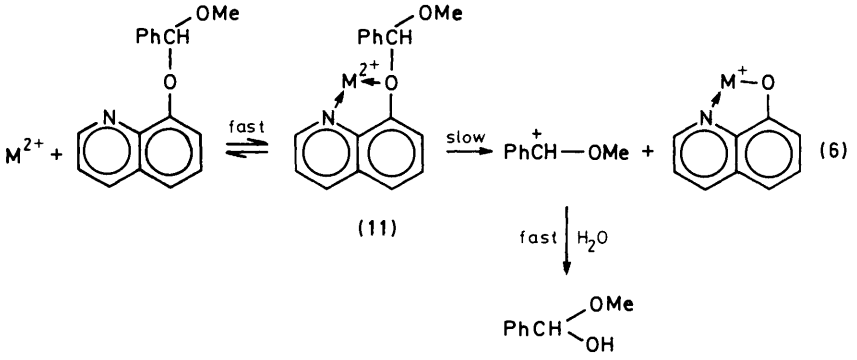
Following Jensen's work,[6] the involvement of the hemiacetal, and its own mechanism of hydrolysis, have become an important area of study. Since hemiacetals are susceptible to base catalysis (*e.g.* equation 5), whereas the parent acetals are not, the hemiacetals are normally much the more easily hydrolysed at high pH, and therefore do not affect the observed kinetics of acetal hydrolysis under these conditions. In acid solutions it appears[18] that, for open-chain acetals, the reactivity of the acetal only approaches or surpasses that of the corresponding hemiacetal for the most-highly reactive acetals, and that therefore normally a significant build-up of hemiacetal will not occur. This result supports the assumptions of earlier years.[1] However, for open-chain/cyclic compounds [*e.g.* (3), X = O] the exocyclic C–O bond normally cleaves first, leaving an endocyclic bond to be cleaved in the hemiacetal. For such compounds the hemiacetal will therefore often be the less reactive, and accumulate during acetal hydrolysis.[19] All the foregoing matters concerning the Brønsted acid-catalysed

[18] A. J. Kresge and Y. Chiang, *J. Org. Chem.*, 1985, **50**, 5038.
[19] R. A. McClelland and N. E. Seaman, *Can. J. Chem.*, 1984, **62**, 1608.

hydrolyses of O,O-acetals are current points of interest; this field is in an exciting and rapidly developing state.

The study[20] of the metal ion-catalysed hydrolysis of O,O-acetals has concerned almost exclusively acetals capable of chelating the metal ion owing to their possession of extra ligands [*e.g.* (11)]; one acetal oxygen atom forms an arm of the chelate, and the metal ion assists this oxygen's departure by rendering it less nucleophilic (equation 6), just as does the proton in the schemes discussed above. For successful catalysis all the chelating groups should be on the leaving group, for otherwise the metal and leaving group can remain attached to the substrate and the acetal can rapidly reform. In suitable systems very large accelerations are observed, and the second-order rate constant for metal ion-catalysis can be comparable to that for hydrogen ion catalysis. In these circumstances, if the pH is appropriately chosen, the slow process becomes hemiacetal hydrolysis.[21] There exist just one or two reports[22] of (feeble) catalysis of the hydrolysis of O,O-acetals *without* extra chelating ligands (by M^{3+} cations).

Metal ion catalysis with O,O-acetals probably always involves pre-equilibrium adduct formation (the analogue of the *A*1 or *A*2 mechanisms) rather than a slow metal transfer (the *ASE*2 analogue). As in all metal ion catalysis involving hard substrates, chelation appears normally required.[23] S-Acetals (soft substrates) provide opportunities for the use of soft metal ions (with which chelating leaving groups are not required).[23] This topic forms a major part of the Review.



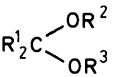
(6)

2 O,S-Acetal Hydrolysis

A. Brønsted Acid Catalysis.—O,S-Acetals have been of considerable interest in the recent resurgence of acetal studies. First because not much is yet known about their behaviour, and secondly because their hydrolyses appear little subject to general acid catalysis.[3,24] Not only do they fail to display general acid catalysis in circumstances under which the corresponding O,O-compound does so, but few

[20] *E.g.* T. H. Fife and T. J. Pryzstas, *J. Am. Chem. Soc.*, 1980, **102**, 4391.
[21] T. H. Fife and T. J. Pryzstas, *J. Am. Chem. Soc.*, 1981, **103**, 4884.
[22] G. Wada and M. Sakamoto, *Bull. Chem. Soc. Jpn*, 1969, **46**, 3378.
[23] D. P. N. Satchell and R. S. Satchell, *Ann. Rep. Prog. Chem., Sect. A*, 1978, 25.
[24] J. L. Jensen and W. P. Jencks, *J. Am. Chem. Soc.*, 1979, **101**, 1476.

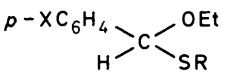
if any unambiguous examples of such catalysis have been found at all for O,S-acetals. Another point of mechanistic interest is whether the C–O or the C–S bond cleaves first. For unsymmetrical O,O-acetals (12) it is normally found (or



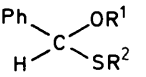
(12)

assumed) that the OR group with the lower electron release cleaves first, since it is a general finding[1] that observed rate constants are more dependent on electron release in the remaining group than in the leaving group (*i.e.* ρ^{rg} more negative than ρ^{lg}, although how unambiguous these findings are it is difficult to know). For O,S-acetals the electronic properties of the S-R groups, as compared with those of the OR groups, do not seem to be clearly understood, and there has sometimes been disagreement as to the sequence of bond cleavage in their Brønsted acid-catalysed reactions.

The most extensive single study of O,S-acetal hydrolysis is due to Jensen and Jencks.[24] In it they supplemented earlier work by Fife, but restricted themselves to open-chain O,S-acetals to avoid the extra complexities involved with cyclic systems (p. 59). As Table 1 shows, O,S-acetals are normally much less reactive under Brønsted acid catalysis than their O,O-analogues. Jensen and Jencks confirmed this and sought to explain it. They studied compounds of type (13) and (14). In (13) X = Cl, H, MeO and NMe_2, and R = Et, CH_2CH_2OH, CH_2CO_2Me, CH_2CF_3 and Ph; in (14) R^1 = Me, Et, Pr^n, CH_2CH_2Cl, $CH{=}CH_2$, and CH_2CF_3, and R^2 = Et and Ph. They measured k_{obs} for appearance of



(13)



(14)

aldehyde as a function of pH in aqueous acid and in buffers, sometimes using aqueous dioxan since S-containing acetals are poorly soluble in water. For a few of the compounds they also studied the position of initial bond cleavage in 90% MeOH–H_2O in the presence of acid, using a trapping technique and an NMR analysis. Deductions from their cleavage experiments involved a complex argument; they often did not isolate their starting O,S-acetals, preparing them in solution by an exchange method monitored by NMR; and they isolated none of their hydrolysis products. If we ignore these slightly worrying features we find they obtained the following principal results: (i) there is no evidence for significant build up of hemiacetal in any hydrolysis. (ii) In (13), with X = H and R = Et, there occurs dominant initial C–O bond cleavage, but with R = Ph dominant C–S cleavage, and with R = CH_2CO_2Me comparable amounts of C–O and C–S cleavage. Increased electron release by X leads to an increase in the proportion of C–O cleavage (Table 2). (The result for the R = Ph, X = H compound is in agreement with Fife and Anderson's for hydrolysis of the

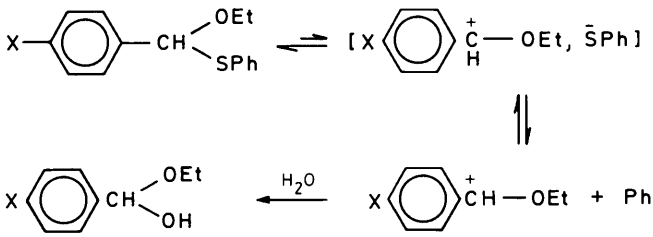
Table 2 *Initial bond cleavage for acetals*

Acetal	*Bond cleaved*
PhCH(OEt)SEt	C–O
PhCH(OEt)SPh	C–S
p-$MeOC_6H_4CH(OEt)SPh$	C–O and C–S
p-$MeOC_6H_4CH(OEt)SCH_2CO_2Me$	C–O
$PhCH(OEt)SCH_2CO_2Me$	C–O and C–S

(Solvent 90% MeOH–H_2O containing 0.1 M HCl)[24]

corresponding OMe derivative in aqueous propanol.[25]) (iii) General acid catalysis is not detectable for (13) with R = Ph, X = H, although it is for the O,O-analogue. (This again is in agreement with results of Fife and Anderson.[25]) (iv) Substituent effects are similar in their general pattern to those obtained with O,O-compounds,[1] with a somewhat lower sensitivity to electron release by the substituent X in the aldehyde function. (v) When R = Ph compounds (13) show a detectable spontaneous hydrolysis; this is quite slow for X = H or OMe, but fast when X = NMe_2. With this X substituent aliphatic groups R also lead to sizeable spontaneous rates.

For want of evidence to the contrary, Jensen and Jencks suggest the acid-catalysed hydrolyses (most of the processes studied) follow the *A*1 mechanism. For the spontaneous reactions, they favour a scheme (equation 7), analogous to



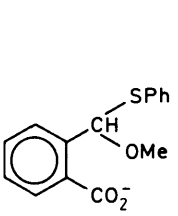
(7)

equation 4, with ion pair separation rate-determining. (The secondary isotope effect[26] for PhCD(OEt)SPh also suggests a fully-formed carbocation in the transition state.)

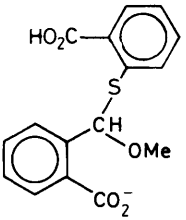
Jensen and Jencks' qualitative rationalizations[24] of the relative reactivities of analogous open-chain O,O-, O,S-, and S,S-acetals in acid-catalysed hydrolyses (Table 1) is rather confusing: they lump together protonatability and leaving group ability in a 'pull' of the leaving group, and, when considering the 'push' of the remaining group, ignore its effect on the protonation of the leaving group. This matter is discussed further on p. 75. They conclude that general acid catalysis is not found for O,S-acetals with C–S bond cleavage because sulphur is too lacking in proton basicity, and H-bonding capacity, for partial transfer to be energetically useful.

[25] T. H. Fife and E. Anderson, *J. Am. Chem. Soc.*, 1970, **92**, 5464.
[26] J. P. Ferraz and E. H. Cordes, *J. Am. Chem. Soc.*, 1979, **101**, 1488.

Much of the early work [3 15 16] on the general acid-catalysed hydrolysis of O,O-acetals is due to Fife and Capon and their co-workers In some cases where an O,O-acetal showed such catalysis, Fife subsequently looked also at the O,S-analogue when this could be expected to hydrolyse *via* C–S cleavage Normally no general acid catalysis was found and an *A*1 mechanism was assumed, as by Jensen and Jencks in the work just described One type of open-chain O,S-system, however, proved very interesting Fife and Pryzstas [27] show that the *spontaneous* hydrolysis of (15) is *ca* 20-fold faster in water than that of the *para*-derivative They attribute this to stabilization or capture, of the carbocation by the CO_2^- group Acetal (16) reacts substantially faster than does (15), especially



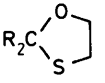
(15)



(16)

in 50% dioxan–water, Fife [3] attributes this to intramolecular general acid catalysis by CO_2H (The increase is much less for the compounds without the CO_2^- group) This may be a genuine case of general acid catalysis of C–S cleavage, but it is difficult to remove ambiguities from intramolecular examples [3] The problem for O,S-acetals remains that protons will transfer completely to S without the C–S bond breaking, but seem reluctant to transfer partially when the C–S bond is breaking The detailed mechanisms and energy profiles of proton transfer to S and O must be different However, *A*-S_E2 mechanisms have been proposed for thiolbenzoate esters [28]

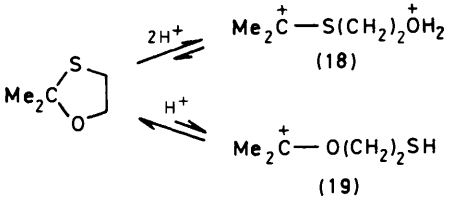
Turning to the acid hydrolysis of cyclic and open-chain/cyclic compounds, there has been some disagreement about the primacy of C–O or C–S bond cleavage For 1,3-oxathiolanes (17) Fife [29] has postulated C–S cleavage, but other



(17)

authors prefer C–O cleavage Two studies by Lamaty seem more compatible with C–O cleavage In the first [30] he found that the stable cation (18) is formed in FSO_3H–SbF_5–SO_2 mixtures (equation 8) This could be because (19), with only one proton on the (less basic) terminal group, can readily re-cyclize Lamaty's

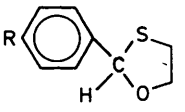
[27] T H Fife and T J Pryzstas, *J Am Chem Soc* 1979, **101** 1202
[28] R A Cox and K Yates, *Can J Chem*, 1982, **60**, 3061
[29] T H Fife and L K Jao, *J Am Chem Soc*, 1969, **91**, 4217
[30] F Guinot, G Lamaty, and H Munsch, *Bull Soc Chim Fr* 1971, 541



(8)

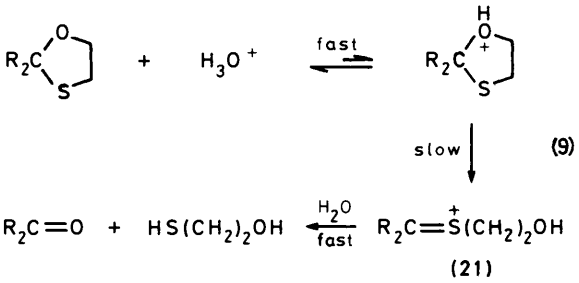
other evidence[31] concerns secondary deuterium isotope effects on the rates of acid-catalysed hydrolysis of the two possible O,S-isomers of a bicyclo-2-cyclohexanone-1,3-oxathiolane in aqueous propanol. He interprets these in terms of an *A*1 mechanism and initial C–O cleavage. Preferential C–O cleavage for simple 1,3-oxathiolanes would certainly be expected if Jensen's conclusions (p. 62) can be extended to cyclic compounds; but whether Lamarty's conclusions would follow if oxathiolanes do not exhibit an *A*1 mechanism (see below) is not certain.

The results of Fedor and De,[32] and of Fife and Jao,[29] for the acid-catalysed hydrolysis of species (20) are in only approximate agreement, although both



(20)

groups of workers find increased electron release by R aids hydrolysis. The replacement of H by Me has a rather small effect on the rate, the solvent isotope effect $k_{D_2O}/k_{H_2O} \simeq 2.0$, $\Delta S^{\ddagger}$ is probably < -50 J K^{-1} mol^{-1}, and there is no evidence of buffer catalysis. Fife and Jao claim the reaction follows the Ho function, and postulate an *A*1 mechanism with protonation on S (see above); Fedor and De favour an *A*2 scheme with C–O cleavage. In a similar study of (XXVIII)—(XXX) in Table 1, Pihlaja[33] interpreted the parallelism of their relative reactivities with those of the O,O-compounds, and the details of the

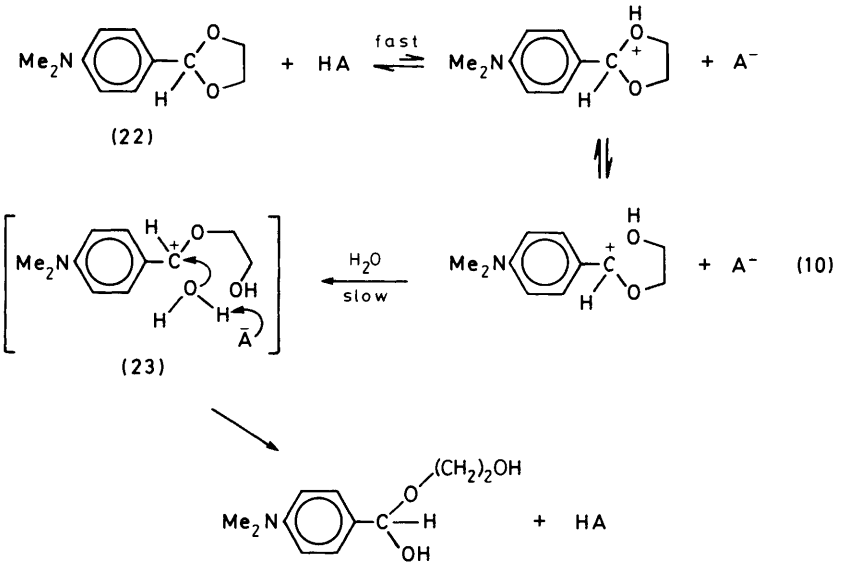


(9)

(21)

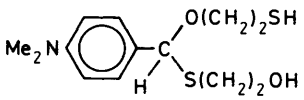
[31] F. Guinot and G. Lamaty, *Tetrahedron Lett.*, 1972, 2569.
[32] N. C. De and L. R. Fedor, *J. Am. Chem. Soc.*, 1979, **90**, 7266.
[33] K. Pihlaja and P. Pasanen, Ch. 18 in ref. 2.

solvent isotope effect over a wide composition range, as implying an *A*1 mechanism with C–O cleavage and a sulphonium ion intermediate (21) [equation 9; *cf.* (8)]. However, recent work by Fife[13] using (20) with R = NMe_2 has revealed general acid catalysis for the free-NMe_2 compound at pH > 4, and also for the corresponding O,O-acetal (22), which is *ca.* 50-fold the more reactive. Fife interprets the (apparent) general acid catalysis as arising from the general base catalysis of the attack of water on the carbocation (23), this being the slow step since it has to compete with rapid re-cyclization in these systems (equation 10,



(10)

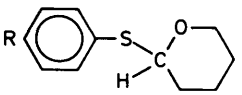
see also p. 60). Fife still favours C–S cleavage for the oxathiolane, and considers now that the *A*1 scheme he previously suggested will apply principally to phenyl dioxolanes (and presumably phenyl oxathiolanes) possessing electron-withdrawing substituents. Preferential C–S cleavage seems unlikely on the basis of Jensen's results (p. 62) but cannot be ruled out. That recyclization is rapid is attested by the fact that (24) has a rate of acid-catalysed hydrolysis identical with that of (20) with R = Me_2N. Fife suggests (24) rapidly cyclizes *via* C–S cleavage. It seems



(24)

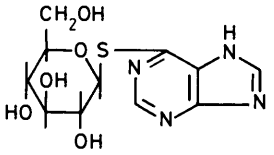
likely to us that many 1,3-dioxolanes and 1,3-oxathiolanes exhibit *A*2-like mechanisms; most facts point to it. There is much work to be done in this area, and also in that of the 1,3-oxathianes (6-membered ring).[33]

The open-chain/cyclic 6-membered system (25) has been studied by Fedor.[34] R was NO_2, Cl, H, Me, and MeO, and the solvent 40% aqueous dioxan containing hydrogen chloride. It is perhaps reasonable to assume C–S cleavage in this system. $\Delta S^{\ddagger}$ is positive, $k_{D_2O}/k_{H_2O} \simeq 1.3$, and $\rho = -0.96$, a value similar to



(25)

that obtained by Fife for leaving groups of this type in open-chain O,S-acetals,[25] and in *para*-substituted thiophenyl-β-glucopyranosides,[35] for both of which an *A*1 mechanism has been suggested. Fedor concurs, and attributes the low isotope effect to the fact that protonation is on sulphur. Fedor, however, postulates[36] an *A*-S_E2 scheme for (26), with C–S cleavage, mainly on the basis of isotope effects. This system requires further study. There is evidence[37] for concurrent initial C–O and C–S cleavage during acid-catalysed hydrolysis of 1-methylthioglycosides.



(26)

B. Soft Metal Ion-promoted Reactions.—The presence of certain soft metal ions greatly accelerates the hydrolysis of O,S-acetals but has a negligible effect on O,O-acetals.[2,34,38] The acceleration arises from soft–soft interactions with sulphur and strictly does not constitute catalysis since the metal remains attached to the thiol product unless deliberately regenerated subsequently (*e.g.* equation 11). In

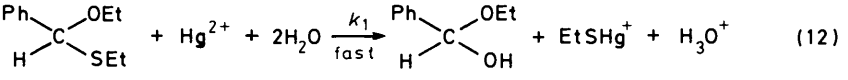
$$R^1_2C(OR^2)(SR^3) + Ag^+ + 2H_2O \longrightarrow R^1_2C{=}O + R^2OH + R^3SAg + H_3O^+ \qquad (11)$$

all these soft metal ion-promoted reactions it seems safe to assume the C–S bond cleaves first. The mercaptide products are sparingly soluble in aqueous solvents, but reaction mixtures remain homogeneous if sufficiently low (*ca.* 10^{-5} M) concentrations of S-acetal are used. Preparative-scale reactions will normally be heterogeneous. In kinetic studies low concentrations of hydrogen ions are usually

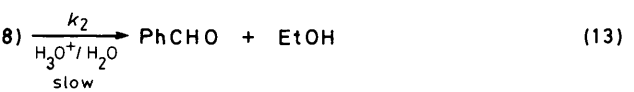
[34] G. Wagner and M. Wagler, L. R. Fedor and B. S. R. Murty, *J. Am. Chem. Soc.*, 1973, **95**, 8407.
[35] G. Wagner and M. Wagler, *Arch. Pharm* (*Weinheim, Ger.*), 1964, **297**, 348.
[36] L. R. Fedor and P. A. Lartey, *Carbohydr. Res.*, 1979, **69**, 89.
[37] C. J. Clayton, N. A. Hughes, and S. A. Saeed, *J. Chem. Soc. C*, 1967, 644.
[38] D. P. N. Satchell, *Chem. Soc. Rev.*, 1977, **6**, 345.

added to reaction mixtures to keep the pH constant, since hydrogen ions are produced in the hydrolyses (equation 11). Anions should normally be perchlorate. So far only three soft metals [Ag^{I}, Hg^{II}, Tl^{III}] have been used in extended kinetic studies; in homogeneous solution at acid pH all three ions are so effective that any concomitant hydrogen ion catalysis is negligible by comparison. On the other hand, under similar conditions, the supposedly soft Cu^{II} and Cd^{II} ions appear kinetically less effective than the hydrogen ion in speeding-up S-acetal hydrolysis.[39] This finding agrees with results for promoted reactions of other types of S-substrate.[38]

(i) *Open-chain Compounds.* Only one open-chain O,S-acetal has been examined kinetically.[40,41] Compound (27), studied using 1% dioxane–water, provided however interesting results. In the presence of even very low (10^{-4} M) concentrations of Hg^{2+} or Tl^{3+} ions, the observed rate of hydrolysis is independent of the metal ion concentration, and displays kinetics characteristic of the corresponding O,O-hemiacetal (28) at the pH concerned. The outline mechanism of equations (12)—(13) applies, with $k_1 \gg k_2$.



(27) (28) (12)



(13)

We have mentioned how a build-up of hemiacetal sometimes affects the kinetics of the hydrogen ion-catalysed hydrolysis of open-chain O,O-acetals, but for such systems it is not usual for the hemiacetal hydrolysis completely to dominate the rate equation. That situation can (significantly), be achieved with open-chain O,O-acetals by using chelating leaving groups and appropriate metal ions (p. 61). Little is yet known about the effects of changes in R^3 (equation 11) on the rates of soft metal ion-promotion of O,S-acetals, but it seems likely that for most such acetals it will be possible to choose Hg^{2+} (or Tl^{3+}) and H_3O^+ concentration ranges in which $k_1 \gg k_2$, so that an effectively quantitative yield of O,O-hemiacetal is formed (transiently) in solution. For (27) with Hg^{2+} or Tl^{3+}, probably $k_1 > 10^6$ l mol^{-1} s^{-1} at 25 °C.

Since, in promoted hydrolysis of S-substrates generally,[38] Ag^+ ions usually lead to rate constants *ca.* 10^3-fold smaller than do Hg^{2+} or Tl^{3+}, and since for (28) k_{H^+} (k_2, equation 12) $\simeq 10^3$ l mol^{-1} s^{-1} at 25 °C, it would be expected that Ag^+ and H_3O^+ concentration ranges could be chosen in which either reaction (13), or the silver ion equivalent of (12), dominates the kinetics of hydrolysis. This

[39] D P N Satchell and T J Weil, *J Chem Soc, Perkin Trans 2*, 1980, 1191
[40] D Penn and D P N Satchell, *J Chem Soc, Chem Commun*, 1982, 54, *J Chem Soc, Perkin Trans 2*, 1982, 1029
[41] D Penn and D P N Satchell, *J Chem Res (S)*, 1982, 220

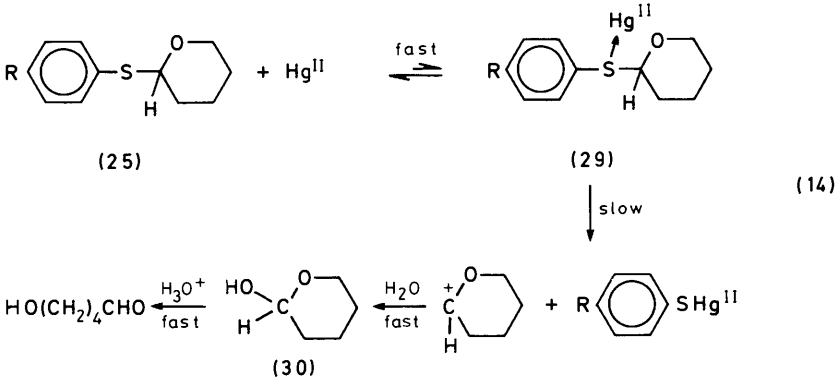
is so.[41] A similar complete switch in rate-determining step can sometimes be achieved in O,O-acetal hydrolysis: for open-chain/cyclic O,O-acetals the hemiacetal can dominate at low pH, but be lost comparatively rapidly at high pH (p. 60).

The details of the kinetics of the fast step (12) for Hg^{2+} and Tl^{3+} are not known. For Ag^+ the kinetic form of reaction (12) is complex (as for most examples of silver ion-promotion[37]): the rate is independent of $[H_3O^+]$, but involves terms in $[Ag^+]$ and $[Ag^+]^2$. Its mechanism is suggested on p. 74. In the presence of hydrogen ions only, (27) has k_{H^+} 1.4 l mol^{-1} s^{-1} at 25 °C. This purely hydrogen ion-catalysed hydrolysis is thus very slow compared with both the metal ion promotion and the hemiacetal hydrolysis; Hg^{2+} and Tl^{3+} are at least 10^6-fold more effective than H_3O^+ in cleaving this O,S-acetal, it being remembered that H_3O^+ will operate *via* C–O cleavage in this instance. With S,S-acetals we might anticipate even larger factors.

(ii) *Open-chain/Cyclic Compounds.* As for the open-chain compounds, only one type of open chain/cyclic O,S-acetal has been studied kinetically using metal ion-promotion: acetals (25). Fedor and Murty[34] conducted experiments, using all five compounds, under conditions similar to those used in the study of the hydrogen ion-catalysed hydrolysis (p. 67). However, reaction mixtures now contained a large, fixed concentration of hydrogen chloride (2 M), and a variable (*ca.* 10^{-4}—10^{-3} M) Hg^{II} ion concentration. The reactions all proved to be first order in $[Hg^{II}]_{total}$, and the apparent second-order rate constants, k_{Hg}, to be 10^2—10^4-fold larger than the corresponding k_{H^+} values (which with this acetal probably reflect C–S cleavage, p. 67). This sizeable acceleration was found in spite of the fact that the Hg^{II} species present in solution must have been almost exclusively $HgCl_3^-$ and $HgCl_4^{2-}$, with the latter predominant.[42] Fedor found ρ + 0.9 (*N.B.* ρ − 0.9 for k_{H^+}) and $\Delta S^{\ddagger}$ + 190 J K^{-1} mol^{-1} for the *p*-Me derivative. With an *A*1 scheme postulated for the hydrogen ion catalysis (p. 67), and the large positive entropy term, Fedor favoured an *A*1-type mechanism for this mercury reaction (equation 14). It is interesting that ρ^{lg} is positive, as for examples of the *A*-S_E2 mechanism for O,O-acetals. Substitution of Cl^- on Hg by the S-acetal is probably involved in this reaction under Fedor's conditions; it is perhaps just possible that the hydrolysis has a slow metal transfer mechanism (analogue of *A*-S_E2) rather than an *A*1 scheme, although the $\Delta S^{\ddagger}$ values argues against it.

Fedor chose his conditions against a background[43] of the frequent use of $HgCl_2$/HCl mixtures in preparative-scale S-acetal hydrolyses, and a claim that the presence of HCl augmented the effects of $HgCl_2$. This claim was tested in a subsequent study[44] using the *p*-chloro derivative (25, R = Cl). Using conditions similar to Fedor's, except that perchloric acid and mercury(II) perchlorate replaced the chlorides, it was found that the hydrolysis proceeds much faster, and

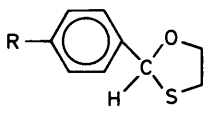
[42] L. G. Sillen and A. E. Martell, 'Stability Constants', Chemical Society Special Publication Numbers 17 and 25, The Chemical Society, London, 1964 and 1971.
[43] D. S. Tarbell and D. P. Harnish, *Chem. Rev.*, 1951, **49**, 1.
[44] D. P. N. Satchell and L. Z. Zdunek, unpublished results.



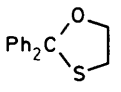
(14)

that the rate falls progressively as chloride ions are added to the reaction mixture. The deceleration is especially marked when Hg^{2+} is largely converted into $HgCl_3^-$ and $HgCl_4^{2-}$. The reactivity sequence $Hg^{2+} \simeq HgCl^+ \simeq HgCl_2 > HgCl_3^- \gg HgCl_4^{2-}$ was obtained, with $k_{Hg^{2+}} > 10^3$ l mol^{-1} s^{-1} at 30 °C. Under Fedor's conditions[34] $k_{Hg} \simeq 3$ l mol^{-1} s^{-1} at 30 °C. Since for hemiacetal (30) it is likely[19] that $k_{H^+} \simeq 10^3$ l mol^{-1} s^{-1}, it is evident that, in contrast to the open-chain –SEt leaving group in (27), there will have been no hemiacetal accumulation in these systems at the Hg^{II} and H_3O^+ concentrations used, even in the total absence of chloride ions. Use of larger Hg^{2+}, and smaller H_3O^+, concentrations could, however, lead to build-up of (30). Acetals (25) are significantly less reactive than is (27) towards Hg^{2+} promotion. The same is true for proton catalysis: for (25, R = Cl) $k_{H^+} \simeq 10^{-4}$ l mol^{-1} s^{-1} at 30 °C, so that $k_{Hg^{2+}} \lesssim 10^7 k_{H^+}$.

(iii) *Cyclic Compounds.* Two types of cyclic O,S-acetal have been studied kinetically with soft metal ions: (20) and (31). Fedor and De[32] extended to



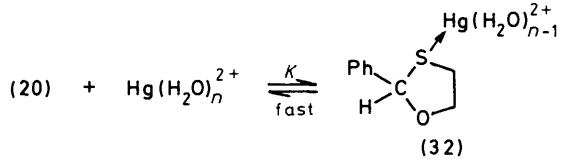
(20)

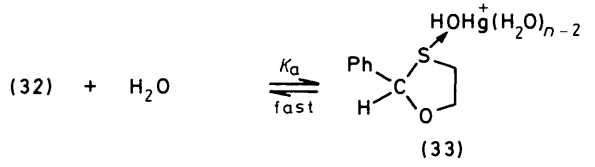


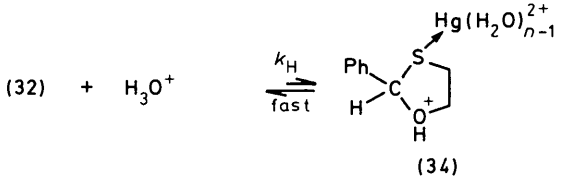
(31)

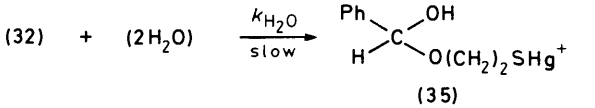
mercury(II) ion-promotion their work on the hydrogen ion-catalysed hydrolysis of acetals (20) with R = MeO, Me, H, Cl and NO_2. The experiments were on similar lines to those used with acetals (25): they employed aqueous solutions of $HgCl_2$ with hydrogen chloride (0.15 M) plus a further fixed concentration of chloride ions. The Hg^{II} species present will again have been mainly $HgCl_3^-$ and $HgCl_4^{2-}$. As for acetals (25), the hydrolyses were found to be first order in $[Hg^{II}]_{total}$. Electron release by R favours reaction (*p*-MeO *ca.* 100-faster than *p*-NO_2) and $\Delta S^{\ddagger} \simeq -30$ J K^{-1} mol^{-1}. An *A*2-like mechanism was suggested, involving a pre-equilibrium in which a small quantity of a 1:1-adduct is formed (*cf.* equation 14).

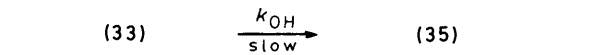
Further study[45] of (20, R = H) with mercury(II) perchlorate using 1% dioxane–water and various ethanol–water mixtures as solvents, and a range of added anion and hydrogen ion concentrations, revealed a complex but interesting kinetic pattern in which the purely hydrogen ion-catalysed hydrolysis was always negligible compared to the promoted reaction. In the absence of ethanol, and using only perchlorate as the counter ion, the kinetics are explicable by the mechanism of equations (15)—(21) with $K = 1.5 \times 10^3$ l mol^{-1}, $K_a = 8 \times 10^{-4}$ mol l^{-1}, $k_{H_2O} = 0.5$ s^{-1}, and $k_{OH} = 20$ s^{-1} at 25 °C. The magnitudes of the

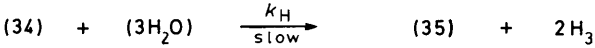


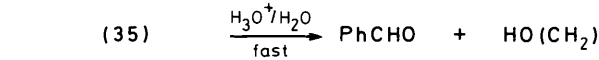












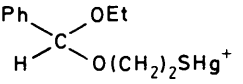
[45] D. Penn and D. P. N. Satchell, *J. Chem. Soc., Perkin Trans. 2*, 1982, 813.

observed rates are compatible with the loss of hemiacetal (35) not being rate-determining, provided that its reactivity is not greatly less than that of (28). The value of K_a is compatible with the known value[42] for equilibrium (22), and that of K

$$Hg(H_2O)_n^{2+} + H_2O \rightleftharpoons HOHg^{+}(H_2O)_{n-1} + H_3O^{+} \qquad pK_a \simeq 3 \qquad (22)$$

with the finding that the rate of hydrolysis becomes independent of $[Hg^{2+}]$ when $[Hg^{2+}] \gtrsim 10^{-2}$ M with $[O,S\text{-acetal}]_{initial} \simeq 4 \times 10^{-5}$ M (saturation effect). The faster rate of C–S cleavage for (33) (k_{OH}) compared with (32) (k_{H_2O}) is significant: step (18) has $\Delta S^{\ddagger} \simeq -4$ J K^{-1} mol^{-1} and is believed to involve intramolecular attack on the pro-carbonyl carbon atom by the Hg-bound OH^- ion in (33). When Cl^-, Br^-, or SCN^- ions are added a sharp maximum in rate is found when $[X^-] = 2[Hg^{2+}]$ (*i.e.* when Hg^{2+} has been effectively quantitatively[42] converted into the neutral species HgX_2); this increase is thought to arise because intramolecular transfer of OH^- will be easier from a neutral than from a positively charged mercury atom. With a greater excess of anion the relatively weak soft acid species HgX_3^- and HgX_4^{2-} are formed, and the rate falls for this reason. Eventually the rate reaches a relatively low value comparable to those reported by Fedor.[32] For reaction of free Hg^{2+} ions *via* species (32), $k_{Hg} \simeq 10^3$ l mol^{-1} s^{-1} at 25 °C. This represents an acceleration of *ca.* 2×10^5-fold compared to the rate of C–O cleavage by the hydrogen ion. The route *via* (32) has $\Delta S^{\ddagger} \simeq -45$ J K^{-1} mol^{-1}. It is significant that the Brønsted acid-catalysed mercury-promoted route *via* (34) is relatively much more important in the presence of chloride ions (which reduce or reverse the charge on mercury).

In 20% ethanol–water very similar behaviour is found except that some (*ca.* 10%) of the product forms *via* (36) which is produced in the analogue of step (18) with ethanol in place of water. Compound (36) hydrolyses in acid relatively very



(36)

slowly compared with (35); in fact (36) is *ca.* 40-fold less reactive than $PhCH(OEt)_2$ towards hydrogen ion-catalysis. This lower reactivity is doubtless due to the effect of the positive charge in (36). It is therefore again interesting and understandable that the effect of added chloride ions on this slow hydrogen ion-catalysed reaction of (36) is to accelerate it; its rate eventually reaches a level *ca.* 4 times smaller than that of $PhCH(OEt)_2$ under the same conditions.[45]

The promoted hydrolysis of the diphenyl derivative (31) was examined in a study[46] analogous to that just described for (20). As for the O,O-analogues, (31) is surprisingly 10—20-fold, less reactive towards hydrogen ion-catalysis ($k_{H^+} = 2.5 \times 10^{-4}$ l mol^{-1} s^{-1} at 25 °C) than is (20, R = H) if the mechanism of the latter's hydrolysis is indeed *A*1 (see p. 66). This is perhaps another pointer to an *A*2-like scheme for these compounds. For Hg^{2+} ion-promotion scheme (14)—

[46] D. Penn and D. P. N. Satchell, *J. Chem. Soc., Perkin Trans. 2*, 1984, 933.

(20) is again needed, although rate-determining hemiacetal hydrolysis intervenes at high values of $[Hg^{2+}]$. Compound (31) is *ca.* 4-fold faster than (20) *via* step (17), but *ca.* 4-fold slower *via* step (18). The latter result is compatible with an intramolecular route for reaction (18): steric restrictions will be greater for the diphenyl compound. The hydrogen ion-assisted mercury promotion *via* (34) is less important for acetal (31), and K for the pre-equilibrium (14) is smaller. These effects, arising from lower inductive release, also reflect the presence of the extra phenyl group in (31) compared with (20).

In contrast to the Hg^{2+} ion-promotion, the kinetics of the Tl^{3+} ion-promoted hydrolysis of (31) are especially simple:[29] the rate is independent of $[Tl^{3+}]$ at least down to $[Tl^{3+}] = 5 \times 10^{-4}$ M, and is independent of $[H_3O^+]$ when $[H_3O^+] \lesssim 0.15$ M. The outline mechanism under such conditions is equations (23)—(24); it involves rapid and stoicheiometric formation of the 1:1 complex

$$\text{O,S-acetal} + Tl(H_2O)_n^{3+} \overset{\text{fast}}{\rightleftharpoons} [(H_2O)_{n-1}Tl \leftarrow \text{O,S-acetal}]^{3+} + H_2O \qquad (23)$$

(37)

$$(37) + xH_2O \xrightarrow{\text{slow}} \text{Products} \qquad (24)$$

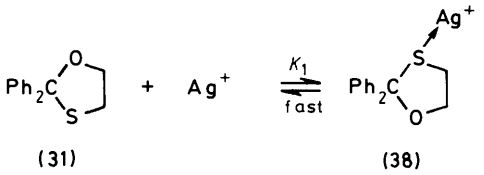
(37) (saturation kinetics). When $[H_3O^+] \gtrsim 0.15$ M the rate falls. In this pH region equilibrium (25) [*cf.* (22)] begins to move to the right.[42] Probably Tl^{2+} is a less powerful promoter than is Tl^{3+}. When $[H_3O^+] \lesssim 0.15$ M the hydrolysis

$$Tl(H_2O)_n^{3+} + H_2O \rightleftharpoons [Tl(OH)(H_2O)_{n-1}]^{2+} + H_3O^+ \qquad (25)$$

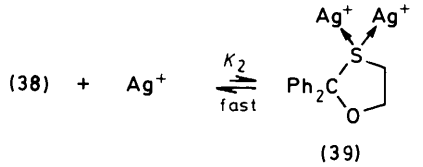
of the intermediate hemiacetal, $Ph_2C(OH)O(CH_2)_2STl^{2+}$, is clearly not rate-determining, for otherwise the observed rate would not be independent of $[H_3O^+]$. The fall in rate at higher pH could be due to the slow hydrolysis of this intermediate, but the same effect in the same pH region is found for a variety of S-acetals with thallium and the lower reactivity of Tl^{2+} is the preferred interpretation. It seems that no intramolecular effects are involved with this metal ion. It is, however, a much stronger Lewis acid towards O,S-acetal (31) than is Hg^{2+}, and the overall rates are slightly faster than in the presence of Hg^{2+}.

The silver ion-promoted hydrolysis[38] of (31) is much slower than the thallium and mercury ion reactions except at relatively high ($>10^{-2}$ M) metal ion concentrations. The silver rate is able to become comparable to those of the other metals under these conditions because saturation kinetics do not intervene to limit the rate for silver, and because (as usual) its rate equation contains terms in $[Ag^+]^2$. The silver reaction is independent of $[H_3O^+]$ at all pH values, and the hemiacetal hydrolysis is not a factor. An outline mechanism for silver ion-promotion found applicable with numerous S-acetals[39] is given in equations (26)—(30).

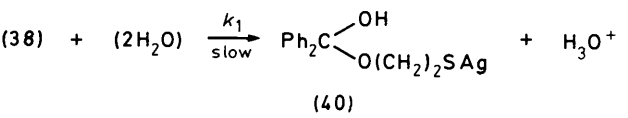
This mechanism provides a rate equation (30a) with both a first- and a second-order term in $[Ag^+]$, and four parameters: K_1, K_2, k_1, and k_2; it can simulate satisfactorily a variety of experimental rate equations and probably underlies



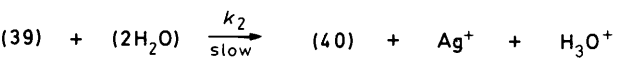
(31) (38) (26)



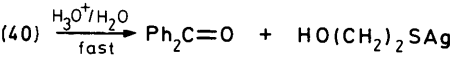
(38) (39) (27)



(40) (28)



(39) (40) (29)



(40) (30)

much silver ion-promotion.[39,47] The second-order terms arise from the presence of two silver ions on the same S atom, and can dominate the observed kinetics, although equilibrium (27) normally lies well to the left.

$$k_{obs} = (k_1K_1[Ag^+] + k_2K_1K_2[Ag^+]^2)/(1 + K_1[Ag^+] + K_1K_2[Ag^+]^2) \quad (30a)$$

As mentioned on p. 70, Fedor postulated an *A*2 scheme for oxathiolane (20), using conditions of high chloride ion concentration. Whether the various O,S-acetal-metal ion complexes formed by Hg^{2+}, Tl^{3+}, and Ag^+ in the absence of added anions decompose unimolecularly, or by reaction with water, is not known, except that complexes derived from $Hg(OH)^+$ appear able to transfer OH^- intramolecularly (reaction 19). The background of evidence for cyclic acetals suggests schemes in which a nucleophile is involved in the slow step; there exists little that is incompatible with that picture, and the existence of routes *via* species such as (33)—if real—argue against *A*1 schemes.

[47] D. Penn, Z. Saidi, D. P. N. Satchell, and R. S. Satchell, *J. Chem. Res.* (*S*), 1987, 200.

3 S,S-Acetal Hydrolysis

A. Brønsted Acid Catalysis and the Relative Reactivities of Acetals.—No extensive study exists of S,S-acetal hydrolysis catalysed by Brønsted acids; we have only some limited measurements made to provide comparisons with the O,O- and O,S-analogues. Two comparisons are given in Table 1 and discussed below.

In attempts to rationalize the S-acetal data in Table 1 it is necessary to distinguish between the various effects involved in replacing O by S in an acetal that are relevant to its ease of hydrolysis. First, whereas hemiacetal formation (normally the slow step in the overall hydrolysis) must involve C–S cleavage for S,S-acetals, and C–O cleavage for O,O-acetals, for O,S-acetals sometimes C–O and sometimes C–S cleavage will be involved. Secondly, if we consider acetal (41), and assume an *A*1 or *A*-S_E2 mechanism, there are four other relevant

$$R^1_2C(XR^2)_2$$

(41) X = O or S

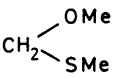
factors that concern the potential leaving groups: (i) the ability of R^2X to accept a proton, (ii) the ability of the other R^2X group to facilitate this acceptance by electron release, (iii) the ability of R^2X to leave as R^2XH, and (iv) the ability of the remaining R^2X group to stabilize the incipient carbocation. These abilities will be tempered to a greater or lesser extent by the nature of the groups R^1. For the present we ignore R^1 and assume these groups remain constant within the comparisons considered.

Compounds I and II in Table 1 probably both undergo primary C–O fission during hydrolysis *via* essentially *A*1 schemes.[12,24] Their comparison involves a comparison of remaining groups. The relevant factors here are therefore just (ii) and (iv). Substituent constants[48] suggest that, of the two remaining groups, EtS will be slightly less able than EtO to facilitate protonation of the cleaving EtO group, and significantly less able to stabilize the incipient carbocation. A lower reactivity for II is therefore expected and found: the combination of these factors amounts in practice for these particular acetals to a rate reduction of *ca.* 120-fold.

Comparison of compounds II and III involves just a comparison of leaving groups; now it is factors (i) and (iii) that are involved. Jensen's argument[24] that RSH and ROH are equally good leaving groups is not convincing; RSH may be better than ROH, just as RS^- is sometimes better than RO^-. However, the dominant factor is certainly likely to be (i), S-ethers being *ca.* 10^4-fold weaker bases than O-ethers.[49] We expect therefore about a 10^3—10^4-fold lower reactivity for III compared to II, and this is found experimentally. S,S-acetals will always be expected to hydrolyse relatively slowly under Brønsted acid catalysis because of the inevitability of initial C–S cleavage coupled with a poor remaining group. A similar comparison and result are available for compounds IV and V. In this case PhSH is probably a significantly better leaving group than PhOH,

[48] J. Shorter, 'Correlation Analysis in Organic Chemistry', Claredon Press, Oxford, 1973.
[49] P. Bonvicini, A. Levi, V. Lucchini, G. Modena, and G. Scorrano, *J. Am. Chem. Soc.*, 1973, **95**, 5960.

leading to the lower factor of *ca* 700, and there is also a difference in mechanism (*A*1 for V, but *A*-S_E2 for IV) Compare also XI and XII



(42)

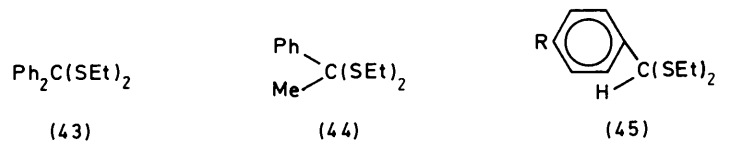
Changes in mechanism are clearly relevant to comparisons of acetal reactivity when the mechanisms differ as much as do *A*1 and *A*2, stabilization of the carbocation is not desirable for an *A*2 scheme This may be the reason that (42) is reported[50] to hydrolyse (presumably *via* initial C–O cleavage) 5-fold *faster* than its O,O-analogue, for simple aliphatic acetals may hydrolyse *via* the *A*2 route[14 17] (see p 60) This point also concerns comparisons of cyclic acetal reactivities since, as we have seen, these acetals may employ an *A*2 mechanism This could be one reason the factor between the reactivities of the corresponding O,O- and O,S-compounds (XXV)—(XXX) is substantially less than 100, although the reactivities of cyclic compounds may also be affected by steric and stereoelectronic effects arising from the different sizes of the S and O atoms[33]* That the differences in reactivity between these and other cyclic O,O- and O,S-compounds is substantially less than 10^4 argues against initial C–S cleavage in the proton-catalysed hydrolyses of the O,S-compounds, in agreement with the views of Lamaty[31] and Pihlaja[33] However, for *phenyl* dioxolanes and oxathiolanes the O,O/O,S rate ratio is *ca* 10^3, so that Fife's preference[29] for C–S cleavage in these cases may be correct (p 66)

In considering the likelihood of primary C–O or C–S cleavage in open-chain O,S-acetals carrying a range of substituents, the important aspect is how any change in substituents affects the balance between factors (i)—(iv) on p 75 If substituents attached to S make it a significantly better leaving group, and reduce further its ability to permit protonation of the O atom, and to stabilize a carbocation, then there will come a point when C–S rather than C–O cleavage will occur in spite of the much lower basicity of the S atom One of Jensen and Jencks' important findings[24] was that a change to C–S cleavage is offset by any increase in the carbocation stabilizing power of the other groups (R^1) in the O,S-acetal (Table 2) This finding is qualitatively intelligible groups which stabilize the cation will favour C–O cleavage relatively more than C–S cleavage because for the latter the remaining group (OR) already provides superior stabilization

Confident predictions about the relative reactivities of O- and S-compounds remain dangerous[24 50 52] However one prediction that follows from our analysis is that for two open-chain O,S- and S,S-analogues that both hydrolyse under acid catalysis *via* C–S cleavage, the former would be expected to be *ca* 100-fold the more reactive There appears no evidence on this point

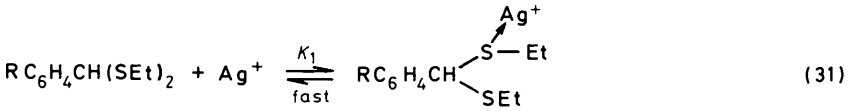
* Sulphur, perhaps for various reasons, performs better when in a ring S pyranose sugars hydrolyse faster than their O-analogues[51]

[50] G Modena, G Scorrano, and P Venturello, *J Chem Soc*, *Perkin Trans 2*, 1979, 1
[51] B Capon, *Chem Revs*, 1969, **69**, 407
[52] R H McClelland and M Ahmad, *J Am Chem Soc*, 1978, **100**, 7031



(43) (44) (45)

(46) (47)



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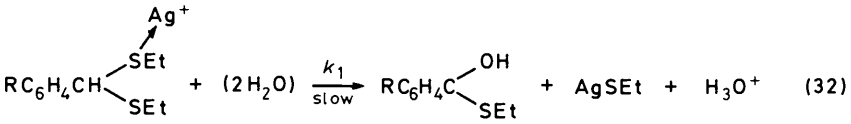
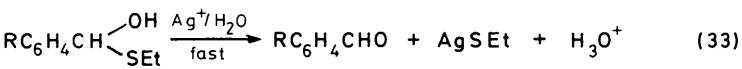


(32)



(33)

B. Preparative Cleavage by Soft Reagents.—Reagents used to hydrolyse S,S-acetals conveniently after they have served their purpose as protecting groups, or as precursors, during synthesis have been reviewed.[53] Most earlier recipes contain salts or oxides of soft metals. More recent reagents[54–57] are $I_2(I^+)$, HNO_2 or i-AmONO (NO^+), t-BuOCl (Cl^+) and $(PhSeO)_2O$ ($PhSeO^+$). Reaction mechanisms have been suggested[54–57] but await vindication by kinetic studies. Like the soft metal ion-promoted reactions discussed with O,S-acetals, strictly speaking these hydrolyses are not catalysed since the cleaving reagent is consumed.

C. Soft Metal Ion-promoted Reactions.—(i) *Open-chain S,S-acetals.* The kinetics of hydrolysis of acetals (43)—(47) inclusive have been studied using Ag^+ ion-promotion, (43), (45, R = H), (46), and (47) have been examined using Tl^{3+} ions, and (43) and (45, R = H) with Hg^{II} ions. We deal with Ag^+ first, and begin with

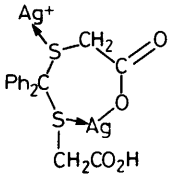
[53] T-L Ho, 'Hard and Soft Acids and Bases Principle in Organic Chemistry', Academic Press, London, 1977.
[54] R. Caputo, C. Ferreri, and G. Palumbo, *Tetrahedron*, 1986, **42**, 2369.
[55] K. Fuji, K. Ichikawa, and E. Fugita, *Tetrahedron Lett.*, 1978, 3561.
[56] K. A. Jorgensen, S. O. Lawesson, and M. El-Wassimy, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2201.
[57] D. H. R. Barton, N. J. Cussans, and S. V. Ley, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1654.

the simple –SEt derivatives, all studied using dioxan–water solvents (usually 1% dioxan).

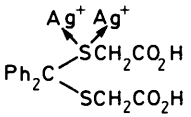
For (43), (44), and (45, R = NO_2, H, Me, MeO) the kinetic behaviour[39,47,58] is similar to that found for O,S-acetals (p. 73), and the general mechanism (26)—(30) probably obtains. The kinetic pattern is simplest for compounds (45) for which[47,58] the second-order terms contribute little when $[Ag^+] \gtrsim 0.15$ M. Under these conditions the mechanism reduces to equations (31)—(33). With S,S-acetals the hemiacetal hydrolysis will also be promoted by the metal ion, and therefore normally be expected to be fast. The rate equation corresponding to equations 31—33 is 34. Values of k_1 and the corresponding activation parameters for acetals (44) and (45) strongly suggest that when the substituents in the aldehyde (or ketone) are more able to stabilize a carbocation than are those of benzaldehyde the hydrolysis mechanism is an *A*1 analogue. With (45, R = NO_2), however, the activation parameters have a quite different pattern with $\Delta S^{\ddagger}$ large and negative, and an *A*2 analogue is suggested.[58] That an important change in mechanism occurs is also indicated by the solvent deuterium isotope effects.[59] Acetal (45, R = H) is probably an intermediate case. Hammett plots are non-linear.

$$k_{obs} = k_1 K_1 [Ag^+]/(1 + K_1[Ag^+]) \qquad (34)$$

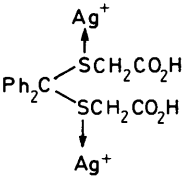
Acetals (46) and (47) display special behaviour[39] arising from their leaving groups. With (46) the hydrolysis step is slow enough to permit direct measurement of the extent of the initial adduct formation between (46) and Ag^+ ions; a $2Ag^+$: S,S-acetal equilibrium is evident, with negligible 1:1-adduct. The overall kinetics show the 2:1-adduct exists principally in a form with one carboxyl proton dissociated, perhaps (48). Hydrolysis occurs only *via* the fully-protonated, doubly-charged adduct (49), which will be in equilibrium with (50). 1:1-Adducts are probably not found because they can exist in a neutral form, and therefore readily add another Ag^+ ion to give (48).



(48)



(49)



(50)

Acetal (47) undergoes initial, rapid, intramolecular alcoholysis (equation 35) originally interpreted[39,60] as a measurable (stopped-flow) Ag^+–S,S-acetal adduct

[58] D. P. N. Satchell and R. S. Satchell, *J. Chem. Res.* (*S*), 1989, 102.
[59] D. P. N. Satchell and R. S. Satchell, *Z. Naturforsch., Teil A*, 1989, **44**, 492.
[60] D. P. N. Satchell and T. J. Weil, *Inorg. Chim. Acta*, 1978, **29**, L239.

formation. The supposed adduct product has, however, a spectrum identical with that of the oxathiolan (31), and hydrolyses at the same rate under the same conditions.

$$Ph_2C(SCH_2CH_2OH)_2 \xrightarrow{Ag^+/H_2O} Ph_2C\begin{matrix}O\\ \diagup\\ \diagdown\\ S\end{matrix} + AgS(CH_2)_2OH + H_3O^+ \qquad (35)$$

(31)

The promoted cyclization is first order in $[Ag^+]$ when $[Ag^+] \lesssim 0.03$ M, and independent of $[H_3O^+]$. It may occur *via* very rapid 1:1 adduct formation with $K_1 \simeq 10$ and a cyclization rate constant of *ca.* 100 s^{-1} at 25 °C. Alternatively, metal ion transfer to S may be concerted with intramolecular attack. That such a mechanism is not entirely fanciful is perhaps supported by the behaviour[39,61] of Hg^{II} and Tl^{3+} ions with the diethyl acetals (43) and (45, R = H). Whereas with Ag^+ we find[47] (43) more reactive than (45), and an *A*1 mechanism, with Tl^{3+} and Hg^{II} the reactions are relatively very fast but (45) is much more reactive than (43). (With Hg^{2+} ions chloride or other anions must be added to decelerate the reactions into the stopped-flow range.) A simple first-order dependence on $[Tl^{3+}]$ is found for (43) and it seems possible these reactions could be metal ion analogues of equation 3.

Acetal (46) reacts[39] with Tl^{3+} rather as it does with Ag^+ (p. 78): the 1:1-adduct (51) forms stoicheiometrically, loses a carboxyl proton (52), and can add a further thallium ion (53). The mechanism, equations (36)—(41), is a more elaborate version of that found with cyclic O,S-acetals (p. 73). The adducts, especially (52), are probably chelated.[39]

$$[Tl(H_2O)_n]^{3+} + H_2O \rightleftharpoons [Tl(OH)(H_2O)_{n-1}]^{2+} + H_3O^+ \qquad \text{Fast (36)}$$

$$[Tl(H_2O)_n]^{3+} + \text{S,S-acetal} \rightleftharpoons \underset{(51)}{[(H_2O)_{n-1}Tl{\leftarrow}\text{S,S-acetal}]^{3+}} \qquad \text{Fast (37)}$$

$$(51) + H_2O \rightleftharpoons \underset{(52)}{[(H_2O)_{n-1}Tl{\leftarrow}\text{S,S-acetal-O}^-]^{2+}} + H_3O^+ \qquad \text{Fast (38)}$$

$$(52) + [Tl(OH)(H_2O)_{n-1}]^{2+} \rightleftharpoons \underset{(53)}{[2Tl{:}1\text{-S,S-acetal}]^{4+}} \qquad \text{Fast (39)}$$

$$(51) \xrightarrow{H_2O} \text{products} \qquad \text{Slow (40)}$$

$$(53) \xrightarrow{H_2O} \text{products} \qquad \text{Slow (41)}$$

Finally, acetal (47) does not undergo a rapid initial Tl^{3+}-promoted cyclization to the oxathiolan (31) as it does with Ag^+. A direct hydrolysis to benzophenone is observed,[39] which is faster than the hydrolysis of (31) under the same conditions. The mechanism involves equations (36)—(38) and (40). The chelation in adducts (51) and (52) prevents the cyclization.

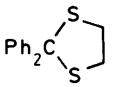
[61] D. Penn and D. P. N. Satchell, unpublished results.

Table 3 *Mercury*(II) *and thallium*(III) *ion-promoted hydrolyses of* (55) *and* (56)
For $\Delta S^{\ddagger}$ (J K^{-1} mol^{-1}), K_1 (l mol^{-1}) and k_1 (s^{-1}) see equations (42)—(43) and text, tp 25 °C; solvent 1% dioxane–water[46,62]

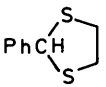
	Tl^{3+}	Hg^{2+}
(55)	K_1 290; k_1 7.0	K_1 4.3 × 10^3, k_1 0.62 $\Delta S^{\ddagger}$ −40
(56)	K_1 54.5; k_1 77 $\Delta S^{\ddagger}$ −13	K_1 3.0 × 10^4; k_1 0.20 $\Delta S^{\ddagger}$ −11

The behaviour of Tl^{3+} with various acetals indicates clearly that it forms more stable adducts with acetals containing both O and S atoms than with those containing only two S atoms.

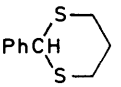
(ii) *Cyclic S,S-Acetals.* Kinetic studies exist for acetals (54)—(56). Only (54) has been used with Ag^+, (55) and (56) hydrolysing inconveniently slowly. The kinetic



(54)



(55)



(56)

pattern for (54) in aqueous dioxan[39] is similar to that found for the open-chain analogue (43). The outline mechanism is probably similar (p. 74), but the observed rate constants are *ca.* 10^4-fold smaller.

With Tl^{3+} (43) and (54) also display similar kinetic patterns (first order in $[Tl^{3+}]$, independent of $[H_3O^+]$, strongly dependent on ionic strength), but the open-chain derivative is only *ca.* 50-fold the more reactive.[39] Compared with Ag^+, Tl^{3+} is a relatively better promoter for the cyclic (*ca.* 10^4-fold) than for the open-chain S,S-acetal (*ca.* 10^2-fold). The mechanistic interpretation is uncertain.

In 1% dioxan–water as solvent both (55) and (56) show evidence of saturation effects arising form simple 1:1-adduct formation using either Hg^{2+} or Tl^{3+} as promoting ion.[46,62] The outline mechanism appears to be equations (42)—(43) in which M^{n+} represents Hg^{2+} or Tl^{3+}. Values of k_1,K_1, and some activation parameters are in Table 3. The $\Delta S^{\ddagger}$ values were obtained under conditions (high $[M^{n+}]$) where k_1 dominates k_{obs} (*cf.* equation 34).

$$M^{n+} + \text{S,S-acetal} \rightleftharpoons M^{n+}\leftarrow\text{S,S-acetal} \qquad \text{Fast, } K_1 \text{ (42)}$$

$$M^{n+}\leftarrow\text{S,S-acetal} + xH_2O \longrightarrow \text{Products} \qquad \text{Slow, } k_1 \text{ (43)}$$

The results are more compatible with an *A*2 mechanism than with an *A*1 analogue, in keeping with conclusions drawn earlier in this Review. Overall (55) and (56) display similar reactivity towards Hg^{2+} and Tl^{3+}. Thus (55) and (56) are less basic towards Tl^{3+} than towards Hg^{2+}, but both Tl^{3+}-adducts react

[62] D P N Satchell and R S Satchell, *J Chem Soc*, *Perkin Trans 2*, 1987, 513

more rapidly than do those of Hg^{2+}. There are, however, interesting differences of detail: (56) is less basic than (55) towards Tl^{3+} whereas the reverse is true towards Hg^{2+}, and the Tl^{3+} adduct of (56) is more reactive than that of (55), whereas the reverse is true of the corresponding Hg^{2+} adducts. Conformational studies of dithianes and dithiolanes[33] suggest the geometry in the vicinity of the S-atoms is similar in the two types of compound. Nevertheless the subtle differences in reactivity noted above show that the (unknown) conformations of the adducts affect to some extent k_1 and K_1. The effects of added Cl^- ions on these Hg^{2+}-promoted reactions are similar to those found for (25) rather than those for (20) and (31).

Much remains to be learnt about thioacetal hydrolyses but the past 10 years have revealed intriguing effects, and laid important foundations.