The reaction of aspirin with base

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**Abstract**

Aspirin anion appears to exist only fleetingly, rearranging via acetyl transfer to the ortho carboxylate group, as indicated by IR, UV and NMR. The resulting mixed anhydride cyclises to the more stable bicyclic orthoacetate isomer, a process facilitated by time and increasing pH. Mechanistic possibilities are discussed to explain these intriguing observations.

In the neutral pH range, and in the high field region, only a singlet resonance was observed at δ 2.36. Interestingly, this was accompanied by a second, minor singlet at δ 1.76, at pH ~ 8.0. The δ 1.76 peak also intensified with increasing pH, reaching a maximum ratio of 1.0:8 at pH ~ 12. (Overnight at pH 8.0, the δ 2.36 peak disappeared leaving behind only the peak at δ 1.76.) There was also insignificant hydrolysis (if any), as 1b could be recovered in 80% yield upon acidification of the mixture at pH 8.0 after 12 h. NMR also did not indicate the formation of acetic acid. These changes in the high field region were accompanied by changes in the aromatic region.

The pK_a of aspirin is 3.5, so it would be practically completely deprotonated at neutral pH. This indeed seemed to indicate that the peak at δ 2.36 was due to the α-acetyl methyl group of the aspirin anion (2). Also, this apparently cyclised at high pH to hemi-ortho ester anion 3a, the peak at δ 1.76 being attributed to the quaternary methyl group in 3a. (The C-Me group in orthoacetates resonates ~ δ 1.45-1.50 and the downfield shift in 3a may be attributed to the electron-withdrawing C=O group.)

The protonation of 3a would lead to its conjugate acid 3b, although the position of equilibrium is unclear. Analogous hemi-ortho acids are believed to possess pK_a ~ 11.0 which possibly indicates the predominance of 3b at most pH values employed herein. In any case, 1H NMR did not indicate an equilibrium mixture, with no variation in chemical shifts with pH; this, again, indicates the presence of 3b rather than 3a.

The above—apparently straightforward—explanation, however, does not account for the intensification of the δ 1.76 resonance, with both time and increasing pH. An alternative explanation would be that the resonance at δ 2.36 is due not to carboxylate anion 2, but to some other species that interconverts with 3b at basic pH.

An intriguing possibility is that aspirin anion (2) initially forms the mixed anhydride 4a (possibly the source of the δ 2.36 resonance). On this basis 2 has only a fleeting existence. Also, the relatively high pK_a of the phenolic hydroxyl group in 4a (~9) ensures

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that it is deprotonated substantially only at relatively high pH. The resulting anion (5) would then cyclise via 3a to 3b. Also, the disappearance of the δ 2.36 peak in the NMR overnight (vide supra) indicates a considerable barrier to the cyclisation of 5 to 3a. But intriguingly, the initial rapid formation of 4a prior to its slow but almost complete cyclisation to 3b, begs the question why—or how—4a was formed at all? (Thus, 4a could not have been formed via the more stable 3b, it would seem.) However, there are two possible explanations for this apparent anomaly, as follows. Firstly, the formation of anhydride 4a from anion 2 may not be mediated by 3a at all: this indicates a preferred intermolecular pathway. Although intramolecular routes are generally preferred, it is possible that, because of steric congestion at the ortho-disubstituted site in 2, the O-acetyl group adopts an unfavourable conformation for its internal transfer (i.e. pointing away from the carboxylate).

Alternatively, it is possible that protonation of 3a to 3b is slower than collapse to 5 and 4a. Although proton transfer is generally

Figure 1. Scanned images (relevant parts) of the 400 MHz 1H NMR spectra of aspirin (1b) in D2O under the following conditions (13C: vide infra): (a) 1b; (b) 1b at pH 8.3 (< 10 min.); (c) 1b at pH 8.3 (12 h); (d) 1b at pH 11.8 (< 10 min.). The O-acetyl Me signal (δ 2.36, originally from 1b, but from 4a in the other cases) is marked 'x', and the evolving orthoester (3b) Me signal (δ 1.76) is marked with an asterisk. (Solvent related peaks and integration markings have generally been elided; the horizontal axes represent δ values relative to sodium dimethylsilapentanesulfonate (DSS); Me singlet peaks are generally truncated.)

Base studies. Aspirin was admixed with Na2CO3 in D2O (at 25 °C) in the molar ratios [1b:base (pH)]: 1:1 (8.32), 1:3 (9.45), 1:6 (10.63), 1:10 (11.78); pH was measured with indicator paper, and cross-checked in H2O with a pH meter. The NMR’s were run within 10 minutes upon basification, and again after 12 h (Fig. 1c); acidification of this mixture led to the recovery of 1b in 80% yield, indicating negligible hydrolysis (if any). (Fig. 1a)

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faster than C–C cleavage, both steric and electronic factors may facilitate this exception: the \( pK_a \) (~11, vide supra) of 3a indicates only moderate basicity, and the quaternary orthoester centre is also congested.

The results so far do not allow a distinction between these two alternatives. However, they do indicate the following order of thermodynamic stability: 3b-4a\( \rightarrow \) 2. The observations also indicate considerable kinetic control over the proportion of 3b to 4a, a fast (possibly intermolecular) route leading to 4a, which cyclises slowly over time to 3b.

In fact, the formation of 4a is not unprecedented. Kinetic studies on several analogs of 4a have been reported, and indicate (pseudo first order) \( t_{1/2} \sim 10^2 \) s in dioxane-H\( _2\)O.\(^{11}\) The equilibrium formation of 4a had also been suspected earlier, on the basis of the marked acetylation ability of 1b in pyridine solution.\(^{12}\)

The predominance of the mixed anhydride 4a (over 2), however, remains intriguing, as anhydrides are generally highly reactive and unstable towards nucleophiles. Clearly, the rearrangement of a carboxylic ester to an apparently more stable carboxylic anhydride calls for explanation. There are two possible reasons for this observation. (Note that the slow formation of 3a, followed by its rapid breakdown via 4a, constitutes the purported nucleophilic catalysis mechanism of aspirin hydrolysis.\(^{4,6}\))

Firstly, carboxylate 2 is a charged species. Indeed, ionic bonds are generally more thermodynamically stable than covalent ones, and carboxylate anions are well-solvated in water. However, these effects may well be counterbalanced by repulsions between the negatively-charged carboxylate group and the lone pairs on the oxygen atoms of the ortho acetyl group in 2 (noting, again, the congested ortho disubstituted environment).

Secondly, anhydride 4a would be stabilised by resonance-assisted hydrogen bonding as indicated in 6. Similar interactions are known to exist in salicyl aldehyde (and tautomers of \( \beta \) dicarboxyl compounds in general).\(^{13}\)

In fact, the formation of anhydride 4a is also indicated by IR spectroscopy (Fig. 2). When chloroform solutions of 1b are treated with increasing amounts of pyridine, the original twin C=O peaks at 1754 cm\(^{-1}\) (acetyl) and 1692 cm\(^{-1}\) (CO\( \text{H} \)) are almost completely replaced by equally intense peaks at 1767 cm\(^{-1}\) and 1713 cm\(^{-1}\) [Fig. 2(a)–(c)]. The effect is clearly discernible with two molar equivalents of pyridine. The twin bands observed are characteristic of carboxylic anhydrides,\(^{14}\) and hence may be attributed to 4a. For comparison, the O-methyl ether 4b was prepared from o-anisic acid 1c, and apparently possessed analogous spectral characteristics to 4a [Fig. 2(d)]. (The lower C=O IR values of 4a presumably indicate chelation, cf. 6; this is also indicated by an upfield shift of ~6 ppm for the \( ^{13}\)C resonance of the acetyl CO group occurring at \( \delta \) 157.22.)\(^{14}\)

The implications of these observations for the mechanism of aspirin hydrolysis are interesting. Fersht and Kirby established the mechanism as mechanistic general base catalysis, essentially on the basis that the mixed anhydride 4a is unreactive (thus ruling out intramolecular nucleophilic catalysis).\(^{6}\) Therefore, the formation of 4a would represent a reversible \textit{cul de sac}, the hydrolysis occurring via 2 that is present in equilibrium concentrations.

It is noteworthy, however, that the second acceleration of the hydrolysis reaction beyond pH 10 has apparently not been explained.\(^{4,5}\) Interestingly, this may now be attributed to attack of hydroxide ion on the lactone carbonyl group in 3a (cf. 7, which indicates overall bond changing, final products being salicylate and acetate); or, for that matter, the attack of hydroxide ion on 5.

In conclusion, the reaction of aspirin with base appears to lead to complex changes, essentially involving the rearrangement of the anion to the mixed anhydride and its hemiortho ester isomer (3b). The changes are pH-dependent with 3b predominating at high pH. All these are indicated by appropriate changes in the IR and NMR spectra, and these conclusions also explain certain UV spectral changes observed by previous workers.

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References and notes

7. Experimental procedures. Aspirin (1b) was prepared by acetylation of salicylic acid,\(^{6}\) purified by recrystallisation and characterised by IR, NMR and mp (132–136 °C, lit.\(^{26}\) 128–135 °C). O-Me ether 4b. A mixture of o-anisic acid (0.152 g, 1.0 mmol) and NaH (0.024 g, 1.00 mmol) in dry THF (5 ml) was stirred until dry N\(_2\) for 0.5 h at 0 °C. The NaH was calculated as a 60% suspension in mineral oil, and was pre-washed with dry pentane). The mixture was treated dropwise with acetyl chloride (0.085 ml, 0.949 g, 1.2 mmol) in dry ether (5.0 ml) and stirred for 2.0 h. The mixture was diluted with ether (10 ml) and washed with NaHCO\(_3\) solution (5 ml), followed by ice-cool water (5 ml). The organics were dried briefly (Na\(_2\)SO\(_4\)), and volatiles removed in vacuo at <30 °C. The resulting yellow semi-solid (0.151 g, 0.78 mmol, 78%) was identified spectroscopically at 4b: \( v_{\text{max}} \) (neat) 2959 (w), 2842 (w), 1780 (s), 1733 (s), 1601 (s), 1579 (s), 1490 (s), 1466 (m), 1438 (m), 1370 (w), 1018 (s) cm\(^{-1}\); \( \delta_H \) (CDCl\(_3\)) 7.88 (m, 1 H, ArH), 7.5 (m, 1 H, ArH), 7.01 (m, 2 H, ArH); 3.92 (s, 3 H, MeO–); 2.32 (s, 3 H, –CO–Me); \( \delta_C \) (CDCl\(_3\)) 166.99 (ArC=O), 161.50 (MeC=O), 159.85 (MeO-C=O), 135.53 (C=O).
132.95 (C₃H₅), 120.40 (C₆H₆), 112.09 (C₆H₅), 55.94 (OCH₃), 21.97 (–CO–Me) (one C₆H₅ could not be clearly identified); HRMS (C.I.): m/z 195.0670 (M+H⁺, Calcd for C₁₀H₁₁O₄ 195.0657).


