Tetrahedron Letters 52 (2011) 3561–3564

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

The reaction of aspirin with base

Sosale Chandrasekhar *, Honnaiah Vijay Kumar

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India

ARTICLE INFO

Article history:
Received 3 February 2011
Revised 20 April 2011
Accepted 24 April 2011
Available online 30 April 2011

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.

Acetylsalicylic acid (**1b**, Scheme 1) is an over-the-counter pharmaceutical that has acquired the status of a household remedy, its generic term 'aspirin' having passed into common parlance.[1] Its well-known analgesic effect has now been supplemented by the recognition of its anti-coagulant and anti-inflammatory properties. The simplicity of its molecular structure, however, belies the rather complex mechanisms mediating its chemical reactivity and pharmacological action.[2,3]

A chemical reaction of particular relevance to aspirin's stability in biological fluids is hydrolysis. Early work by Edwards,[4] later extended by Garrett,[5] indicated that aspirin was unstable in nearly all pH regions, the pH-rate profile being characterised by a minimum at pH ~ 2.2 and a broad plateau region at pH ~ 5–10. An initial mechanistic proposal based on intramolecular nucleophilic catalysis by carboxylate was later overturned by the extensive work of Fersht and Kirby,[6a] in favour of mechanistic general base catalysis. It is noteworthy, however, that the balance between the two alternatives is a subtle one: the former mechanism, which is perhaps 'deceptively obvious' in the case of the parent aspirin, is actually preferred in the 3,5-dinitro derivative.[6b]

Furthermore, aspirin hydrolysis has been studied by UV spectroscopy, but it is particularly intriguing that the deprotonation of aspirin is accompanied by a decrease in absorption intensity.[4] Salicylic acid (**1a**) itself displays a high intensity short wavelength band (236 nm) and a low intensity long wavelength band (302 nm); upon deprotonation, both these suffer marginal hypsochromic shifts and lowering in intensity. In the case of aspirin, however, increasing pH leads to a gradual weakening of the long wavelength band at 275 nm, with its near disappearance at pH ~ 5.

The difference in the behaviour of salicylic acid and aspirin towards base is indeed striking. In order to gain further insight, we have studied the changes in the ^{1}H NMR spectrum of aspirin in D_2O at various pH values, as described below (Fig. 1).[7,8]

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.[4–6] This indeed seemed to indicate that the peak at δ 2.36 was due to the *O*-acetyl methyl group of the aspirin anion (**2**). Also, this apparently cyclised at high pH to hemiortho 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,[9] and the downfield shift in **3a** may be attributed to the electron-withdrawing C=O group.)

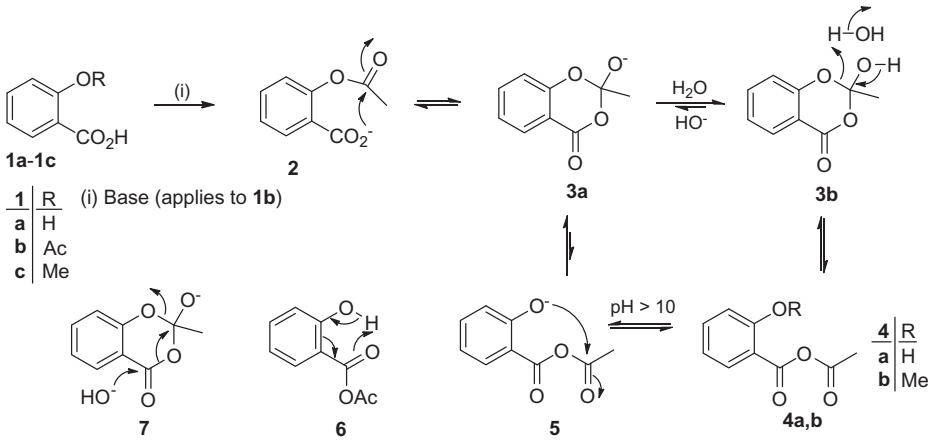
The protonation of **3a** would lead to its conjugate acid **3b**, although the position of equilibrium is unclear. Analogous hemiortho acids are believed to possess pK_a ~ 11,[10a] which possibly indicates the predominance of **3b** at most pH values employed herein. In any case, ^{1}H NMR did not indicate 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

* Corresponding author. Tel.: +91 80 22932689; fax: +91 80 23600529.
E-mail address: sosale@orgchem.iisc.ernet.in (S. Chandrasekhar).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.04.096



Scheme 1. Consequences of deprotonating aspirin **1b**, the mixture essentially consisting of the mixed anhydride **4a** at moderate pH, with increasing amounts of orthoester **3b** at higher pH; also, **3b** apparently predominates overwhelmingly at equilibrium, and a parallel intermolecular route between **2** and **4a** appears likely.

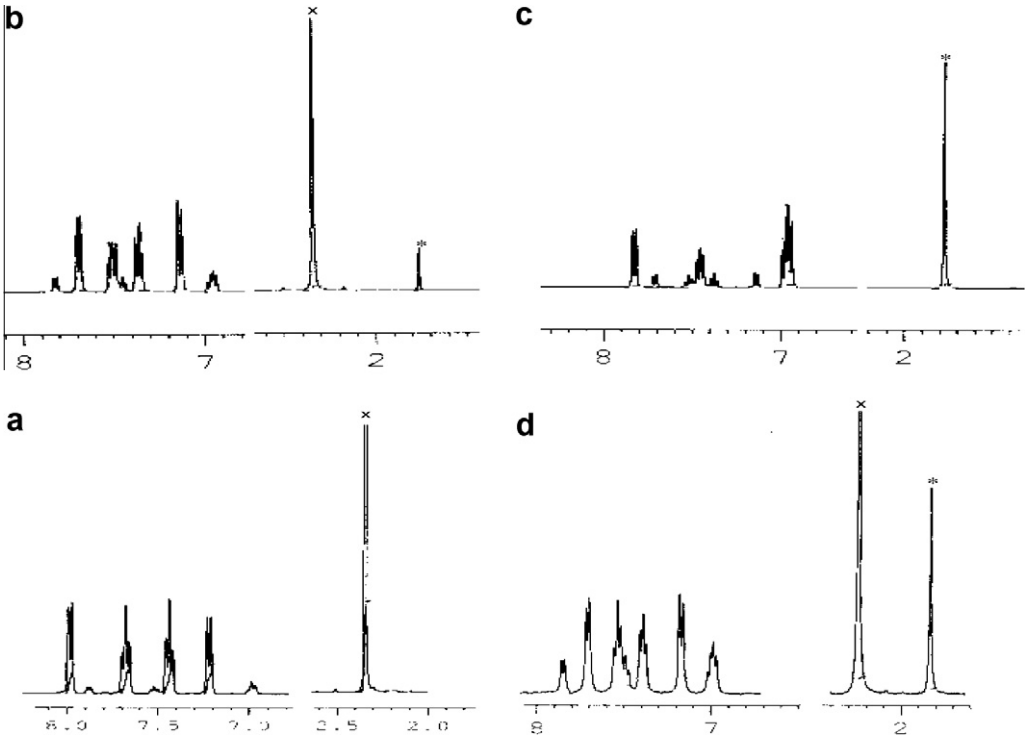


Figure 1. Scanned images (relevant parts) of the 400 MHz ^{1}H NMR spectra of aspirin (**1b**) in D_2O under the following conditions (^{13}C: *vide infra*): (a) **1b;** (b) **1b** at pH 8.3 (< 10 min.); (c) **1b** at pH 8.3 (12 h); (d) **1b** at pH 11.8 (< 10 min.). The *O*-acetyl Me signal (δ 2.36, 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 Na_2CO_3 in D_2O (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 H_2O 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) δ_C ($CDCl_3$) 169.95 (Ar*C*=O), 169.77 (Me*C*=O), 151.19 (O-C_{Ar}), 134.87 (C_{Ar}), 132.48 (C_{Ar}), 126.15 (C_{Ar}), 123.96 (C_{Ar}), 122.15 (C_{Ar}), 20.99 (C_{Me}). (Fig. 1b; presumed to be largely **4a**): δ_C (D_2O) 173.14 (Ar*C*=O), 157.22 (Me*C*=O), 133.93 (C_{Ar}), 132.31 (C_{Ar}), 129.16 (C_{Ar}), 125.09 (C_{Ar}), 122.08 (C_{Ar}), 118.98 (C_{Ar}), 23.32 (C_{Me}). (Fig. 1c; presumed to be essentially **3b**): δ_C (D_2O) 176.20 (*C*=O), 162.24 (O-C_{Ar}), 136.71 (C_{Ar}), 133.98 (C_{Ar}), 133.18 (C_{Ar}), 122.10 (C_{Ar}), 120.69 (C_{Ar}), 119.01 ($C_{orthoester}$), 26.11 (C_{Me}).

that it is deprotonated substantially only at relatively high pH.[10b] 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

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**>**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) $t_{1/2} \sim 10^3$ s in dioxane-H_2O.[11] The equilibrium formation of **4a** had also been suspected earlier, on the basis of the marked acetylating 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 countervailed 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 β dicarbonyl 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_2H) 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 occuring at δ 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 *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 bonding changes, 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.

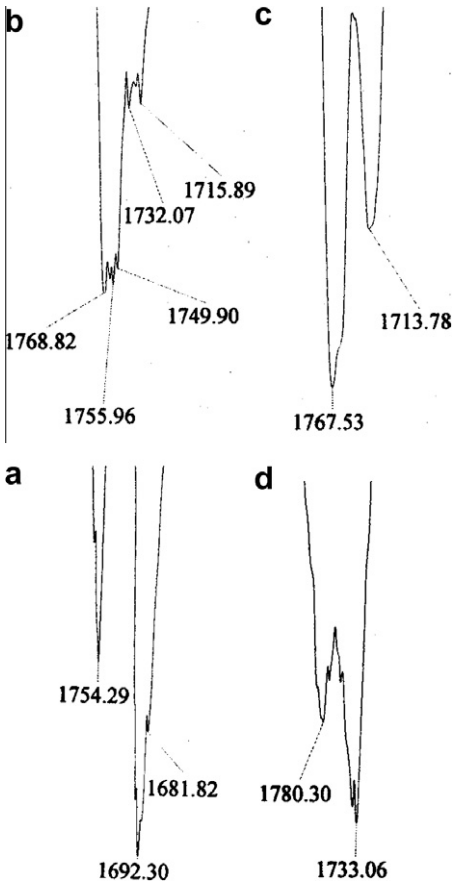


Figure 2. Scanned images of C=O IR bands in $CHCl_3$. **1b** with pyridine: (a) 1:0; (b) 1:1; (c) 1:2; **4b** only: (d).

Acknowledgements

We thank University Grants Commission (New Delhi) for a D. S. Kothari postdoctoral fellowship to H.V.K. We also remain grateful to a referee for several constructive suggestions which led to a vastly improved manuscript.

References and notes

1. *The Merck Index*, 13th ed.; O'Neil, M. J., Ed.; Merck: Whitehouse Station, NJ, 2001; # 856, pp 145–146.
2. Botting, R. M. *Pharmacol. Rep.* **2010**, *62*, 518–525.
3. Vane, J. R.; Botting, R. M. *Thromb. Res.* **2003**, *110*, 255–258.
4. Edwards, L. J. *Trans. Faraday Soc.* **1950**, 723–735.
5. Garrett, E. R. *J. Org. Chem.* **1961**, *26*, 3660–3663. and references cited therein.
6. (a) Fersht, A. R.; Kirby, A. J. *J. Am. Chem. Soc.* **1967**, *89*, 4857–4863; (b) Fersht, A. R.; Kirby, A. J. *Ibid* **1968**, *90*, 5826–5832.
7. *Experimental procedures.* Aspirin (**1b**) was prepared by acetylation of salicylic acid,[8] purified by recrystallisation and characterised by IR, NMR and mp (132–136 °C; lit.[8] 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 (10 ml) was stirred under 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, 0.094 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_2SO_4), and volatiles removed in vacuo at <30 °C; the resulting yellow semi-solid (0.151 g, 0.78 mmol, 78%) was identified spectroscopically as **4b**; ν_{max} (neat) 2947 (w), 2842 (w), 1780 (s), 1733 (s), 1601 (s) 1580 (m), 1490 (s), 1466 (m), 1438 (m), 1370 (w), 1018 (s) cm^{-1}; δ_H ($CDCl_3$) 7.88 (m, 1 H, Ar*H*), 7.56 (m, 1 H, Ar*H*), 7.01 (m, 2 H, Ar*H*), 3.92 (s, 3 H, O*Me*), 2.32 (s, 3 H, –CO–*Me*); δ_C ($CDCl_3$) 166.99 (Ar*C*=O), 161.50 (Me*C*=O), 159.85 (MeO-C_{Ar}), 135.53 (C_{Ar}),

132.95 (C_{Ar}), 120.40 (C_{Ar}), 112.09 (C_{Ar}), 55.94 (O*Me*), 21.97 (–CO–*Me*) (one C_{Ar} could not be clearly identified); HRMS (C.I.): *m*/*z* 195.0670 ($M+H^+$, Calcd for $C_{10}H_{11}O_4$ 195.0657).

8. Furniss, B. S.; Hannaford, A. J.; Rogers, V.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 4th ed.; Longman: Harlow, 1986; pp 831–832.
9. Pouchert, C. J. In *The Aldrich Library of NMR Spectra, 2nd ed.*; Aldrich Chemical: Milwaukee (WI), 1983; Vol. 1, pp 185–186.
10. (a) Chandrasekhar, S.; Karri, P. *Tetrahedron Lett.* **2006**, *47*, 2249–2251; (b) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 6th ed.; John Wiley: Hoboken, 2007; pp 359–364.
11. Garrett, E. R. *J. Pharm. Sci.* **1962**, *51*, 113–116.
12. Davidson, D.; Auerbach, L. *J. Am. Chem. Soc.* **1953**, *75*, 5984–5986.
13. Krygowski, T. M.; Zachara-Horeglad, J. E. *Tetrahedron* **2009**, *65*, 2010–2014.
14. Kemp, W. *Organic Spectroscopy*, 3rd ed.; Macmillan: London, 1994; pp 78, 199–200.