Tetrahedron Letters 50 (2009) 3234–3236

Contents lists available at ScienceDirect

Tetrahedron Letters

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

A readily observed base-catalyzed isotopic exchange in a 2,4-dinitroalkyl benzene

Nick Backstrom, C. Ian F. Watt *

School of Chemistry, University of Manchester, Manchester, M13 9PL, UK

ARTICLE INFO

Article history:
Received 8 January 2009
Accepted 2 February 2009
Available online 7 February 2009

ABSTRACT

The behaviour of solutions of the sodium salt of 4-(2,4-dinitrophenyl)pentanoic acid in D_2O is readily monitored by ^1H NMR spectroscopy. In the presence of excess NaOD, these show exchange of hydrogen at the 3-position of the benzene ring with $k_{OD} = 1.23(0.03) \times 10^{-4}\ M^{-1}\ s^{-1}$ at 25 °C. Rates of exchange using solutions with triethylamine buffers show no dependence on buffer concentration and an estimate of the acid dissociation constant, $pK_a \approx 29.3$, of the dinitrobenzene is made. Under the conditions, there is no detectable exchange at the benzylic position.

The nitro group ($-NO_2$) occupies a special place in organic chemistry. It ranks with 'superelectrophilic' modified sulfone groupings,[1] amongst the most effective uncharged electron-withdrawing substituents. Unlike like the sulfones, however, its effects reflect distinct contributions from both resonance and induction, illustrated well by the behaviour of nitroalkanes.[2] These are sufficiently acidic ($7 < pK_a < 11$) for conjugate bases to accumulate in aqueous solution, with the anion best represented as a nitronate, sharing negative charge between the oxygen atoms of the group. Rates of deprotonation, however, are ca. 10^6 less than for normal[3] acids of comparable pK_a. This disconnection between kinetic and thermodynamic acidity, historically described as the nitroalkane anomaly, has been explained by a delayed onset of the anion-stabilizing resonance (emphasized by accompanying solvation changes) and is central to structure–reactivity relationships in proton transfers from carbon acids.[4] The acidic behaviour of nitroarenes, **1** (R, R′ = H or alkyl), is less well characterized, but also of interest since the charge on a nitroaryl anion should be associated with an orbital orthogonal to the π-array of the benzene ring and its substituents. Inductive effects will operate, but the absence of an anion-stabilizing resonance is expected to reduce the thermodynamic stability of these anions relative to alkyl cousins without a corresponding effect on their kinetic acidity, so that nitroarenes should be normal carbon acids as, for example, are chloroform[5] and alkynes.[6]

The ready decarboxylation of dinitrobenzoic acids,[7] **2**, demonstrates the accessibility of aryl anions, **3**, and an early study[8] of the action of dilute NaOD/D_2O in DMF on 1,3-dinitrobenzene gave qualitative indication that exchange at its 2-position occurred rather quickly, consistent with the localized nature of the aryl anion. Characterization of the acid–base chemistry of nitroarenes, however, is not straightforward, with the proton transfers of interest competing with nucleophilic additions,[9] electron transfers,[10] and, if benzylic hydrogens are present, alternative deprotonations,[11,12] all of which yield highly coloured resonance-stabilized anionic species such as **4** and **5** (see Fig. 1), often with line-broadened NMR spectra. Despite these complications, later experiments have generally confirmed the early qualitative conclusion[13] and rate constants have been reported for detritiation[14] of 1,3-dinitro[2-^{3}H]benzene ($k = 2.8 \times 10^{-5}\ M^{-1}\ s^{-1}$) and for dedeuteriation[15] of 1,3-dinitro[2-^{2}H]benzene ($k = 1.1 \times 10^{-5}\ M^{-1}\ s^{-1}$) by methoxide in methanol at 25 °C. Nevertheless, deprotonations, or

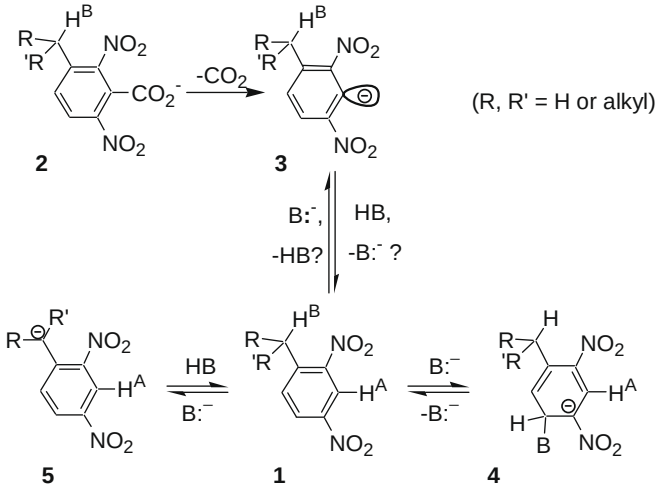

Figure 1. Some relationships in the formation and reactions of dinitroaryl anions.

* Corresponding author.
E-mail address: Ian.Watt@manchester.ac.uk (C.F. Watt).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.02.002

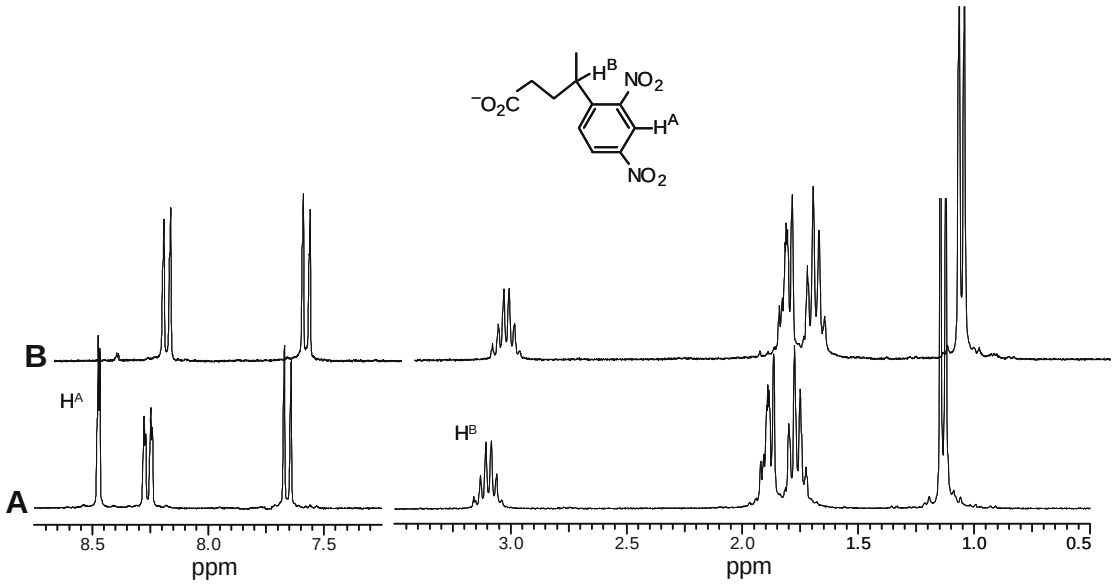

Figure 2. ^{1}H NMR spectrum of the sodium salt of **1** (R = H, R′ = CH_2CH_2COOH) in D_2O (trace **A**) and in D_2O with 0.4 M NaOD after 1 h at 50C (trace **B**).

isotopic exchange, in purely aqueous solutions have not yet been described, and we report here the remarkably uncomplicated observation by H NMR spectroscopy of deuterium exchange in a water-soluble 2,4-dinitroalkyl benzene and measurement of rate constants for the process.

Nitration of 4-phenylpentanoic acid[16] yields 4-(2,4-dinitrophenyl)pentanoic acid, **1** (R = Me. R′ = CH_2CH_2COOH),[17] and the H NMR spectrum of its sodium salt in D_2O is shown above (trace **A** in Fig. 2). Signals associated with the hydrogens at the 3-position of the benzene ring and at the benzylic position are readily identified and are labelled H^A and H^B.

The carboxylate group provides the aqueous solubility and carries the potential for intramolecular catalysis of deprotonation at H^B (but not H^A) via a 6-centre cyclic array. Effective molarities for closely similar intramolecular deprotonations of nitroalkanes,[18,19] however, are low and the salt solutions, a light straw colour, do not show any indication of exchange over many days at T = 50 °C. Addition of NaOD (up to 0.5 M) does not induce noticeable colour change and spectra remain sharp, but the signal associated with H^A decreases and disappears completely (see trace **B** in Fig. 2). The decay is first order, and monitoring of solutions which were 0.223 and 0.493 M in NaOD at 25 °C (see Fig. 3) yielded $k_{exc} = 2.56 \times 10^{-5}$ and 6.07×10^{-5} s^{-1}, respectively, so that the second rate constant for catalysis by DO^- is $k_{OD} = 1.23(\pm 0.03) \times 10^{-4}$ M^{-1} s^{-1}. After allowance for primary isotope effects, and differing conditions, this value is not inconsistent with the measurements cited earlier for 1,3-dinitrobenzene itself. No other changes in the spectrum are observed (apart from loss of a small splitting in the other two aromatic signals). Material recovered after acidification is chromatographically indistinguishable from reactant and mass spectrometry (−ve electrospray) confirms introduction of a single deuteron.

We know of no estimate for the pK_a of 1,3-dinitrobenzene or of alkylated derivatives but if this salt is indeed a normal carbon acid, then deuteration of the carbanion should be rate-limited by the reorganization of solvent around the hydrogen-bonded carbanion (see Fig. 4) to position a molecule to deliver the deuteron.[20] This has been identified with the dielectric relaxation[21] of water, $k_{reorg} \approx 10^{11}$ s^{-1}, and catalysis by buffer acids is not expected. We have observed the exchange, $k = 7.7(\pm 0.3) \times 10^{-7}$ s^{-1} at 46 °C in buffered triethylamine with $[Et_3ND^+]/[Et_3N:] = 1.3$, and can detect no dependence of rate on buffer concentration, consistent with normal acid behaviour. The pK_a of the hydrocarbon should then be related to pK_w and rate constants for deprotonation (k_{OH}) and reprotonation ($k_{H_2O} \approx 10^{11}$ s^{-1}) by the relationship:

$$pK_a = pK_w + \log(k_{H_2O}/k_{OH})$$

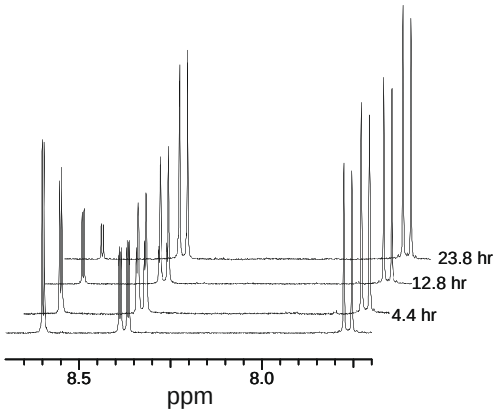

Figure 3. Evolution of the aromatic region of the NMR spectrum of a solution of **6**-Na in NaOD (0.223 M) at 25 °C.

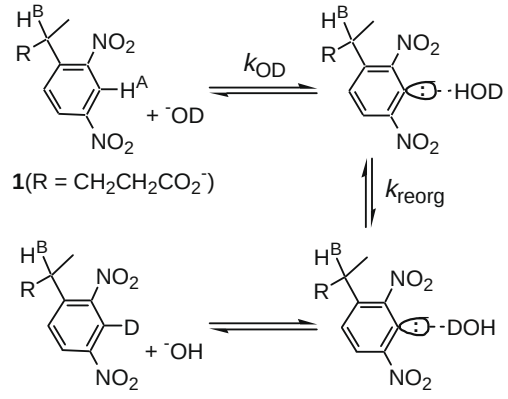

Figure 4. Isotopic exchange in **1** (R = Me, R′ = $CH_2CH_2COO^-$) via a localized hydrogen-bonded carbanion.

With correction for solvent isotope effect[22] ($k_{OH} = k_{OD}/2.4$), it is therefore possible to estimate that $pK_a = 29.3$ for deprotonation of the ring. The value might be compared with the $pK_a = 37$ for benzene deduced from electrochemical measurements on organomercurials.[23]

As noted earlier, we detect no exchange at the benzylic position (H^B) under the conditions used, and estimate $k_{H^A}/k_{H^B} > 100$. While the absence of reactivity at H^B may simply reflect a particularly unstable benzylic anion, the pK_a reported[11] for benzylic deprotonation of 2,4-dinitrotoluene is 16 (with 4-nitrotoluene some 7.5 units higher), and it seems unlikely to us that the combined steric and electronic effects of the added benzylic residues in **6** would increase the site's pK_a to greater than 29. Alternatively and more plausibly, the higher kinetic barrier is associated with the reorganization of charge, structure and solvation required for formation of the fully delocalized benzylic anion, so that the behaviour of **1** (R = Me, R′ = CH_2CH_2COOH) illustrates nicely the contrasting effects of induction and resonance in the behaviour of nitro groups as substituents and the link to normal and pseudo acidity.

Acknowledgements

We thank EPSRC (Grant No. GR/580486/01) for a studentship (to Nick Backstrom) and Dr. Andrew Regan (University of Manchester) for comment and discussion.

References and notes

1. Terrier, F.; Magnier, F.; Kizilian, E.; Wakselman, C.; Buncel, E. *J. Am. Chem. Soc.* **2005**, *127*, 5563. and references cited therein.
2. Lewis, E. S. In *The Chemistry of the Functional Groups*; Patai, S., Ed.; John Wiley and Sons, 1982. Suppl. F2, Chapter 16.
3. Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1–19.
4. Bernasconi, C. F. *Adv. Phys. Org. Chem.* **1992**, *27*, 119.
5. Margolin, Z.; Long, F. A. *J. Am. Chem. Soc.* **1973**, *95*, 2757–2762.
6. Kresge, A. J.; Lin, A. C. *J. Am. Chem. Soc.* **1975**, *97*, 6257–6258.
7. Segura, P.; Bunnett, J. F.; Villanova, L. *J. Org. Chem.* **1985**, *50*, 1041–1045.
8. Pollitt, R. J.; Saunders, B. C. *Proc. Chem. Soc. (London)* **1962**, 176.
9. Crampton, M. R.; Greenhalgh, C. *J. Chem. Soc., Perkin Trans. 2* **1986**, 187–192. and references cited therein.
10. Bacaloglu, R.; Bunton, C. A.; Cherichelli, G.; Ortage, F. *J. Am. Chem. Soc.* **1988**, *110*, 3495–3503.
11. Fogel, P.; Farrell, P. G.; Lelievre, J.; Chatrousse, A. P.; Terrier, F. *J. Chem. Soc., Perkin Trans. 2* **1985**, 71.
12. Lelievre, J.; Farrell, P. G.; Terrier, F. *J. Chem. Soc., Perkin Trans. 2* **1986**, 333.
13. Buncel, E.; Zabel, A. W. *J. Am. Chem. Soc.* **1967**, *89*, 3082–3084.
14. Crampton, M. R.; Gold, V. *J. Chem. Soc. (B)* **1966**, 498–502.
15. Bellobono, I. R.; Sela, G. *J. Chem. Soc., Perkin Trans. 2* **1972**, 169–172.
16. Brauman, J. I.; Pandell, A. J. *J. Am. Chem. Soc.* **1967**, *82*, 5421.
17. In 73% yield by reaction with 2:1 wt:wt concd H_2SO_4/concd HNO_3 at 55°C for 2 h. Recrystallization from ether/hexane yielded off-white crystals, mp 93–94 °C. δH ($CDCl_3$, 300 MHz) 1.38 (3H, d, J = 7.0), 2.05 (2H, q, J = 7.4), 2.31 (2H, complex multiplet, W = 63.3), 3.39 (1H, sextet, J = 7.0), 7.71 (1H, d, J = 8.6), 8.42, 1H, dd, J = 8.7 and 2.2), 8.58 (1H, d, J = 2.2), 11.85 (1H, br s); δC ($CDCl_3$, 75 MHz) 21.72, 31.90, 32.03, 33.63, 119.58, 126.86, 129.59, 146.13, 147.32, 150.03 and 179.27, ν_{max} /cm^{-1}, 3200 to 2780 (br) 3107, 2890, 1709, 1604, 1523, 1348, 1217 and 910; m/z (−ve ES) 205 (9.2%), 228 (5.6%), 267(M−1, 100%, found 276.0621, calcd for $C_{11}H_{12}N_2O_6$ 267.0617).
18. Backstrom, N.; Burton, N. A.; Turega, S.; Watt, C. I. F. *J. Phys. Org. Chem.* **2008**, *21*, 603–613.
19. Wilson, H.; Caldwell, J. D.; Lewis, E. S. *J. Org. Chem.* **1973**, *38*, 564.
20. Amyes, T. L.; Diver, S. T.; Richard, J. P.; Rivas, F. M.; Toth, K. *J. Am. Chem. Soc.* **2004**, *126*, 4366.
21. Kaatze, U.; Pottel, R.; Schumacher, A. *J. Chem. Phys.* **1992**, *96*, 6017.
22. Kresge, A. J.; More O'Ferrall, R. A.; Powell, M. F.. In *Isotopes in Organic Chemistry*; Buncel, E., Lee, C. C., Eds.; Elsevier: New York, 1987; Vol. 7,.
23. Butin, K. P.; Beletskaya, I. P.; Kashin, A. N.; Reutov, O. A. *J. Organomet. Chem.* **1967**, *10*, 197–210.