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Reversible cyclisation of a sulfonated arylazo compound containing an *o*-acetylamino substituent

David I. Gibson[a], John A. Parkinson[b,*], Anita C. Jones[a], Warren J. Ebenezer[c], Michael G. Hutchings[c]

[a] *School of Chemistry, The University of Edinburgh, West Mains Road, Edinburgh, EH9 3JJ, UK*
[b] *WestCHEM, Department of Pure and Applied Chemistry, The University of Strathclyde, 295 Cathedral Street, Glasgow, G1 1XL, UK*
[c] *DyStar UK Ltd, School of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL, UK*

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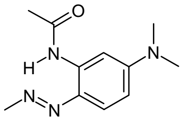
Abstract

A sulfonated *o*-acetylamino arylazo compound unexpectedly cyclised to a cationic benzo-1,2,4-triazinium species under thermal or acid conditions, reversible with base. The same substrate underwent trans to cis-azo photoisomerisation, observable by NMR spectroscopy, under steady state laser irradiation conditions.

Keywords: Arylazo; Benzo-1,2,4-triazine; Cyclisation; Photoisomerism

The *o*-acylamino arylazo substructure **1** is common amongst dyestuffs including commercialised materials, simultaneously introducing favourable coloristic properties and remaining stable under most conditions to which it is likely to be exposed.[1] In the case of a specific example of **1**, we recently encountered an uncharacteristic reaction for this substructure. Precedent was initially found only amongst two patents, although in one case the material was further published in a relatively obscure journal (vide infra). Even so, characterisation data were lacking and there was a degree of ambiguity in the structure assignment, as discussed further below. Azo dyes find application in modern technologies well beyond conventional colouration. Furthermore, exceptions to empirical reactivity generalisations are of wider interest. For both of these reasons we report here the results of our studies.

The context of our work was an investigation by a concatenated laser irradiation-NMR experiment[2] of the photoreactivity of the water-soluble azo dye **2**. This was expected to be a routine extension of previous studies, in which a consistent pattern of behaviour was established amongst relatively close structural analogues.[3] In the course of our studies, it was found that **2** unexpectedly undergoes thermal or acid-induced cyclisation to a cationic 1,2,4-triazinium species **3**, and that the cyclisation is reversible.



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The key 1D and 2D NMR assignments for the starting material **2** are summarised in Table 1.[4] Some of the proton shift assignments for **2** could be made by inspection, while others depended on a ^{1}H–^{1}H NOESY experiment. One benzenoid singlet correlated with the methoxy group and was assigned as the proton *ortho* to the azo linkage. The other benzenoid singlet correlated with the amide NH proton and is thus *ortho* to the amide and NH_2 groups. Interestingly, the amide NH also showed NOE correlation

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[*] Corresponding author. Tel.: +44 141 548 2820; fax: +44 141 548 4822.
E-mail address: john.parkinson@strath.ac.uk (J. A. Parkinson).

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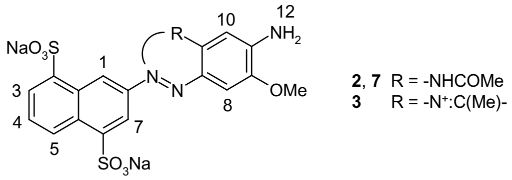
Table 1
^{1}H NMR data[a]



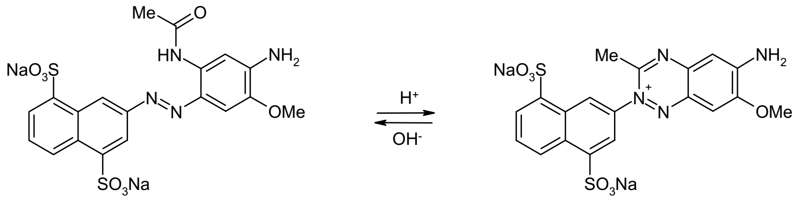
No[a]	2	3		7	
	δ[b]	δ 10 mM	Δδ 10 mM	δ[b]	Δδ
1 *(1)*	9.36	9.16	−0.20	8.70	−0.66
3 *(4)*	8.00	8.07	+0.07	7.97	−0.03
4 (5)	7.49	7.64	+0.15	7.42	−0.07
5 *(6)*	8.88	8.98	+0.10	8.82	−0.06
7 *(9)*	8.51	8.25	−0.26	7.35	−1.16
8 *(18)*	7.36	7.57	+0.21	5.79	−1.57
10 *(15)*	7.68	6.92	−0.76	7.64	−0.04
12 *(22)*	6.18	8.98, 9.59	c	5.87	−0.31
NHAc	9.97			9.93	−0.04
OMe	3.90	4.11	+0.21	2.80	−1.10
CMe	2.24	2.65	+0.41	2.22	−0.02

[a] Proton numbers refer to the arbitrary numbering scheme shown, which is consistent across **2**, **3** and **7**. Italicised numbers in brackets refer to the atom designation used for complete NMR assignment of **3** (see Supplementary data for details). Δδ values for **3** and **7** are differences with shifts of **2**.

[b] Shift data for **2** and **7** taken from the PSS mixture of an initial 0.1 mM DMSO-d_6 solution of **2** irradiated at 530 nm.

[c] ^{1}H resonances for the NH$_2$ group not observed for **2** at 10 mM concentration.

to both naphthalenic protons *ortho* to the azo group, indicating fast torsion about one or both of the arylazo C–N bonds on the NMR timescale. The NH$_2$ group of **2** showed concentration-dependent behaviour, and only appeared at low concentration (0.1 mM), as a singlet at δ >6.18 ppm. Other features of the NMR spectra suggest that **2** aggregates or at least dimerises in DMSO solution at concentrations above 0.1 mM.[5]



2 **3**

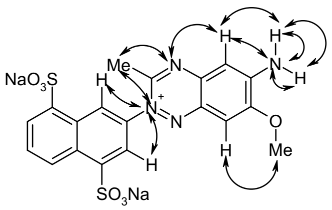
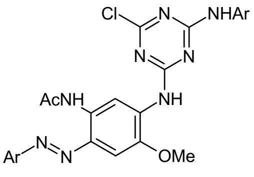


Fig. 1. Significant NMR correlations in 1,2,4-triazinium derivative **3**, determined by a combination of [^{1}H–^{1}H] NOESY, [^{1}H–^{15}N] HSQC, and [^{1}H–^{15}N] HMBC experiments.

It was initially observed that a 10 mM solution of **2** in DMSO-d_6 gradually gave rise to a second series of peaks in its ^{1}H NMR spectrum, eventually showing about 90% conversion to the new species after 15 days at ambient temperature. Warming a DMSO solution of **2** or treatment of its aqueous solution with acid led cleanly and quickly to the same new product as indicated by HPLC and NMR comparison. The new product, assigned structure **3** as discussed below, could be isolated from either reaction mixture.[4] Basification of the solutions of **3** brought about reversion of the reaction, evidenced by HPLC behaviour and regeneration of the ^{1}H NMR spectrum characteristic of **2**. The **2**⇆**3** interconversions were repeatable a number of times by a continuing sequence of alternate acidification and basification. The electrospray mass spectrum of **3** showed loss of OH with respect to **2**, and its IR spectrum revealed loss of the amide peaks. Like **2** (λ_{max} 482 nm in DMSO), the product **3** is coloured (λ_{max} 431 nm in DMSO), but unlike azo dye **2**, product **3** on a TLC plate is highly fluorescent under UV light, a property atypical of conventional arylazo structures. The gross ^{1}H NMR features present in **2** were also present in **3** apart from the loss of the amide NH resonance at δ ca.10 ppm previously present in **2**. Key 2D NMR correlations are summarised diagrammatically in Figure 1. A [^{1}H–^{15}N] HSQC NMR experiment[6] showed two peaks corresponding to labile protons each bound to a single nitrogen atom, confirming the existence of a single NH$_2$ group. This is apparently not undergoing fast torsion about the C–N bond on the NMR timescale. Further [^{1}H–^{15}N] HMBC correlations[6] confirmed that the NH$_2$ group is positioned *ortho* to a benzenoid proton, which also displayed a NOE correlation with both of the NH$_2$ protons. This benzenoid proton further correlated with another N atom over three bonds, and this in turn showed 3-bond correlation to the non-methoxy methyl group. This methyl group also showed a second three-bond correlation with yet another nitrogen atom. Finally, this nitrogen atom showed 3-bond correlations to two *meta*-coupled naphthalene doublets, proving it to be one of the former azo nitrogen atoms, a result that can only derive from the cyclised structure **3**. The relative shielding of the proton *ortho* to the NH$_2$ group in **3** (H-10, Δδ = −0.76, Table 1) is consistent with the loss of the deshielding *o*-amide carbonyl group of **2**.

Cyclisation is not general even for closely related analogues of **2**. For example, dye **4** based on a 4-*N*-halotriazinyl derivative of **2** is stable to mild acid treatment, and shows no sign of cyclisation analogous to that now being reported for **2**. The weaker donor strength of the 4-triazinylamino group of **4** compared with the NH_2 group of **2** is presumably sufficient to decrease the nucleophilicity of the conjugated azo nitrogen and thus vitiate attack by the latter at the *o*-acetylamino group. Furthermore, simply replacing the 4,8-disulfonate substituents of **2** by 3,6,8-trisulfonate gives an analogous dye, which does not cyclise under the conditions described for **2**.[4]



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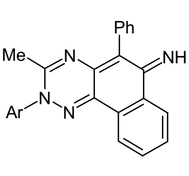

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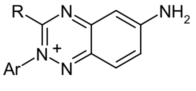
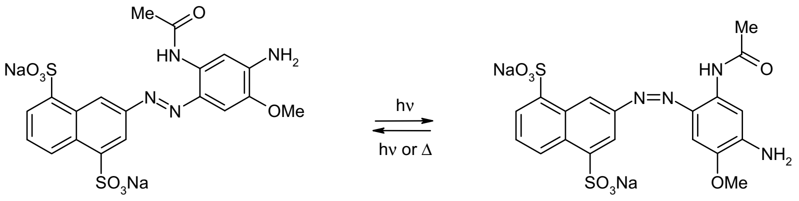


6

Cyclisation of the substructure **1** to benzo-1,2,4-triazine derivatives has only been reported sparsely. In a first patent and attendant paper,[7] it was claimed that 4-amino-naphthylazo dyes containing an appropriately positioned acetylamino group cyclise to anti-bacterial benzotriazine derivatives **5**. Here, the benzo-1,2,4-triazine heterocyclic system was shown in a neutral quinonoid form due to the deprotonation of the appended NH_2 group. Furthermore, it was reported that simpler examples of **1** did not undergo the same ring closure. In a second patent,[8] it was reported that non-sulfonated *o*-NHCOR arylazo dyes in various acidic or electrophilic solvents cyclised to cationic 1,2,4-triazinium products **6**, which could be isolated as coloured salts by the addition of appropriate counter anions, and which were claimed to be of use as dyes for polyacrylonitrile. Although both these patents provide precedent for the reaction now being reported for **2**, in neither case was the characterisation of the new 1,2,4-benzotriazine-based heterocyclic system reported in the published patent specification. Moreover, our evidence indicates that the NH_2 substituent of **3** does not undergo deprotonation to give imine as suggested for **5**, at least under our conditions, and that the 2-arylated 1,2,4-triazine heterocycle bears a formal positive charge analogous to **6**. None of the prior literature reported ready base-induced reversibility of the cyclisation.

The technique underpinning our photochemical studies uses a coupled laser irradiation-NMR experiment.[2] In this, a solution of a chromophore of interest in a conventional NMR sample tube in the cavity of an NMR spectrometer is photo-excited with continuous laser irradiation delivered to the sample by means of an optical fibre. Various NMR experiments are then applied to an analysis of any new, sometimes metastable, species generated. Moreover, the kinetics of the various reaction pathways can be analysed quantitatively both under conditions of irradiation as well as when the laser source is switched off. The photoisomerism of trans-arylazo dyes and the photo and thermal reversion of the cis-isomer thus generated have been of particular interest.[9] Under these conditions, the benzotriazinium species **3** is stable to irradiation in DMSO-d_6. In contrast, its trans-azo precursor **2** undergoes the expected trans to cis-azo photoisomerisation to **7** in DMSO-d_6 when irradiated at 530 nm in a 0.1 mM solution. The photoisomerisation is photoreversible and at a concentration of 0.10 mM a photostationary state is attained comprising 49% of **2** and 51% of **7**. Removal of the laser irradiation results in thermal reverse isomerisation of **7** back to **2** (100%); thus the cis-azo species **7** is only metastable, as expected, and cannot be isolated. The ^1H NMR spectrum of **7** is related to that of **2** in a manner wholly analogous to the spectra of trans and cis isomers of sulfonated azo dyes seen in previous studies.[3] Thus, all resonances for protons in **7** are shifted to lower δ ppm compared with those for trans-isomer **2** (Table 1). Particularly, large shifts are observed for the OMe group ($\Delta\delta = -1.1$ ppm) and its *ortho*-proton ($\Delta\delta = -1.57$ ppm), as well as for the two naphthyl protons *ortho* to the azo linkage ($\Delta\delta = -1.17$ and -0.66 ppm).



2 **7**

The calculated[10] conformation for the free acid analogue[11] of **7** (Fig. 2) helps explain these shifts. The non-planar ground state conformation is presumably favoured because of energetically favourable retention of the amide NH···N(azo) interaction,[12] while minimising unfavourable non-bonded naphthyl–phenyl interactions now introduced across the cis-azo structure of **7** by torsions about the C–N(azo) bonds. Furthermore, the methyl of the OMe group is oriented away from the *o*-NH_2 group, presumably to minimise steric clash and to optimise interaction between NH and a lone electron pair on O. The

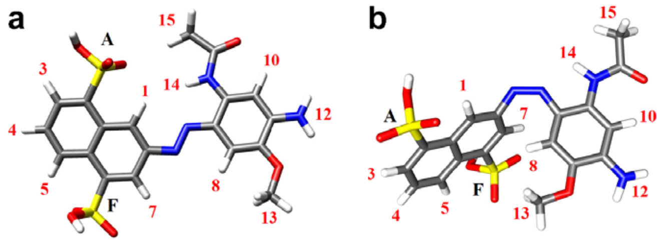


Fig. 2. Minimum energy structures for the free-acid analogues of (a) **2** and (b) **7**. DFT calculations were conducted at the B3LYP/6-31g(d,p) level.

result of these effects is that the OMe group and its *o*-CH proton sit over a shielding face of the naphthyl group. Similarly, the two protons of the naphthyl ring *ortho* to the azo group are positioned over the benzenoid ring, also resulting in shielding as reflected by the observed differences in chemical shifts (Table 1).

There is no evidence to suggest **7** undergoes cyclisation to **3** when generated under the steady state laser irradiation conditions.

Acknowledgement

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Supplementary data

Additional detailed spectroscopic data are included. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.12.081.

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4. *Experimental procedures*: Azo dye precursors were from bulk commercial samples. Other reagents were standard laboratory stock. HPLC was carried out on a HP1100 machine with diode array detection using a 25 cm BDS Hypersil C18 column, with elution by an acetonitrile–water gradient, the latter containing Bu_4NHSO_4 and K_2HPO_4 as ion pair agent. *Synthesis of 3-(2-acetylamino-4-amino-5-methoxy-phenylazo)-naphthalene-1,5-disulfonic acid disodium salt* (**2**)—3-Aminonaphthalene-1,5-disulfonic acid (87.4 g, 0.2 mol) was suspended in water (400 ml) with stirring. The pH was adjusted to 6 with 1 M sodium carbonate solution and the mixture filtered. Sodium nitrite (15.18 g, 0.22 mol) was dissolved in the filtrate, and this solution was then added dropwise to a stirred solution of hydrochloric acid (50 ml of 37% dissolved in 400 ml water) at 0–5 °C while maintaining the pH at or below 2. After 1 h, sulfamic acid (15 ml of 10% solution in water) was added to destroy the slight excess of nitrous acid. The resultant suspension of diazonium salt was added portionwise to a stirred mixture of 4-methoxy-3-aminoacetanilide in water (400 ml) at pH 4 over 20 min. After addition, the pH was adjusted to 6 and the mixture was stirred overnight at room temperature, after which the crude product was filtered off, triturated with acetone, re-filtered, and dried at 40 °C to give the product as an orange powder (101.7 g, 91%; HPLC showed a single peak; ν_{max} (KBr)/cm^{-1} 1709, 1662, 1618; λ_{max} (water)/nm 481 (23,600); $C_{19}H_{16}N_4Na_2O_8S_2{\cdot}H_2O$ requires C, 41.01; N, 10.07; found C, 40.80; N, 10.06. NMR data reported in full above). *Synthesis of 6-amino-2-(4,8-disulfo-naphthalen-2-yl)-7-methoxy-3-methyl-benzo[1,2,4]triazin-2-ium sodium salt* (**3**)—Dyebase **2** (0.245 g; 0.44 mmol) was dissolved in DMSO (5 ml) and heated to 75 °C for 1.5 h. The mixture was cooled and poured into dilute hydrochloric acid (10 ml, 2 N). On cooling in an ice bath, a precipitate formed which was filtered off, washed with cold acetone, and dried. HPLC revealed peak-to-peak conversion to a single new product, and the absence of the starting material. The product was isolated as a bright reddish-yellow powder (0.15 g; 62%; ν_{max} (KBr)/cm^{-1} 1654; electrospray MS 476 (M$^+$); λ_{max} (water)/nm 421 (15,800), 381 (16,000); $C_{19}H_{15}N_4NaO_7S_2{\cdot}3H_2O$ requires C, 41.30; N, 10.14; found C, 41.78; N, 10.02. NMR data reported in full above and in the Supplementary data). *Equilibration of* **2** *and* **3**—An aqueous solution of **3** was treated with a few drops of 2 N HCl. The bright greenish-yellow colour of **3** remained unchanged, as did its HPLC trace. Addition of 2 N NaOH solution gave a rapid bathochromic shift to a dull orange shade. HPLC confirmed that **3** had been converted into **2**. Acidification by the addition of sufficient 2 N HCl led to reversion to the bright greenish-yellow colour of **3**, again confirmed by HPLC. This process could be repeated, in all cases without the appearance of any species other than **2** and **3** in the HPLC. *Coupled NMR-laser irradiation experiments*: Procedures outlined in previous papers[2,3] for the study of azo molecules were adopted in the study of **2**. UV–vis spectroscopy was employed to decide on the most suitable irradiation wavelength through acquiring the molar absorption coefficients for the available laser lines, and calculating the possible sample concentrations from this. This was based on the constant absorption conditions described previously.[3] A 5 µl aliquot of aqueous base (Na_2CO_3, 0.1 M) was added to the sample in DMSO-d_6 prior to the irradiation studies to ensure no acid-catalysed isomer reversion. Because of this, the DMSO solutions are wet. For 1D ^{1}H NMR spectra recorded at low sample concentration, pre-saturation of the significant water signal, combined with 512 scans, was necessary to give a spectrum with sufficient signal to noise to conduct the analysis. Two-dimensional ^{1}H–^{1}H NOESY NMR experiments were recorded using a phase-sensitive pulse sequence (noesyph, Bruker). These studies were conducted at 298 K, and used a high sample concentration (10 mM, DMSO-d_6) due to the low sensitivity of the technique. HSQC and HMBC NMR techniques are reported in Supplementary data.
5. Further evidence for the aggregation of **2** in DMSO solution includes the negative signs of the off-diagonal cross-correlations in the two dimensional ^{1}H–^{1}H NOESY spectrum of **2** and an apparent intermolecular NOE between the remote protons H-10 and H-1 again from the two dimensional ^{1}H–^{1}H NOESY spectrum of **2** (see Table 1 for atom numbering scheme).
6. HSQC = heteronuclear single quantum correlation, which identifies one-bond couplings $^1J_{HC}$ Bodenhausen, G.; Ruben, D. J. *Chem. Phys. Lett.* **1980**, *69*, 185; HMBC = heteronuclear multiple bond correlation, which identifies 2 or more bond couplings $^nJ_{HC}$ ($n \geqslant 2$) Bax, A.; Summers, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 2093.
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10. DFT calculations were carried out at the B3LYP/6-31g(d,p) level using the Gaussian suite of software. Torsions around the C(aryl)–N(azo) bonds were adjusted to probe the possible minimum energy conformations. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr.,

J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian 03, Revision B.02, Gaussian, Wallingford, CT, 2004.

11. Justification for the use of free acid SO_3H in the place of sulfonate anion in the calculation of sulfonated molecule conformation has been provided elsewhere.[3]
12. Interestingly, the calculated ground state conformation of the trans isomer, **2**, also has the amide NH unit adjacent to the nearest azo N atom (Fig. 4a), and not forming a 6-ring H-bond with the more remote azo N atom (as implied in **1**). It seems that the energies of these conformations are very similar, as has been observed experimentally in the solid phase McGeorge, G.; Harris, R. K.; Chippendale, A. M.; Bullock, J. F. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1733–1738; McGeorge, G.; Harris, R. K.; Batsanov, A. S.; Churakov, A. V.; Chippendale, A. M.; Bullock, J. F.; Gan, Zhehong *J. Phys. Chem. A* **1998**, *102*, 3505–3513.