Unusual stereochemical consequences during the substitution of V-shaped diaryl derivatives

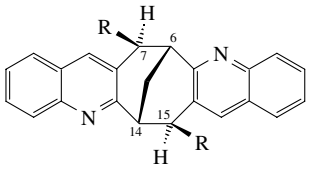
Christopher E. Marjo, Roger Bishop,* Donald C. Craig and Marcia L. Scudder

School of Chemistry, The University of New South Wales, UNSW Sydney NSW 2052, Australia.
Fax: +61 2 9385 6141; e-mail: r.bishop@unsw.edu.au

DOI: 10.1070/MC2004v014n06ABEH002002

The benzylic bromination of diquinoline derivative 1 proceeds in a regio- and stereo-selective manner to yield *exo*,*exo*-dibromide 2, whose subsequent hydrolysis to a diol product takes place with retention of configuration as demonstrated by the X-ray structure of 3·H_2O. Related V-shaped diaryl systems behave in a similar manner, and the unusual stereochemistry of these reactions is discussed and explained.

We have previously reported the preparation of diquinoline derivative **1** in 74% yield by condensation of two equivalents of 2-aminobenzaldehyde with one of bicyclo[3.3.1]nonane-2,6-dione.[1] In turn, this substance forms *exo*,*exo*-dibromide **2** (71%) on reaction with *N*-bromosuccinimide (NBS),[1] and the subsequent hydrolysis of **2** yields diol **3** as its monohydrate (90%). The unusual stereochemical outcomes of the last two reactions are the subject of this report.



1 R = H
2 R = Br
3 R = OH

The Wohl–Ziegler reaction, namely, allylic or benzylic free-radical bromination using NBS in a refluxing aprotic solvent, is a well-established synthetic organic procedure.[2] Recently, we have synthesised a series of new brominated diquinoline lattice inclusion hosts,[3,4] where the final step involved benzylic NBS bromination in refluxing CCl_4. The conversion of **1** to **2** is typical of these regio- and stereo-selective processes.

There are two benzylic sites at which reaction of **1** could occur, namely, the secondary C(7)/C(15) and the tertiary C(6)/C(14) positions. The initial free-radical hydrogen abstraction step is endothermic and, therefore, its transition state is product-like (here, radical-like).[5] An attack at C(7)/C(15) affords a *p*-orbital well-aligned with the aromatic π-system, whereas that generated at C(6)/C(14) would be nearly orthogonal and not delocalised. Hence, abstraction at the secondary benzylic site, rather than the tertiary one, is energetically favoured. Once this radical has been generated, the V-shaped molecular skeleton ensures that bromination will occur predominantly on the more exposed *exo*-face to yield **2** as the final product.

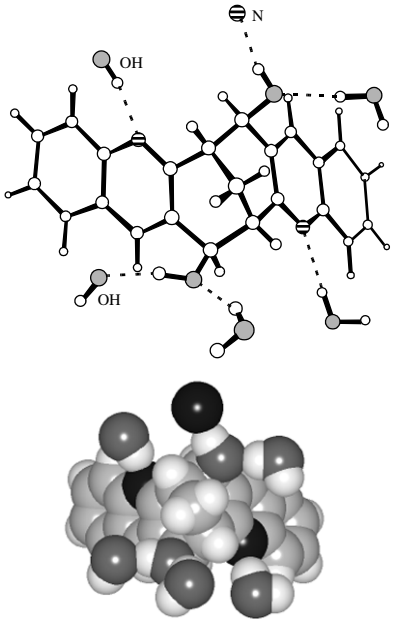


Figure 1 Crystallographically independent molecule A in the structure of 3·H_2O. Upper: ball and stick representation (N horizontally hatched, O stippled, hydrogen bonding represented by dashed lines). Lower: space filling representation (N and O dark, C medium, H light shading).

Reflux of **2** in aqueous acetone afforded a single C_2-symmetric diol product,† and X-ray structure determination‡ revealed this to be monohydrate 3·H_2O. There are two crystallographically independent molecules of diol **3** (A and B) present in the asymmetric unit, and these have different hydrogen bonded connectivities.

For molecule A (Figure 1), both nitrogen atoms accept one hydrogen bond (from a water molecule and from an alcohol group). Both hydroxy groups accept a hydrogen bond from a

† Compound **3**: dibromide **2** (629 mg, 1.31 mmol) was refluxed in 50 ml acetone–H_2O (4:1) for 20 h. Most of the acetone was evaporated under reduced pressure, then aq. NaOH (2 M, 1 ml) was added to give a white suspension, which was filtered and washed with water (3 ml). Recrystallization from aq. methanol gave fine needles of 3·H_2O (441 mg, 90%), mp 289–290 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.70 (t, 2H, *J* 2.8 Hz), 3.57 (dt, 2H, *J* 2.8 and 2.8 Hz), 4.86 (dd, 2H, *J* 2.8 and 4.9 Hz), 5.89 (d, 2H, OH, *J* 4.9 Hz), 7.46 (m, 2H), 7.67 (m, 2H), 7.78 (d, 2H, *J* 8.0 Hz), 7.95 (d, 2H, *J* 8.4 Hz), 8.07 (s, 2H). ^{13}C NMR ([$^2H_6$]DMSO) δ: 17.67 (CH_2), 44.29 (CH), 71.96 (CH), 126.19 (CH), 127.42 (C), 127.90 (CH), 128.37 (CH), 129.82 (CH), 131.21 (C), 138.8 (CH), 147.49 (C), 158.87 (C). Found (%): C, 74.08; H, 5.47; N, 7.36. Calc. for $C_{23}H_{18}N_2O_2·H_2O$ (%): C, 74.18; H, 5.41; N, 7.52.

‡ *Crystallographic data for* 3·H_2O at 294 K: $C_{23}H_{18}N_2O_2·H_2O$, monoclinic, space group $P2_1/c$, a = 12.950(1), b = 23.333(1) and c = = 12.150(1) Å, β = 90.993(4)°, V = 3670.7(4) Å^3, Z = 8, M = 572.4, d_{calc} = 1.35 g cm^{-3}, μ(CuKα) = 0.689 mm^{-1}, final R = 0.042 for 4934 independent observed reflections and 505 variables [$I/\sigma(I) > 2$].

Reflection data were measured with an Enraf-Nonius CAD-4 diffractometer in a $\theta/2\theta$ scan mode using nickel filtered copper radiation (λ = 1.5418 Å). Data were corrected for absorption. Reflections with $I > 2\sigma(I)$ were considered observed. The positions of all non-hydrogen atoms in both molecules in the asymmetric unit were readily determined by direct phasing. The positions of the water molecules and hydroxy hydrogen atoms were determined from a difference map, while all other hydrogen atoms were included in calculated positions. All hydrogen atoms were assigned thermal parameters equal to those of the atom to which they were bonded. Positional and anisotropic thermal parameters for the non-hydrogen atoms were refined using full matrix least squares. Reflection weights used were $1/\sigma^2(F_0)$, with $\sigma(F_0)$ being derived from $\sigma(I_0) = [\sigma^2(I_0) + (0.04I_0)^2]^{1/2}$. Atomic scattering factors and anomalous dispersion parameters were taken from International Tables for X-ray Crystallography.[8] Structure solution was by MULTAN80[9] and refinement used BLOCKLS, a local version of ORFLS.[10]

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 256883. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2004.

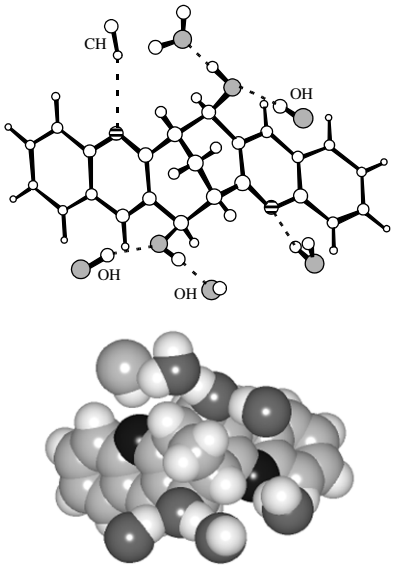


Figure 2 Similar representations of crystallographically independent molecule B in the crystal structure of the diol monohydrate.

water molecule and also donate their hydrogen atom (to a nitrogen and to an alcohol oxygen).

For molecule B (Figure 2), both nitrogen atoms accept one hydrogen bond (from a water molecule and from a C–H group[6]). Both hydroxy groups accept a hydrogen bond (from two different alcohol groups) and also donate their hydrogen atom (to a water oxygen and to an alcohol oxygen). The unit cell packing of **3**·H_2O is illustrated in Figure 3.

The *exo*,*exo*-diol configuration of the reaction product is clearly visible in Figures 1 and 2. This retention of configuration during the hydrolysis reaction of **2** into **3** is most unexpected. If the process had taken place through an S_N2 mechanism, then inversion would have resulted, and an S_N1 process should have resulted in racemisation of the stereocentres. Our explanation is that the hydrolysis does take place by the S_N1 pathway, but that the molecular V-shape creates an exposed *exo*-surface and a less accessible *endo*-surface. Hence, reaction of water with the benzylic carbenium ion intermediate affords predominantly *exo*,*exo*-diol **3**.

Similar behaviour was observed for the reaction of **2** with other poor nucleophiles, for example, alcohols, giving *exo*,*exo*-bis(ether) products. Stronger nucleophiles, however, have an alternative option in carrying out addition reactions to the pyridine ring.[7]

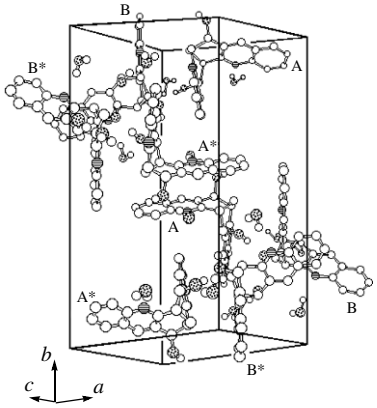


Figure 3 Relative locations of water molecules, the two independent molecules of **3** (A and B) and their enantiomers (A* and B*) in the crystal structure of **3**·H_2O.

The stereochemical outcome of the two substitution reactions does not depend on the nature of the aromatic residue, and we have observed similar behaviour using a range of V-shaped diaryl derivatives (for example, the dibenzo analogue). Although the products of the two reaction types are different from those predicted using the usual simple models, they are perfectly reasonable when the three-dimensional properties of the reagents and intermediates are also taken into account.

This work was supported by the Australian Research Council.

References

1 C. E. Marjo, M. L. Scudder, D. C. Craig and R. Bishop, *J. Chem. Soc., Perkin Trans. 2*, 1997, 2099.
2 C. Djerassi, *Chem. Rev.*, 1948, **43**, 271.
3 R. Bishop, *Chem. Soc. Rev.*, 1996, **25**, 311.
4 (*a*) A. N. M. M. Rahman, R. Bishop, D. C. Craig and M. L. Scudder, *Eur. J. Org. Chem.*, 2003, 72; (*b*) A. N. M. M. Rahman, R. Bishop, D. C. Craig and M. L. Scudder, *Org. Biomol. Chem.*, 2003, **1**, 1435; (*c*) J. Ashmore, R. Bishop, D. C. Craig and M. L. Scudder, *Mendeleev Commun.*, 2003, 144.
5 R. J. Fessendon and J. S. Fessendon, *Organic Chemistry*, Willard Grant Press, Boston, 2nd Student Edition, 1982, ch. 6, pp. 226–228.
6 G. R. Desiraju and T. Steiner, *The Weak Hydrogen Bond in Structural Chemistry and Biology*, Oxford Science Publications, Oxford, 1999.
7 C. E. Marjo, *Ph.D. thesis*, The University of New South Wales, 1996.
8 *International Tables for X-Ray Crystallography*, eds. J. A. Ibers and W. C. Hamilton, Kynoch Press, Birmingham, 1974, vol. 4.
9 P. Main, S. J. Fiske, S. E. Hull, L. Lessinger, G. Germain, J.-P. Declercq and M. M. Woolfson, *MULTAN80*, University of York, England and Louvain, Belgium, 1980.
10 W. R. Busing, K. O. Martin and H. A. Levy, *ORFLS*, Oak Ridge National Laboratory, Tennessee, USA, 1962.

Received: 30th July 2004; Com. 04/2327