Configurationally stable axially chiral *N*,*N*′-dialkyl-2,2′-biphenylene-*N*,*N*′-ureas

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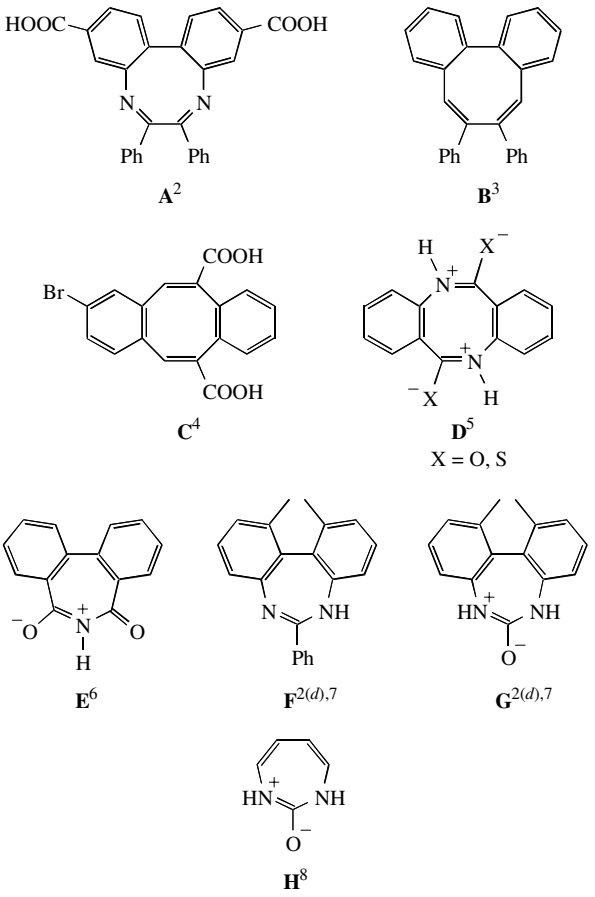
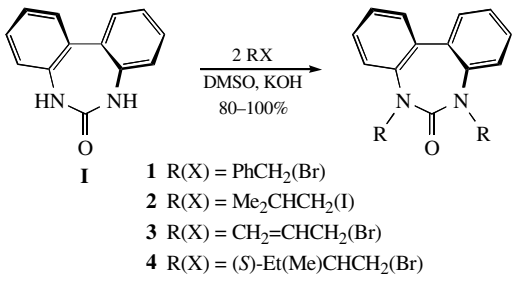
The configurational stability of compounds 1–4 has been confirmed by NMR spectroscopy and chiral chromatography (analytical separation of enantiomers 1 and 2); the antiaromatic (4*n*) destabilisation of the planar transition state of enantiomerisation is discussed.

2,2′-Disubstituted and 2,2′,6,6′-tetrasubstituted biaryls are classical stereochemical objects.[1] Of particular interest are bridging biaryls with a fragment linking the 2- and 2′-positions. For example, dibenzodiazocine **A** (Scheme 1) was obtained in an optically active form;[2] it undergoes racemisation only on heating to 268 °C, which is accompanied by decomposition (the racemisation barrier is about 36 kcal mol^{-1}).[2(c),(d)] Such a high configurational stability of compound **A** can be explained by the anti-aromatic (4*n*) destabilisation of the planar transition state of racemisation, similarly to its carbon analogue **B** (the racemisation barrier is 30 kcal mol^{-1} at 100 °C).[3] The high configurational stability is also observed in compound **C** (the racemisation barrier is about 27 kcal mol^{-1})[4] and nitrogen analogues, *viz*., dianthranilides **D** obtained in optically active forms, which exist in the boat chiral conformation (X-ray diffraction analysis).[5] Although biaryls containing a saturated three- or four-carbon 2–2′ bridge have limited configurational stability (the barriers are 12.3 and 23.2 kcal mol^{-1}, respectively),[2(a),(c),3] the enantiomerisation of diphenimide **E** occurs quickly even on the NMR time scale (the calculated barrier is 3.8 kcal mol^{-1}).[6] This can be explained by the absence of the anti-aromatic destabilisation of a planar transition state in **E**. If it is the case, this destabilisation should exist for compounds **F**, **G** and **H**. In fact, compounds **F** and **G** have been obtained in optically active forms[2(d),7] (Scheme 1). However, the configurational stability of these compounds, their 6,6′-unsubstituted analogues and compound **H**[8] has not been studied.



Scheme 1



Scheme 2

In this work, we studied *N*,*N*′-dialkyl-2,2′-biphenylene-*N*,*N*′-ureas (dibenzodihydro-1,3-diazepin-2-ones) **1**–**4**. Initial compound **I** was obtained by a reaction of 2,2′-diaminobiphenyl with urea.[2(d),9] Unlike other ureas,[10] compound **I** did not give N-derivatives in reactions with either formaldehydes or aminomethylating reagents, namely, $(Me_2N)_2CH_2$ or bis(1-morpholino)methane. However, compound **I** can be readily alkylated by an alkyl halide taken in an excess in DMSO in the presence of KOH (Scheme 2).†

The NMR spectra of compounds **1**–**4**† suggest that the chiral cyclic system is stable on the time scale of this method. The CH_2N protons display diastereotopicity, which is maintained at 90 °C for compound **1** (in this case, $\Delta\nu$ in C_5D_5N increases from 226 Hz at 20 °C to 233 Hz at 90 °C). For compound **2**, neither exchange broadening of lines nor their coalescence occurs on heating to 110 °C; conversely, a considerable increase in $\Delta\nu$ is observed for CH_2N. Methyl groups in compound **2** are also diastereotopic: in the ^{1}H NMR spectrum, $\Delta\nu$ = 64 Hz at 20 °C; it decreases to 48 Hz at 110 °C. In the ^{13}C NMR spectrum at 90 °C, $\Delta\nu$ = 15.8 Hz (at 75 MHz) for the carbon atoms of methyl groups.

According to NMR data, compound **4** obtained from an optically active alkyl halide is a 1:1 mixture of diastereomers (Figure 1), which cannot be separated by TLC or by crystallisation from ethanol or hexane.

The HPLC separation of compounds **I**, **1** and **2** on a Chiralcel OD column was studied. Compound **I** gives one peak; derivative **2** gives a split peak, whereas compound **1** gives two peaks resolved at about half-height; the retention times are 10.77 and 11.46 min (Figure 2).

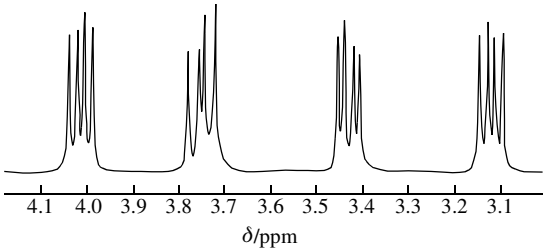


Figure 1 ^{1}H NMR spectrum of CH_2N protons in compound **4**.

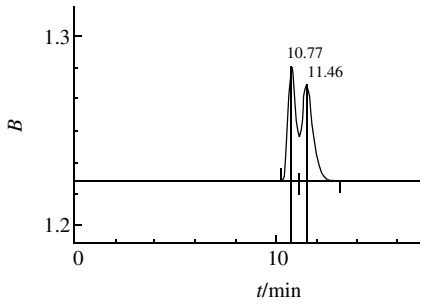


Figure 2 Chromatogram of compound **1**.

Thus, as expected, the test compounds are configurationally stable axially chiral systems.

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† ^{1}H NMR spectra were recorded on a Bruker WM-400 spectrometer (400.13 MHz); ^{13}C NMR spectra were measured on a Bruker AM-300 spectrometer (75.47 MHz) for compound **3** or on a Bruker AC-200 instrument (50.32 MHz) for compound **5**. HPLC was carried out using a Chiralcel OD column (4.6×250 mm); 10% Pr^{i}OH in hexane was an eluent (flow rate of 1 ml min^{-1}); UV detection at 254 nm was performed.

For **I**: a solution of 2,2′-diaminobiphenyl (0.77 g, 4.18 mmol) and urea (0.50 g, 8.4 mmol) in 3 ml of AcOH was refluxed for 3 h, diluted with 10 ml of propan-2-ol and cooled. The residue (bright colourless thin plates) was filtered off and dried *in vacuo*. Yield 0.63 g (72%), mp 319 °C (subl.), (lit.: mp 311–313 °C,[6] 328–330 °C[4]); after crystallisation from BuOH, mp 318–320 °C. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 7.08 (d, 2H, H-6, ^3J 8.0 Hz), 7.14 (t, 2H, H-5, ^3J 7.4 Hz), 7.29 (t, 2H, H-4, ^3J 7.6 Hz), 7.44 (d, 2H, H-3, ^3J 7.6 Hz), 8.77 (br. s, 2H, HN).

Alkylation of **I**, *general procedure*. DMSO (2 ml) and an alkyl halide (2.0 mmol) were added to a mixture of compound **I** (105 mg, 0.5 mmol) and crushed KOH (140 mg, ~2.0 mmol). The reaction mixture was stirred for 12 h. Water was added (20 ml); the amorphous precipitate was filtered off and dried *in vacuo*.

For **1**: yield 70% (cryst. from EtOH), mp 144 °C. ^{1}H NMR of CH_2N protons ($CDCl_3$, 20 °C) δ: 4.93 (m, 4H, 2CH_2N, AB spectrum, $\Delta\nu$ 200 Hz, ^2J –15.2 Hz). ^{1}H NMR of CH_2N protons ([^{2}H$_6$]DMSO, 80 °C) δ: 4.90 (m, 4H, 2CH_2N, AB spectrum, $\Delta\nu$ 148 Hz, ^2J –15.5 Hz). ^{1}H NMR of CH_2N protons (C_5D_5N, 20 °C) δ: 5.01 (m, 4H, 2CH_2N, AB spectrum, $\Delta\nu$ 226 Hz, ^2J –15.3 Hz). ^{1}H NMR of CH_2N protons (C_5D_5N, 90 °C) δ: 5.03 (m, 4H, 2CH_2N, AB spectrum, $\Delta\nu$ 233 Hz, ^2J –15.2 Hz).

For **2**: yield 85%, mp 119 °C (EtOH). ^{1}H NMR ([^{2}H$_6$]DMSO, 20 °C) δ: 0.38 (d, 6H, A-2Me, ^3J 6.6 Hz), 0.54 (d, 6H, B-2Me, ^3J 6.6 Hz), 1.46 (m, 2H, 2CH), 3.45 (m, 4H, 2CH_2N, ABX spectrum, $\Delta\nu$ 148 Hz, $^2J_{AB}$ –13.4 Hz, $^3J_{AX}$ 6.1 Hz, $^3J_{BX}$ 8.3 Hz), 7.27 (t, 2H, H-5, ^3J 7.4 Hz), 7.33 (d, 2H, H-6, ^3J 7.9 Hz), 7.41 (t, 2H, H-4, ^3J 6.9 Hz), 7.53 (d, 2H, H-3, ^3J 6.7 Hz). ^{1}H NMR of the alkyl fragment ([^{2}H$_6$]DMSO, 110 °C) δ: 0.43 (d, 6H, 2A-Me, ^3J 6.6 Hz), 0.55 (d, 6H, 2B-Me, ^3J 6.6 Hz), 1.49 (m, 2H, 2CH), 3.50 (m, 4H, 2CH_2N, ABX spectrum, $\Delta\nu$ 196 Hz, $^2J_{AB}$ –13.4 Hz, $^3J_{AX}$ 6.1 Hz, $^3J_{BX}$ 8.3 Hz). ^{13}C{^{1}H} NMR ([^{2}H$_6$]DMSO, 90 °C) δ: 19.26 (A-Me), 19.47 (B-Me), 26.51 (CH), 54.86 (CH_2), 121.47, 124.87, 127.81, 128.30 (C-3-6), 134.05 (C-1), 143.90 (C-2), 164.45 (CO).

For **3**: yield 98%, mp 170–175 °C. ^{1}H NMR ($CDCl_3$) δ: 4.35 (m, 4H, 2CH_2N, ABX spectrum, $\Delta\nu$ 152 Hz, $^2J_{AB}$ –15.9 Hz, $^3J_{AX}$ 5.9 Hz, $^3J_{BX}$ 5.1 Hz), 4.98–5.05 (m, 4H, 2H_2C=), 5.67 (m, 2H, 2-CH=), 7.21–7.28 (m, 4H, H-5 and H-6), 7.38 (t, 2H, H-4, ^3J 8 Hz), 7.50 (d, 2H, H-3, ^3J 8 Hz).

For **4**: yield 89%, mp 96–99 °C (aq. MeOH). ^{1}H NMR ($CDCl_3$) δ: 1:1 diastereomer mixture, arbitrary assignment, diastereomer A: 0.41 (d, 6H, 2*Me*CH, ^3J 6.6 Hz), 0.61 (t, 6H, 2*Me*CH_2, ^3J 7.4 Hz), 0.77, 0.91 (m, 4H, 2CH_2Me), 1.39 (m, 2H, 2CH), 3.57 (m, 4H, 2CH_2N, ABX spectrum, $\Delta\nu$ 360 Hz, $^2J_{AB}$ –13.2 Hz, $^3J_{AX}$ = $^3J_{BX}$ = 7.4 Hz), 7.19–7.27 (m, 4H, H-6 and H-5), 7.37 (t, 2H, H-4, ^3J 7.5 Hz), 7.49 (d, 2H, H-3, ^3J 7.6 Hz); diastereomer B: 0.53 (d, 6H, 2*Me*CH, ^3J 6.6 Hz), 0.68 (t, 6H, 2*Me*CH_2, ^3J 7.4 Hz), 1.00, 1.12 (m, 4H, CH_2Me), 1.46 (m, 2H, 2CH), 3.59 (m, 4H, 2CH_2N, ABX spectrum, $\Delta\nu$ 128 Hz, $^2J_{AB}$ –13.2 Hz, $^3J_{AX}$ 5.5 Hz, $^3J_{BX}$ 8.8 Hz), H-3-6 is identical to that of diastereomer A. ^{13}C{^{1}H} NMR ($CDCl_3$) δ: 10.71, 11.00 (*Me*CH_2), 16.52, 16.77 (*Me*CH), 26.49, 27.01 (*C*H_2Me), 32.69, 33.02 (CH), 53.35, 54.06 (CH_2N), 121.58, 121.72, 124.94, 127.99, 128.13, 128.22 (C-3-6), 134.39, 134.53 (C-1), 143.67, 144.53 (C-2), 166.17 (CO).

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