Edge-to-face aromatic interactions in alkenes, nitrones and imines

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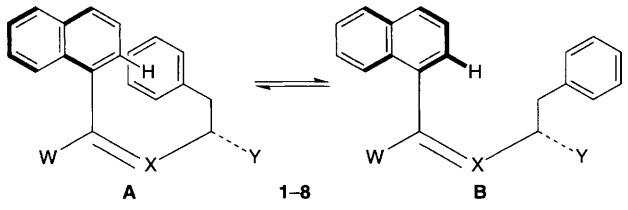
NMR spectroscopic and X-ray crystallographic studies indicate that the title compounds prefer a congested conformation with an attractive non-classical intramolecular edge-to-face interaction between aromatic residues.

Attractive edge-to-face interactions between aromatic rings can play a significant role in protein folding, nucleoside base stacking, host–guest binding and drug–receptor interactions.[1,2] The interactions been discussed in terms of electrostatic and van der Waals forces.[3]

There have been relatively few reports of intramolecular edge-to-face aromatic interactions in small conformationally flexible molecules.[4–6] We now report NMR spectroscopic and X-ray crystallographic evidence that edge-to-face interactions have an important role in determining the preferred conformations of some alkenes, nitrones and imines (**1–8**) both in solution and in the crystalline state.

(*Z*)-Alkenes **1** and **2** show two sets of signals in their ^{1}H NMR spectra (ratio 55:45) attributed to atropisomerism associated with slow rotation on the NMR timescale about the twisted 1-naphthyl–alkene bond. This chiral axis coupled with the presence of the stereogenic allylic centre leads to the observation of the two diastereoisomers **A** and **B** (Scheme 1). The more abundant atropisomer (**A**) shows an aromatic signal (dd, *J* 6.9 and 1.2 Hz) at an abnormally high field position (δ 6.3–6.4, Table 1) in the ^{1}H NMR spectrum at ambient temperature assigned to H-2′ of the 1-naphthyl ring. The aromatic protons in



Scheme 1

Table 1 ^{1}H NMR data and equilibrium atropisomer ratios for **1–8**

Comp.	W	X	Y	δ_{20}[a]	δ_{-90}[a]	A (%)[b]	ΔG^c kcal mol^{-1}
1	Me	CH	Me	6.42	5.98	55	0.16
2[d]	Me	CH	Me[d]	6.26	5.83	56	0.14
3	Et	N→O	Me	5.60	5.03	72	0.55
4	Pr^i	N→O	Ph	5.72	5.06	75	0.64
5	Me	N→O	CO_2Me	5.38	4.83	64	0.33
6	CMe_2OH	N	Me	5.77	5.12	70	0.49
7	CMe_2OH	N	Ph	5.87	5.22	70	0.49
8	Et	N	CO_2Me	5.78	5.18	65[e]	0.45

[a] Chemical shift of H-2′ of the major atropisomer (**A**) in CD_2Cl_2 solution. [b] Relative abundance of atropisomer **A** measured at equilibrium ($CDCl_3$, 20 °C); [c] Free energy difference ($-RT\ln K$) between **A** and **B** at 20 °C in $CDCl_3$. [d] *o*-MeO substituent on the benzyl group. [e] 5% (*E*)-isomer at equilibrium.

atropisomer **B** and in the (*E*)-isomer of these alkenes† resonate in the normal aromatic region δ 7–8.

The stereochemically equivalent (*E*)-nitrones **3–5** (note the change in the configurational descriptor), where the C=C bond is replaced by C=N, have been synthesised and show an even greater upfield shift of the naphthyl H-2′ proton in the more abundant atropisomer **A** (δ 5.4–5.7 at 20 °C, Table 1).†

Similar upfield shifts of H-2′ are observed in the major atropisomer (**A**) of the α-hydroxyimines **6** and **7**. These compounds were the unexpected autoxidation products isolated from the attempted preparation of the corresponding *C*-isopropylimines by condensing isopropyl 1-naphthyl ketone with 1-methyl-2-phenylethylamine or 1,2-diphenylethylamine. Compounds **6** and **7** are exclusively in the (*E*)-configuration due to steric repulsion between the bulky CMe_2OH group and the *syn*-*N*-alkyl group. The major atropisomer (**A**) of the predominant (*Z*)-form of imine **8** again exhibits an upfield naphthyl H-2′ signal (Table 1).

Compounds **2–8** (compound **1** is a liquid) afforded crystals which showed spectra of the major atropisomer (**A**) when NMR spectra were recorded immediately after dissolution in $CDCl_3$. On standing in solution for a period of time equilibration of the **A** and **B** atropisomers was observed for the less hindered compounds **2–5** and **8**. The more bulky hydroxyimines **6** and **7** have a higher barrier to rotation about the 1-naphthyl–imino bond, and equilibration did not occur at ambient temperature inferring that $\Delta G^{\#} > 23$ kcal mol^{-1} (1 cal = 4.184 J).

The upfield shift of H-2′ in the major atropisomer of compounds **1–8** is ascribed to an edge-to-face interaction between the naphthyl and phenyl rings. This proton experiences ring current shielding from the face of the proximate benzyl ring. The free energy preference of 0.16–0.64 kcal mol^{-1} in favour of atropisomer **A** is consistent with the attractive nature of the interaction and may provide a rough estimate as to the magnitude of these effects..

Confirmation of the proposed edge-to-face interaction and the relative configurations of the atropisomers follows from representative X-ray crystal structures of **3** and **7** (Figs. 1 and 2).† Nitrone **3**, prepared from enantiopure (*S*)-1-methyl-2-phenylethylamine, has the expected *E*-configuration about the

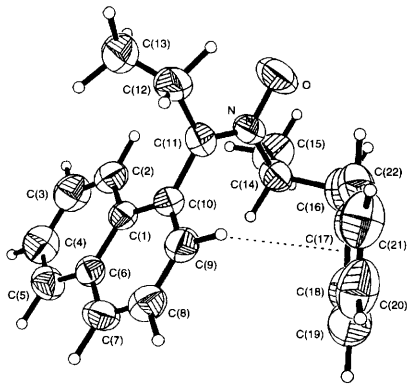


Fig. 1 ORTEP drawing of the solid-state structure of nitrone **3**

C=N bond and the configuration of atropisomer **A** about the chiral axis is seen to be *S*, *M*. The hydroxyimine **7** prepared from racemic 2,3-diphenylethylamine has the same (*E*)-configuration about the C=N bond and the equivalent geometry about the chiral axis relative to the stereogenic centre as depicted for atropisomer **A** in Scheme 1.

Both **3** and **7** exhibit a solid-state geometry consistent with a tilted-T (edge-to-face) attractive interaction between the 1-naphthyl and benzyl groups. Specifically H-2′ [C(9)–H in Figs. 1 and 2] on the 1-naphthyl ring is located at close-contact perpendicular distances of 2.68 and 2.63 Å above the face of the benzyl ring in **3** and **7**, and offset from the ring centre by only 0.33 and 0.40 Å, respectively. In the crystals of both **3** and **7** the NCH hydrogen is located *syn* to the C=N bond. This conformation minimises allylic steric interactions. In the preferred atropisomer **A** the Y group is located on the same face of the C=N bond as the naphthyl B-ring, and the benzyl group is on the same face as the naphthyl H-2′ hydrogen.

The strong temperature dependence of the upfield shift of the H-2′ proton in these compounds (Table 1) is rationalised in terms of a fast conformational equilibrium in solution between the 'closed' edge-to-face conformer **I**, and a more entropically favoured 'open' conformation **II** where the aryl rings are remote (Scheme 2). This offers the possibility of analysing quantitatively the thermodynamics of the system.

Thus the observed chemical shift (δ_{obs}) of the H-2′ proton can be expressed in terms of the limiting chemical shifts, δ_I and δ_{II}, and fractional populations, P_I and P_{II}, of the closed and open conformations, respectively (Scheme 2). The temperature dependence of K and hence δ_{obs} is determined by the conformational enthalpy (ΔH) and entropy (ΔS) differences, and a simple computer program enables calculation of δ_{obs} as a function of temperature from input values of δ_I, δ_{II}, ΔH, and ΔS.[4] This four parameter system is effectively reduced to three since the limiting chemical shift δ_{II} in the open conformation is expected to lie in the normal region δ 7.6–8.0 for a naphthyl β-hydrogen with an electron-withdrawing C=N *ortho*-substituent.§ Nitrone **5** was selected for a detailed variable temperature NMR investigation.

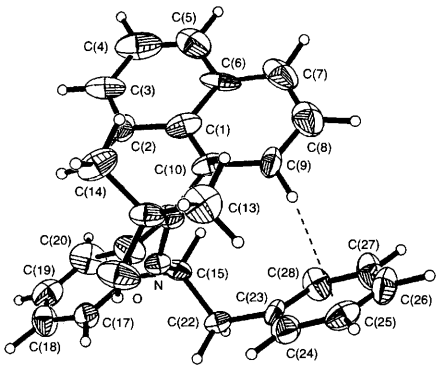
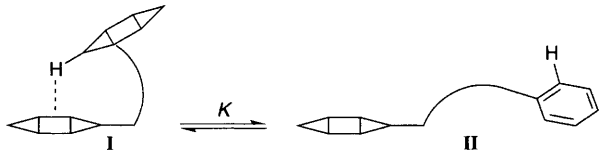


Fig. 2 ORTEP drawing of the solid-state structure of hydroxyimine **7**



Scheme 2 $\delta_{obs} = P_I\delta_I + (1 - P_I)\delta_{II}$; $(1 - P_I)/P_I = K = \exp[(T\Delta S - \Delta H/RT]$

Table 2 Experimental enthalpy and entropy values for the proposed edge-to-face interaction in the major atropisomer of nitrone **5**

Solvent	*T*/°C	ΔH/ kcal mol^{-1}	ΔS/cal mol^{-1} K^{-1}	ΔG^a/ kcal mol^{-1}	δ_I/ ppm	δ_{II}/ ppm
CD_2Cl_2	−98 to 20	1.2	2.2	0.56	4.59	7.77
$C_2D_2Cl_4$	−35 to 130	1.4	2.5	0.67	4.54	7.90

[a] Calculated at 20 °C.

The optimised ΔH and ΔS values (along with δ_I and δ_{II}) are given in Table 2. The results indicate that the closed tilted-T conformation **I** has *ca.* 1.3 ± 0.3 kcal mol^{-1} lower enthalpy than the open conformation **II**. It is reassuring that the free energy preference for the closed conformation (*ca.* 0.6 kcal mol^{-1}) is of a similar magnitude to the free energy preference for atropisomer **A** *vs* **B** in compounds **3–8** (Table 1).

As would be expected, the tilted T-conformation **I** has unfavourable entropy, and the marked temperature dependence of the upfield shift is due to the interplay of the enthalpy (ΔH) and entropy ($T\Delta S$) terms. Although other factors might also influence the conformational equilibrium, the above ΔG, ΔH and ΔS values probably provide an experimental estimate of the energy and entropy associated with a single tilted edge-to-face interaction. Previous theoretical estimates of the energy of this interaction lie in the range 1.0–2.5 kcal mol^{-1},[1,3] but the present study indicates that entropy is also an important factor.

The interactions described here are not restricted to 1-napthyl systems, as work in progress indicates that similar upfield shifts of a phenyl *ortho* hydrogen (H-6) are observed in imines and nitrones derived from 2-substituted acetophenones.

Footnotes

† Satisfactory ^{1}H NMR and microanalytical data have been obtained on the new compounds **1–8**. The (*Z*)-alkenes **1** and **2** were separated from their (*E*)-isomers by preparative TLC on silica gel.

‡ *Crystal data* for **3**: $C_{22}H_{23}NO$, M = 317.4, orthorhombic, space group $P2_12_12_1$ (no. 19), a = 7.691(5), b = 14.329(9), c = 16.500(8) Å, U = 1818(1) Å^3, D_c = 1.16 g cm^{-3}, Z = 4, $F(000)$ = 680, μ(Cu-Kα) = (0.07 cm^{-1}; 3297 unique reflections were collected, 1240 with $I > 2\sigma(I)$, $R1$ = 0.068, R_w = 0.062. For **7**: $C_{28}H_{27}NO$, M = 393.5, orthorhombic, space group *Pbca* (no. 61), a = 15.590(5), b = 15.786(4), c = 18.119(7) Å, U = 4459(1) Å^3, D_c = 1.17 g cm^{-3}, Z = 8, $F(000)$ = 1680, μ(Cu-Kα) = 0.07 cm^{-1}; 5156 unique reflections were collected, 1116 with $I > 2.5\ \sigma(I)$, $R1$ = 0.081, R_w = 0.071.

The structure was solved using SHELX-76. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Isue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/212.

§ δ_{II} was varied over the range δ 7.3–8.0 to optimise the agreement with δ_{obs} especially at the high temperature end of the plot. A guide to the expected value of δ_I (5.0 ± 0.5) is provided by ring current tables using the ring to H-2′ distance of *ca.* 2.65 Å provided by the crystal structures of compounds **3** and **7** which show similar upfield shifts. However, δ_I was varied along with ΔH and ΔS to optimise the agreement between the calculated and experimental plots of δ_{obs} *vs.* T.

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Received, 25th June 1996; Com. 6/04408E