Bonded *peri*-interactions govern the rate of racemisation of atropisomeric 8-substituted 1-naphthamides†

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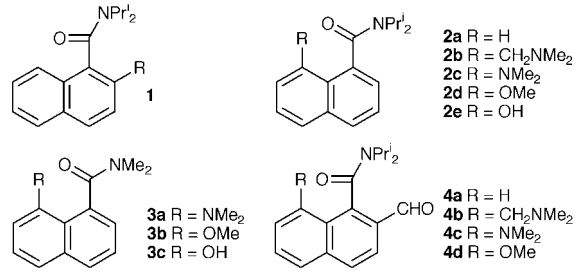
8-Substituted tertiary 1-naphthamides are chiral, atropisomeric compounds at room temperature, and the rate at which they racemise (by rotation about the Ar–CO bond) depends principally on the extent to which the 8-substituent undergoes incipient nucleophilic addition to the amide carbonyl group, as indicated by X-ray crystallography.

Substituents at the 1- and 8-positions of a *peri*-disubstituted naphthalene lie too close for comfort. Strain is the driving force behind their reactions, and anything that relieves strain is enormously favoured over anything that makes it worse.[1,2] Strain governs the shape of 1,8-disubstituted naphthalenes too: the rings are frequently severely distorted, with the 1- and 8-substituents bending away from one another both in the plane of the ring and perpendicular to it.[3]

Our interest in hindered naphthalenes began with the discovery that 2-substituted tertiary naphthamides **1**, which are axially chiral by virtue of restricted rotation about the Ar–CO axis,[4] undergo highly stereoselective reactions: reagent approach is governed by differentiation of the two faces of the naphthalene ring by the steric and electronic properties of the amide group.[5] Here we show that an 8-substituent can provide a barrier to Ar–CO bond rotation sufficiently large that 8-substituted-1-naphthamides **2** can be configurationally stable chiral compounds even without a bulky 2-substituent. Moreover, we demonstrate that the role of the 8-substituent in hindering rotation is not a steric but an electronic one, depending on the degree of bonded interaction between the 8-substituent and the amide group. [6]

In order to study the rate of racemisation of 8-substituted 1-naphthamides we made four 8-substituted amides **2b**–**e** and, from them, three 2,8-disubstitued amides **4b**–**d**. For crystallographic comparison we also made the *N*,*N*-dimethylamide **3a**.[7] Each of the six compounds **2b**–**d** and **4b**–**d** was resolved by



HPLC on a chiral stationary phase (Whelk-O1 from Regis or Chiralpak-AD from Daicel),[4,8–11] and the separated enantiomers were allowed to racemise in 5–20% EtOH or Pr^{i}OH in hexane at the temperatures shown in Table 1. The change in ee with time was followed by HPLC and in each case showed a simple first order decay—the rate constant for enantiomerisation, *k*, is given in Table 1. $\Delta G^{\ddagger}$ for this process, which represents the barrier to Ar–CO bond rotation, was calculated using the Eyring equation and is also shown in Table 1, along with an estimated half-life for racemisation of each compound at 20 °C, assuming the invariance of $\Delta G^{\ddagger}$ with temperature.[4]

Clearly, 8-substituted 1-naphthamides are atropisomeric: they have a half life at 20 °C greater than 1000 s[12] even in the absence of a 2-substituent, and the most effective 8-substituent, the OMe group, raises the barrier to rotation about the Ar–CO bond by over 30 kJ mol^{-1} (compare entries 1 and 4; 9 and 12)—an OMe group in the 2-position has a similar effect.[4] Despite their greater steric size,[13] the CH_2NMe_2 and NMe_2 substituents have less significant effects in both the 8- and 2,8-disubstituted naphthamides: an 8-CH_2NMe_2 substituent

† A colour version of Fig. 1 is available from the RSC web site, see http://www.rsc.org/suppdata/cc/1999/2059/

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Table 1 Correlating kinetic and crystallographic measurements

Entry	Compound	*T*/°C	k[a]/10^{-5} s^{-1}	$\Delta G^{\ddagger}$[b]/kJ mol^{-1}	$t_{1/2}$[c] (20 °C)	Lenth/Å			Angle (°)							
						d	δC	δN	θ_1	θ_2	θ_3	θ_4	α	β	γ	δ
1[d]	**2a**	—	—	74.5[e]	1 s	—	—	—	—	—	—	—	—	—	—	—
						2.90	0.034	0.000	113.8	124.2	121.6	118.8	87.7	104.7	81.4	83.8
2[d,f]	**2b**	2	2.6 ± 0.5	91.3	16 min	2.89	0.032	0.009	113.3	124.6	121.0	118.8	90.0	102.7	81.0	84.8
3	**2c**	50	19.5 ± 1.8	102.2	27 h	2.76	0.051	0.017	114.0	125.4	118.5	121.2	96.7	98.6	80.5	90.4
4	**2d**	55	4.3 ± 0.4	108.0	12 days	2.62	0.049	0.028	116.0	124.2	114.8	124.2	97.0	98.6	79.8	95.4
						2.83	0.076	0.030	115.3	123.7	116.9	121.2	97.9	95.8	81.4	93.4
5[f]	**2e**	—	—	—	—	2.67	0.083	0.051	116.0	123.2	116.7	122.8	101.6	92.6	80.7	93.3
6[g]	**3a**	—	—	96.9	3 h	2.70	0.055	0.060	115.5	124.7	117.0	122.9	98.7	96.5	81.3	91.4
7[h]	**3b**	—	—	—	—	2.60	0.039	0.113	115.1	124.0	114.4	122.7	103.3	90.0	80.8	96.4
8[h]	**3c**	—	—	—	—	2.62	0.051	0.070	116.2	123.6	116.5	122.7	97.0	97.8	81.2	94.2
9[d]	**4a**	2	4.2 ± 0.1	90.2	12 min	—	—	—	—	—	—	—	—	—	—	—
10[d]	**4b**	50	4.4 ± 0.2	106.2	6 days	—	—	—	—	—	—	—	—	—	—	—
11	**4c**	50	0.39 ± 0.05	112.7	80 days	—	—	—	—	—	—	—	—	—	—	—
12	**4d**	60	< 0.05	> 122	> 10 years	—	—	—	—	—	—	—	—	—	—	—

[a] Rate of enantiomerisation (1/2 × rate of racemisation). [b] Barrier to enantiomerisation. [c] Estimated half-life for racemisation at 20 °C. [d] Kinetic data from ref. 4. [e] Determined by variable temperature NMR. [f] Two molecules in unit cell, crystallographic data given for both. [g] Kinetic data from ref. 9. [h] Crystallographic data from ref. 3.

raises the barrier to rotation about Ar–CO by only about half as much as a comparably sized 2-substituent.[4] There is evidently a non-steric effect at work in the 8-substituted naphthamides,[14] and in order to clarify the nature of that effect we determined the X-ray crystal structures of **2b**–**e** and **3a**. These are shown in Fig. 1.§

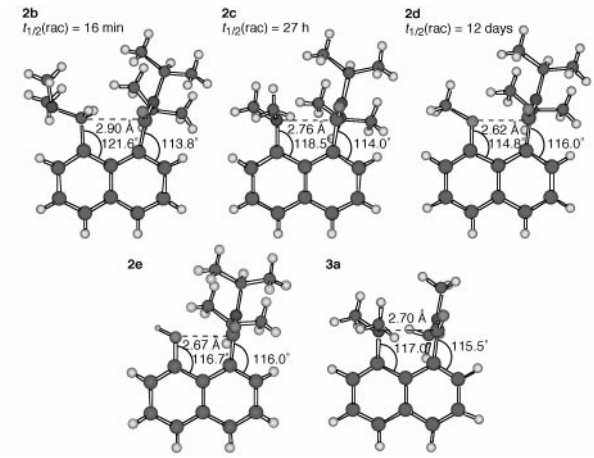

Fig. 1 X-Ray crystal structures. $t_{1/2}$(rac) = half-life for racemisation in solution at 20 °C.

The X-ray structures show that, far from repelling one another, the R and carbonyl groups of **2**, **3** and **4** are drawn together when R = NMe_2 or OMe: only **2b**, with R = CH_2NMe_2, has θ_4 (see Fig. 2) < 120°. Dunitz[3] has shown that pairs of *peri* substituents, one an electrophilic carbonyl group and the other a nucleophilic heteroatom, can exhibit bonding interactions, and we believe this is what we are observing here.

Increasing bonding between R and C=O should lead to several effects, illustrated in Fig. 2. R should bend in towards C=O (θ_4 and δ increase as θ_3 decreases), while the distance *d* between R and the carbonyl carbon atom should decrease as the bond begins to form. The C=O group should adjust its alignment relative to R to let R approach at the 'Burgi–Dunitz angle'[15] of 107° (α should move from 90° towards 107°). The arrangement of atoms around the carbonyl group should move away from trigonal planar towards tetrahedral (δC measures the displacement of the carbonyl carbon atom from the plane of its neighbours), and for the amides the amide nitrogen atom should begin to pyramidalise as it loses conjugation with C=O, the lone pair developing *anti* to the incoming nucleophile (δN measures the displacement of this nitrogen atom from the plane of its neighbours). These values were measured from the crystal structures, and are shown in Table 1. Also included for comparison are the data for the known[3] structures **3b** and **3c**.

The consistent changes in all measured values from entry 2 through entry 3 to entry 4, and from entry 5 to entry 6, makes it clear that the degree of *peri*-bonding increases as R changes from CH_2NMe_2 to NMe_2 to OMe. This is also the order of increasing barrier to Ar–CO bond rotation, and we deduce that this barrier to rotation is controlled not primarily by a repulsive, steric interaction with R but by an attractive bonding interaction. The stereogenic axis of **2** has moved some way towards being a stereogenic centre with a much higher barrier to thermal inversion. The same trend is evident in the barriers to enantiomerisation of **4**.

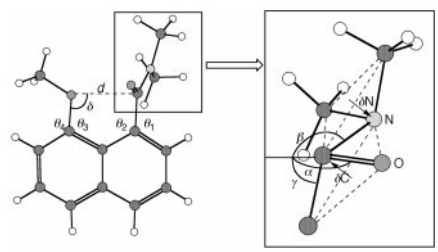

Fig. 2 Geometry of the crystal structures: key measurements. δC and δN are the deviation of each atom from the plane of its neighbours.

The degree of *peri*-bonding also increases to some extent as the amide changes from NPr^i_2 to NMe_2. The last effect is presumably steric in origin, and it is more significant with R = NMe_2 (compare entries 3 and 6) than with R = OMe (compare entries 4 and 7). This may explain why, surprisingly, R = OMe seems to be a acting as a better nucleophile than R = NMe_2: NMe_2 is simply bigger and so cannot get as close to the amide—especially an *N*,*N*-diisopropylamide.

We conclude from these observations that 8-substituted 1-naphthamides can be atropisomeric even in the absence of a 2-substituent, and that the principal factor controlling their rate of racemisation is the electronic nature of the 8-substituent and its ability to form a partial bond to the amide carbonyl group. Given their potential as chiral reagents, ligands or auxiliaries,[16] we expect 8-alkoxy or 8-amino substituents to be an important feature of thermally stable chiral atropisomeric amides.

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Notes and references

§ *Crystal data* for **2b**: $C_{20}H_{28}N_2O$, M = 312.45, triclinic, $P\bar{1}$, μ = 4.95 cm^{-1}, R = 0.074, R_W = 0.055, a = 11.245(2), b = 16.635(2), c = 10.714(2) Å, α = 96.95(1), β = 101.14(2), γ = 73.22(1)°, V = 1878.0(6) $Å^3$, T = 23.0 °C, Z = 4, 8399 reflections, 7668 unique, R_{int} 0.038. For **2c**: $C_{29}H_{26}N_2O$, M = 298.43, orthorhombic, *Pbcn*, μ = 5.26 cm^{-1}, R = 0.053, R_W = 0.046, a = 15.514(6), b = 15.239(2), c = 15.305(3) Å, α = 96.95(1), β = 101.14(2), γ = 73.22(1)°, V = 3618(1) $Å^3$, T = 23.0 °C, Z = 8, 4041 reflections. For **2d**: $C_{28}H_{23}NO_2$, M = 285.39, monoclinic, $P2_1/n$, μ = 5.86 cm^{-1}, R = 0.048, R_W = 0.033, a = 7.956(1), b = 14.530(1), c = 14.392(2) Å, β = 97.53(1)°, V = 1649.3(4) $Å^3$, T = 23.0 °C, Z = 4, 3731 reflections, 3494 unique, R_{int} 0.022. For **2e**: $C_{27}H_{21}NO_2$, M = 271.36, monoclinic, $P2_1/c$, μ = 5.59 cm^{-1}, R = 0.065, R_W = 0.040, a = 10.790(3), b = 25.204(4), c = 11.938(2) Å, β = 104.56(2)°, V = 3142(1) $Å^3$, T = 23.0 °C, Z = 8, 6753 reflections, 6392 unique, R_{int} = 0.026. For **3a**: $C_{25}H_{28}N_2O$, M = 242.32, monoclinic, $P2_1/c$, μ = 5.44 cm^{-1}, R = 0.056, R_W = 0.050, a = 8.753(2), b = 13.781(2), c = 12.168(1) Å, β = 107.865(10)°, V = 1397.0(3) $Å^3$, T = 23.0 °C, Z = 4, 3079 reflections, 2911 unique, R_{int} 0.021. CCDC 182/1412. See http://www.rsc.org.suppdata/cc/1999/2059 for crystallographic data in .cif format.

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