

## Conformation and Stereodynamics of *N,N*-Dialkylbenzamides; a $^1\text{H}$ and $^{13}\text{C}$ Nuclear Magnetic Resonance Investigation of *para*-Substituted 4-Benzoyl-*cis*-2,6-dimethylmorpholines

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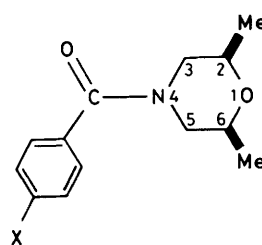
A high-field  $^{13}\text{C}$  n.m.r. study of the title compounds below  $-80^\circ\text{C}$  has enabled measurement of the barriers to rotation around the aryl-C(O) bond. These barriers ( $\Delta G^\ddagger$  7.7–9.5 kcal mol $^{-1}$ ), and those for rotation around the C(O)-N bond ( $\Delta G^\ddagger$  13.6–15.6 kcal mol $^{-1}$ ) determined by  $^1\text{H}$  n.m.r. at higher temperatures, correlate well with Hammett  $\sigma^+$  substituent parameters. The ground-state conformation has the phenyl ring twisted out of the amide plane. Some  $^1\text{H}$  and  $^{13}\text{C}$  chemical shift correlations are also reported.

Following the pioneering work of Phillips,<sup>1</sup> and of Gutowsky and Holm<sup>2</sup> on dimethylformamide, there has been a plethora of dynamic n.m.r. studies on amides. Most investigations have been concerned with internal rotation around the C(O)-N bond, but slow rotation around the Ar-C(O) bond has been observed in *ortho*-mono- and -di-substituted benzamides by using either a prochiral probe<sup>3</sup> (for unsymmetrically substituted compounds) or a chiral substituent<sup>4</sup> or an optically active shift reagent<sup>5</sup> (for symmetrically *ortho*-disubstituted benzamides). Apart from a recent preliminary report from this laboratory,<sup>6</sup> no measurements appear to have been carried out on the Ar-C(O) rotational process in ring-unsubstituted or *para*-monosubstituted benzamides. The impression is given that one *ortho*-substituent is required for an appreciable Ar-C(O) rotational barrier.

In order to render this process observable by n.m.r. without resort to optically active additives, a series of *para*-substituted 4-benzoyl-*cis*-2,6-dimethylmorpholines (1)–(8) were prepared for investigation. The presence of the chiral centres in these compounds ensures that the *ortho*- and *meta*-hydrogen and carbon atoms are diastereotopic even if the frozen ground-state conformation has the phenyl ring orthogonal to the amide plane or rapidly oscillating through this plane. The 2,6-dimethylmorpholine moiety used previously by Fulea and Kruger<sup>7</sup> and by Berg<sup>8</sup> in studies of thioamides was chosen for this study because of its commercial availability. The *cis*-isomers were used, though in principle the *trans*-compounds would also have been appropriate. An advantage of the *cis*-compounds is that slow inversion of the morpholine ring should not lead to spectral changes, in view of the negligible proportion of the ring conformation with the methyl groups diaxial.

### Results and Discussion

The benzamides were generally prepared by a standard procedure from commercial 2,6-dimethylmorpholine which contained ca. 70% of the *cis*-isomer. The presence of the hydroxy group in (7) necessitated an indirect preparative route *via* the thioamide. In all cases multiple recrystallisation of the crude product afforded the pure *cis*-amide, which was shown to be free of the *trans*-isomer by  $^1\text{H}$  n.m.r. analysis. The n.m.r. spectra of most of these compounds recorded at ambient temperature showed considerable signal broadening due to an intermediate rate of rotation around the amide bond on the n.m.r. time-scale. However on lowering the temperature to ca.  $-50^\circ\text{C}$  the  $^1\text{H}$  n.m.r. spectra was resolved into two AMPX<sub>3</sub> systems for the morpholine group and an [AM]<sub>2</sub> system for the *para*-substituted benzoyl group. At this temperature rotation around the C(O)-N bond is slow but Ar-C(O) rotation remains rapid



- |                         |                          |
|-------------------------|--------------------------|
| (1) X = NO <sub>2</sub> | (5) X = Me               |
| (2) X = CN              | (6) X = OMe              |
| (3) X = Cl              | (7) X = OH               |
| (4) X = H <sub>2</sub>  | (8) X = NMe <sub>2</sub> |

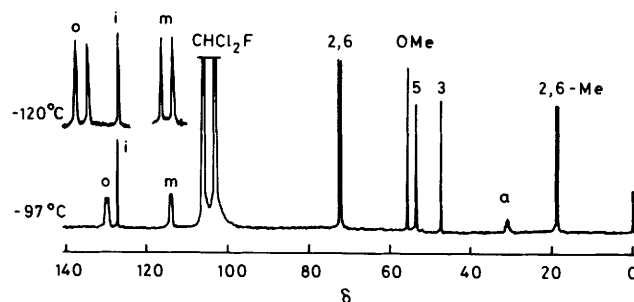


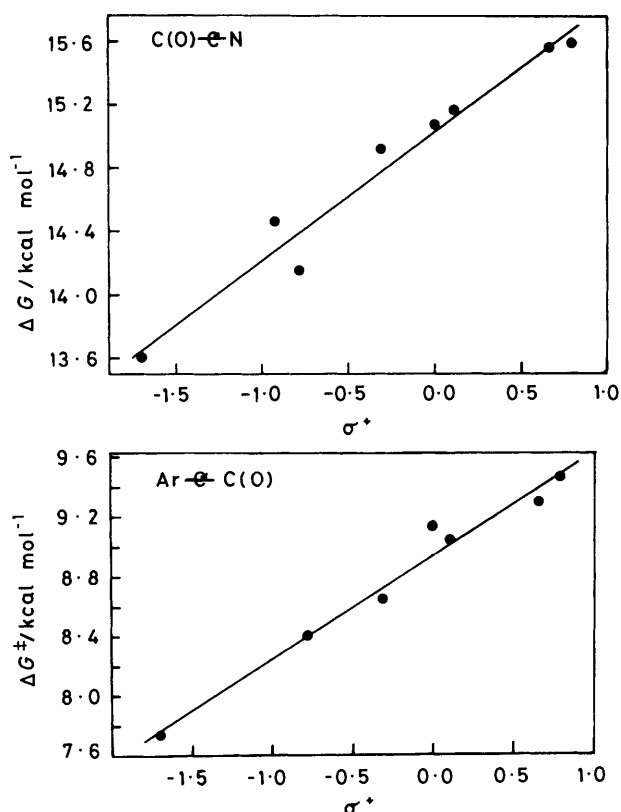
Figure 1.  $^{13}\text{C}$  N.m.r. spectrum (100.6 MHz) of the amide (6) recorded at  $-97^\circ\text{C}$  ( $\text{CHCl}_2\text{F}$  solution) (inset at  $-120^\circ\text{C}$  on an expanded scale). The *para*-carbon signal at  $\delta$  160.9 is not shown; i = *ipso* quaternary carbon, a = [ $^2\text{H}_6$ ]acetone used as internal lock

on the n.m.r. time-scale. On further cooling to ca.  $-100^\circ\text{C}$  some of these compounds showed changes in the aromatic region of the  $^1\text{H}$  n.m.r. spectrum, but quantitative measurements were hindered by small shift separations and signal overlap. The  $^{13}\text{C}$  n.m.r. spectra were superior for investigating this low-temperature process, though a high-field instrument was required to resolve clearly the diastereotopic pairs of *ortho*- and *meta*-resonances at temperatures in the range  $-90$  to  $-120^\circ\text{C}$  (Figure 1). At these temperatures the *ipso*-, *para*- and carbonyl carbon signals remained as single lines, and the morpholine carbon signals remained essentially unchanged from the six-line pattern observed at  $-50^\circ\text{C}$ . The anisochronous *ortho*- and *meta*-signals coalesced between  $-77$  and  $-105^\circ\text{C}$  (depending on the *para*-substituent), and bandshape analysis gave the rate constants and free energy barriers for phenyl ring rotation listed in Table 1. The barriers to rotation around the amide bond, determined by analysis of the  $^1\text{H}$  n.m.r. bandshapes of the

**Table 1.** Dynamic n.m.r. data for rotation around the phenyl and amide bonds in *para*-substituted benzamides

Compound	X	$\delta_p^+$	Ar-C(O) rotation <sup>a</sup>			C(O)-N rotation <sup>b</sup>		
			$T/^\circ\text{C}$	$k/\text{s}^{-1}$	$\Delta G^\ddagger/\text{kcal mol}^{-1}$	$T/^\circ\text{C}$	$k/\text{s}^{-1}$	$\Delta G^\ddagger/\text{kcal mol}^{-1}$
(1)	NO <sub>2</sub>	0.79	-77	115	9.46	28	29.5	15.59
(2)	CN	0.66	-83	86.4	9.26	23	19.6	15.56
(3)	Cl	0.11	-86	113	9.04	17	22.0	15.16
(4)	H	0.0	-97	18.4	9.13	16	24.8	15.07
(5)	Me	-0.31	-92	142	8.64	10	17.8	14.92
(6)	OMe	-0.78	-97	137	8.40	-1	33.5	13.99 <sup>c</sup>
(7)	OH	-0.92	<i>d</i>			6	27.2	14.46
(8)	NMe <sub>2</sub>	-1.7	-105	300	7.74	-15	15.9	13.60

<sup>a</sup> Determined by <sup>13</sup>C n.m.r. (100.6 MHz) analysis of the coalescing *ortho*- and/or *meta*-signals in CHCl<sub>2</sub>F solution. <sup>b</sup> Determined by <sup>1</sup>H n.m.r. (100.0 MHz) analysis of the coalescing morpholine ring methyl doublet signals in CDCl<sub>3</sub> solution. <sup>c</sup> Analysis of the coalescing NCH bands at 17 °C gave  $\Delta G^\ddagger = 14.15 \text{ kcal mol}^{-1}$ ; the mean  $\Delta G^\ddagger = 14.06 \text{ kcal mol}^{-1}$  was used in the correlation analysis. <sup>d</sup> Not measured owing to poor solubility at low temperature.

**Figure 2.** Plots of  $\Delta G^\ddagger$  (kcal mol<sup>-1</sup>) for rotation around the C(O)-N (upper) and Ar-C(O) (lower) bonds vs. Hammett  $\sigma^+$ 

coalescing morpholine methyl signals in the temperature range -15 to +28 °C, are also given in Table 1.

**The C(O)-N Barrier.**—The data in Table 1 show that electron donation from the *para*-substituent accelerates rotation about both the Ar-C(O) and the C(O)-N bonds. The free energy barriers for both processes decrease by *ca.* 2 kcal mol<sup>-1</sup> on changing X from NO<sub>2</sub> to NMe<sub>2</sub>. On a quantitative basis, a good correlation was observed between  $\Delta G^\ddagger$  and Hammett  $\sigma^+$  for both rotations (Figure 2). The  $\rho^+$  values and the correlation coefficients (*r*) are given in Table 2.

Correlations between the C(O)-N rotational barrier and substituent constants have been reported for other benzamides.<sup>9,10</sup> The reported  $\rho^+$  value<sup>9</sup> of 1.13 (*r* 0.96) for *N,N*-

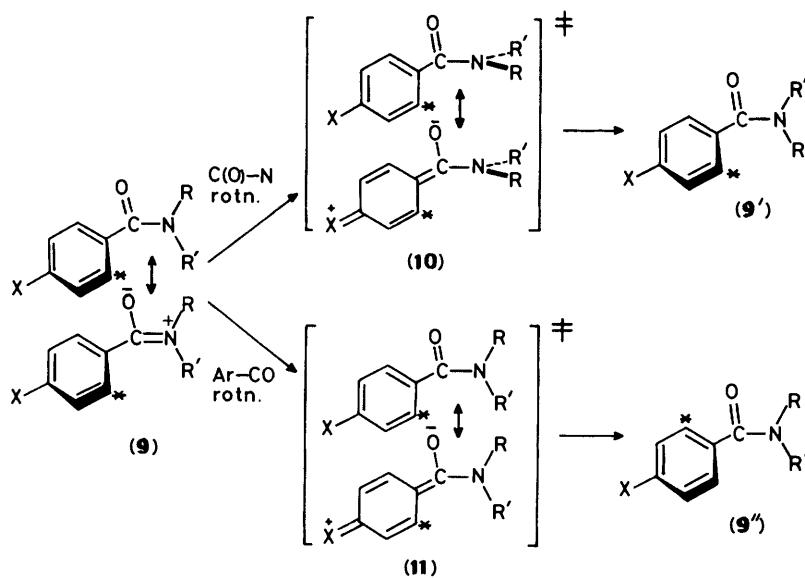
**Table 2.** Hammett correlations

Ar-C(O) rotation	$\Delta G^\ddagger = 0.68 \sigma_p^+ + 8.93 \text{ kcal mol}^{-1}$ ( <i>r</i> = 0.99)
C(O)-N rotation	$\Delta G^\ddagger = 0.81 \sigma_p^+ + 15.03 \text{ kcal mol}^{-1}$ ( <i>r</i> = 0.98)
C(5)-H <sub>eq</sub> shift	$\delta = -0.14 \sigma_p^+ + 3.59$ ( <i>r</i> = 0.98)
C(5) shift	$\delta = -0.35 \sigma_p^+ + 52.89$ ( <i>r</i> = 0.99)
C(3) shift	$\delta = -0.21 \sigma_p^+ + 46.98$ ( <i>r</i> = 0.97)

dimethylbenzamides compares reasonably well with the value of 0.81 (*r* 0.98) in the present series. Clearly, electron-donating *para*-substituents stabilize the transition state (10) for C(O)-N rotation (Scheme) more than the ground state (9), thereby lowering the barrier. Two factors may contribute to this effect. In the ground state (9) the amide nitrogen lone pair and the aromatic ring are in competitive conjugation with the carbonyl  $\pi$ -bond. On a simple valence bond argument this will tend to reduce the interaction between the carbonyl group and the aromatic ring in the ground state as compared with the transition state (10) where the nitrogen *p*-orbital is orthogonal to the carbonyl  $\pi$ -orbital. Secondly, steric interactions between the *ortho*-hydrogen and the NR' moiety are considerably reduced in the twisted transition state (10) for C(O)-N rotation. Hence the phenyl ring could become more coplanar with the carbonyl group in the transition state (10) and lower its energy (relative to the ground state) when the *para*-substituent is a  $\pi$ -donor by more effective conjugation.

The C(O)-N rotational barrier in the *N*-benzoyl compound (4),  $\Delta G^\ddagger$  15.1 kcal mol<sup>-1</sup>, is slightly higher than that reported<sup>11</sup> for 4-benzoylmorpholine,  $\Delta G^\ddagger$  14.4 kcal mol<sup>-1</sup> in deuteriochloroform solution. The origin of this remote 2,6-dimethyl effect on the amide barrier is not evident, but it might conceivably be associated with a change in the morpholine ring geometry during the rotational process. Possibly the nitrogen, which is probably essentially planar *sp*<sup>2</sup>-hybridised in the ground state, becomes pyramidal in the transition state (10) for C(O)-N rotation (Scheme) owing to the loss of conjugation with the carbonyl group.

**The Ar-C(O) Barrier.**—With regard to the substituent effect on the Ar-C(O) rotation, the positive  $\rho^+$  value indicates that the ground-state conformation around this bond is not coplanar. Conjugation with the carbonyl group is maximised when the phenyl ring is coplanar with the O=C-N moiety ( $\phi_{\text{Ar}} = 0^\circ$ ), and if this were the ground-state arrangement the Ar-C(O) barrier would be raised by electron donation (ground-state stabilization). Accordingly the coplanar arrangement (11) is the transition state for Ar-C(O) rotation which lies 7.7–9.5 kcal mol<sup>-1</sup> above the twisted ground state. The torsional energy



Scheme.

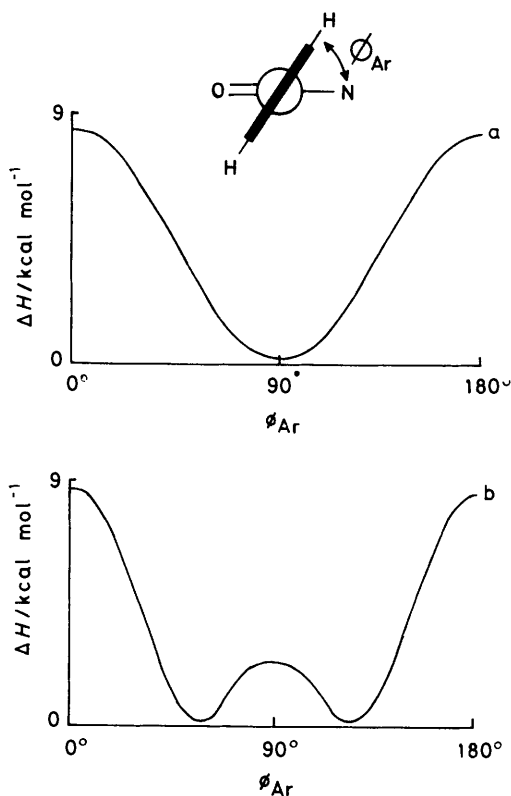


Figure 3. Qualitative energy profiles for rotation around the Ar-C(O) bond

profile around the Ar-C(O) bond therefore resembles the form depicted in Figure 3 where the ground-state  $\phi_{Ar}$  is either  $90^\circ$  (Figure 3a) or between  $30$  and  $90^\circ$  (Figure 3b). Electronic considerations indicate that if the latter situation pertains, the barrier to oscillation through the conformation where  $\phi_{Ar} = 90^\circ$  is likely to be very small, as shown in Figure 3b. An X-ray crystallographic investigation<sup>12</sup> of 4-bromo-*N,N*-dimethylbenzamide has shown that  $\phi_{Ar} = 45^\circ$ , though the ground-state twist angle in compounds (1)–(8) could be greater than  $45^\circ$ , owing to more severe steric interactions between the

*ortho*-hydrogen and the adjacent equatorial morpholine NCH proton. It is possible that the ground-state twist angle  $\phi_{Ar}$  may decrease somewhat along the series (1)–(8) owing to increasing cross-conjugation between electron-donating *para*-substituents and the carbonyl group (see later).

It should be noted that although conformation (10), where  $\phi_{Ar} = 0^\circ$  and  $\phi_{NR_2} = 90^\circ$ , is in principle a possible common transition state for both Ar-C(O) and C(O)-N rotations, a much lower energy pathway exists for the former process ( $\Delta G^\ddagger$  7.7–9.5 kcal mol<sup>-1</sup>) involving the non-synchronous rotation of the phenyl ring past the essentially coplanar ground-state C(O)-NR<sub>2</sub> moiety [via (11) in the Scheme].

**The Chemical Shifts.**—The morpholino <sup>1</sup>H and <sup>13</sup>C chemical shifts for compounds (1)–(8), measured at  $-50^\circ\text{C}$  where amide bond rotation is slow, are listed in Tables 3 and 4. It has been established previously that NCH protons situated *syn* to the carbonyl group in *N,N*-dialkylbenzamides are deshielded relative to *anti* NCH protons.<sup>13</sup> Accordingly the low-field doublet at *ca.*  $\delta$  4.6 was assigned to the *syn* equatorial C(3)-H. Homonuclear <sup>1</sup>H decoupling experiments on compound (1) at 400 MHz then allowed unambiguous identification of the *syn* and *anti* AMPX<sub>3</sub> systems. The corresponding <sup>13</sup>C signals were assigned by selective <sup>1</sup>H decoupling experiments. The assumption that the *syn* equatorial C(3)-H resonates at lowest field is confirmed by the conclusion that the attached C(3) resonates at higher field than the *anti* C(5), in agreement with previous observations on other benzamides.<sup>14</sup>

In the <sup>1</sup>H spectra only the equatorial NC(5)-H resonance position was significantly affected by the *para*-substituent. The position of this signal correlates well with Hammett  $\sigma^+$  (Table 2). It is probably significant that the equatorial C(5) proton is the closest in space to the aryl ring. Accordingly the observed *para*-substituent effect could operate by an indirect through-space mechanism rather than the normal through-bond electronic perturbation. Thus electron-donating *para*-substituents may reduce the ground-state aryl twist angle ( $\phi_{Ar}$ ), owing to cross-conjugation with the carbonyl group. This would lead to a deshielding of the equatorial C(5)-H by the aromatic current effect. Estimates of the ring current effect on the shift of this signal, using the Johnson-Bovey tables<sup>15</sup> and distance measurements from a scale molecular model, indicate that owing to the close proximity of C(5)-H to the aromatic ring only a modest

**Table 3.** Selected  $^1\text{H}$  chemical shifts ( $\delta$ ) measured at  $-50^\circ\text{C}$ ; solvent deuteriochloroform<sup>a,b</sup>

Compound	X	C(3)-H <sub>eq</sub>	C(5)-H <sub>eq</sub>	C(3)-H <sub>ax</sub>	C(5)-H <sub>ax</sub>	C(2)-Me	C(6)-Me
(1)	NO <sub>2</sub>	4.61	3.44	2.64	2.94	1.31	1.16
(2)	CN	4.59	3.55	2.63	2.93	1.31	1.16
(3)	Cl	4.58	3.56	2.59	2.90	1.29	1.15
(4)	H	4.61	3.61	2.60	2.89	1.29	1.14
(5)	Me	4.60	3.65	2.58	2.88	1.29	1.14
(6)	OMe	4.58	3.70	2.59	2.91	1.29	1.16
(7)	OH	4.57	3.74	2.62	2.91	1.29	1.16
(8)	NMe <sub>2</sub>	4.55	3.83	2.56	2.91	1.27	1.14

<sup>a</sup> C(2) and C(3) are *syn* to the carbonyl group and C(5) and C(6) are *anti*; numbering starts at the morpholino oxygen. <sup>b</sup> Chemical shifts for C(2)-H and C(6)-H are not listed, as they gave broad overlapping multiplets (at 100 MHz) centred at *ca.*  $\delta$  3.64 for all compounds.

**Table 4.**  $^{13}\text{C}$  Chemical shifts ( $\delta$ ) of the aliphatic carbons measured at  $-52^\circ\text{C}$ ; solvent deuteriochloroform<sup>a</sup>

Compound	X	C(3)	C(5)	C(2,6)	C(2)-Me	C(6)-Me
(1)	NO <sub>2</sub>	46.85	52.63	71.66	18.71	18.52
(2)	CN	46.85	52.63	71.73	18.78	18.52
(3)	Cl	46.98	52.89	71.79	18.78	18.52
(4)	H	46.91	52.89	71.79	18.78	18.52
(5)	Me	46.98	52.95	71.73	18.78	18.52
(6)	OMe	47.17	53.21	71.79	18.78	18.58
(8)	NMe <sub>2</sub>	47.36	53.47	71.79	18.78	18.52

<sup>a</sup> Signals were assigned from the attached proton resonances by selective decoupling experiments; for numbering system see footnote to Table 3.

(*ca.*  $15^\circ$ ) reduction in  $\phi_{Ar}$  along the series (1)–(8) would be required to account for the observed downfield shift of *ca.* 0.4 p.p.m. (Table 3).

The  $^{13}\text{C}$  chemical shifts of the morpholine ring carbon atoms at  $-52^\circ\text{C}$  are listed in Table 4. Only those of C(3) and C(5) are significantly affected by the *para*-substituent, and good correlations were again obtained with Hammett  $\sigma^+$  (Table 2). The *syn* carbon C(3) is too remote to be significantly affected by the ring current effects, and the change in the *anti* C(5) shift along the series (1)–(8) is too large to be attributed to the change in  $\phi_{Ar}$ . Accordingly it is reasonable to conclude that a normal through-bond transmission of substituent effects occurs for both these carbon atoms [though a ring current effect could make a minor contribution to the C(5) shift variation]. It has been reported<sup>16</sup> that N- $^{13}\text{C}$  chemical shifts in some *para*-substituted *N*-benzylidenealkylamines (imines) and related oxaziridines correlate well with substituent parameters. However, the  $\rho$  values are of opposite sign to those obtained for C(3) and C(5) in (1)–(8) despite the presence of the same number of bonds (three) between the observed carbon atoms and the phenyl ring in these systems. Clearly these long-range *para*-substituent effects are very sensitive to the bonding situation in the side-chain.

## Experimental

The *para*-substituted 4-benzoyl-*cis*-2,6-dimethylmorpholines (1)–(6) and (8) were prepared by dropwise addition of an equimolar mixture of commercial 2,6-dimethylmorpholine (containing *ca.* 70% of the *cis*-isomer) and anhydrous triethylamine to an equimolar proportion of the appropriate benzoyl chloride in anhydrous diethyl ether at  $0^\circ\text{C}$ . The mixture was then refluxed for 2–3 h and filtered, and the filtrate washed with water to remove residual triethylamine hydrochloride. Removal of the solvent left the crude amide, which was purified by recrystallisation until shown to be free of the *trans*-isomer by  $^1\text{H}$  n.m.r. analysis.

4-(*p*-Nitrobenzoyl)-*cis*-2,6-dimethylmorpholine (1) had m.p.  $197$ – $199^\circ\text{C}$  [from light petroleum (b.p.  $80$ – $100^\circ\text{C}$ )–chloroform (1:1)] (Found: C, 59.2; H, 6.1; N, 10.9.  $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_4$  requires C, 59.1; H, 6.1; N, 10.6%). 4-(*p*-Cyanobenzoyl)-*cis*-2,6-dimethylmorpholine (2) had m.p.  $212$ – $214^\circ\text{C}$  (from ethanol) (Found: C, 68.8; H, 6.6; N, 11.3.  $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_2$  requires C, 68.8; H, 6.6; N, 11.5%). 4-(*p*-Chlorobenzoyl)-*cis*-2,6-dimethylmorpholine (3) had m.p.  $151$ – $153^\circ\text{C}$  (from diethyl ether) (Found: C, 61.2; H, 6.1; Cl, 14.3; N, 5.7.  $\text{C}_{13}\text{H}_{16}\text{ClNO}_2$  requires C, 61.5; H, 6.3; Cl, 14.0; N, 5.5%). 4-Benzoyl-*cis*-2,6-dimethylmorpholine (4) had m.p.  $90$ – $92^\circ\text{C}$  (from tetrachloromethane) (Found: C, 70.9; H, 7.7; N, 6.5.  $\text{C}_{13}\text{H}_{17}\text{NO}_2$  requires C, 71.2; H, 7.8; N, 6.4%). 4-(*p*-Methylbenzoyl)-*cis*-2,6-dimethylmorpholine (5) had m.p.  $132$ – $133^\circ\text{C}$  [from diethyl ether–chloroform (10:1)] (Found: C, 72.1; H, 8.5; N, 6.0.  $\text{C}_{14}\text{H}_{19}\text{NO}_2$  requires C, 72.1; H, 8.2; N, 6.0%). 4-(*p*-Methoxybenzoyl)-*cis*-2,6-dimethylmorpholine (6) had m.p.  $70$ – $72^\circ\text{C}$  [from light petroleum (b.p.  $60$ – $80^\circ\text{C}$ )–diethyl ether (2.5:1)] (Found: C, 67.7; H, 7.7; N, 5.9.  $\text{C}_{14}\text{H}_{19}\text{NO}_3$  requires C, 67.5; H, 7.7; N, 5.6%). 4-(*p*-Dimethylaminobenzoyl)-*cis*-2,6-dimethylmorpholine (8) had m.p.  $131$ – $132^\circ\text{C}$  [from diethyl ether–chloroform (5:1)] (Found: C, 68.8; H, 8.6; N, 10.7.  $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_2$  requires C, 68.7; H, 8.5; N, 10.7%).

4-(*p*-Hydroxybenzoyl)-*cis*-2,6-dimethylmorpholine (7).—The presence of the hydroxy group prevented synthesis by the normal method, so this compound was prepared *via* the thioamide. In a Willgerodt–Kindler reaction,<sup>17</sup> 2,6-dimethylmorpholine (11.3 g, 0.098 mol), sulphur (3.14 g, 0.098 g atom), and 4-hydroxybenzaldehyde (8.0 g, 0.065 mol) were heated at  $150^\circ\text{C}$  for 4 h. Extraction of the cooled mixture with chloroform afforded the crude thioamide (12.5 g), which was stirred with aqueous 10% potassium hydroxide (165 cm<sup>3</sup>) and 30% hydrogen peroxide (39 cm<sup>3</sup>) for 48 h at ambient temperature.<sup>18</sup> Careful acidification with conc. hydrochloric acid followed by extraction with chloroform and several recrystallisations from ethanol gave the pure 4-(*p*-hydroxybenzoyl)-*cis*-2,6-dimethylmorpholine (1.2 g), m.p.  $225$ – $227^\circ\text{C}$  (Found: C, 66.7; H, 7.3; N, 6.2.  $\text{C}_{13}\text{H}_{17}\text{NO}_3$  requires C, 66.4; H, 7.3; N, 6.0%).

*N.m.r. Studies.*—The dynamic  $^{13}\text{C}$  n.m.r. experiments were performed at 100.6 MHz with the S.E.R.C. regional Bruker WH-400 instrument at Warwick University.  $^{13}\text{C}$  Chemical shifts at  $-52^\circ\text{C}$  were measured at 15.0 MHz using a JEOL FX-60 instrument. All  $^1\text{H}$  n.m.r. spectra were obtained at 100 MHz using a Varian XL-100 spectrometer operating in CW mode. For solvents see Tables. Probe temperatures were measured with a digital copper-constantan thermocouple inserted in a dummy sample tube. Exchange-mediated spectra were analysed using the classical multi-site program INMR.<sup>19</sup> Components of the exchanging morpholine methyl doublets in the  $^1\text{H}$  n.m.r. spectra were treated in the computations as separate sites with the appropriate relative intensity.

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