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The Effect of Exocyclic Conjugation on the Inversion of a Saturated Six-Membered Ring. A Dynamic NMR Study of N-Substituted Morpholines[1].

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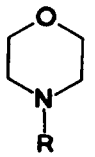
Abstract. The effect of exocyclic conjugation on the inversion of a saturated six-membered ring is shown in a dynamic nmr study of a series of N-substituted morpholines where the substituents have similar shapes but different conjugating ability As conjugation increases the ring inversion barrier decreases, in contrast to previous observations of an unsaturated ring with conjugating substituents

Two aspects of molecular structure whose study has been particularly helped by dynamic nmr spectroscopy are the effect of structural modifications on barriers to ring inversion[2], and the extent that conjugation produces double bond character in the carbon-nitrogen bond in amides and similar compounds[3] There has been surprisingly little systematic study of ring inversions when one of the atoms in the ring is conjugated with a substituent so that the double bond character lies in the exocyclic bond

Sandstrom[4] has reported that the barrier to inversion of the saturated ring in N-substituted morpholines 1, is much reduced when the substituent is formyl, acetyl or benzoyl compared with a model methyl



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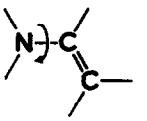
a) R = H
b) R = CH_3
c) R = CHO
d) R = $COCH_3$
e) R = COPh
f) R = cyclohexyl
g) R = cyclohexenyl
h) R = phenyl
i) R = 4-aminophenyl
j) R = 4-nitrophenyl



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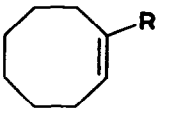

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substituent, see 1b - 1e in Table 1, but felt that comparisons along the series are complicated by the different steric interactions of the substituents Harris and Spragg[5] failed to observe slowing of ring inversion in the spectrum of 1d and 1h at -95° and attributed this to conjugation reducing the ring inversion barrier

Table 1. Barriers to ring inversion (chair to twist boat) of morpholine and some N-substituted morpholines The free energies of activation ($\Delta G^{\#}$ in kCal/mol) were obtained in the temperature range indicated in parentheses

Substituent R		$\Delta G^{\#}$		Reference
1a	H	10 0	(203)	4
		9 9	(203)	5
		10 12	(177-211)[a]	this work
		10 05	(191-211)[b]	this work
1b	CH_3	11 5	(233-243)	5,6
		11 05	(224-283)[c]	7
		11 9	(249-291)[d]	7
1c	CHO	7 5	(155)	4
1d	$COCH_3$	6 8	(149)	4
1e	COPh	7 6	(166)	4
1f	cyclohexyl	10 6	(222-227)	this work
1g	1-cyclohexenyl	9 1	(187-208)	this work
1h	phenyl	7 2	(150-162)	this work
1i	4-aminophenyl	8 0	(157-171)	this work
1j	4-nitrophenyl	5 5	(127)	this work

a) in CD_2Cl_2 $\Delta H^{\#} = 11\,3 \pm 3$ Kcal/mol $\Delta S^{\#} = 5\,8 \pm 2$ e u
b) in CD_3OD $\Delta H^{\#} = 11\,3 \pm 4$ Kcal/mol $\Delta S^{\#} = 6\,1 \pm 2$ e u
c) in CS_2 $\Delta H^{\#} = 11\,3 \pm 2$ Kcal/mol $\Delta S^{\#} = 0\,8 \pm 0\,8$ e u
d) gas phase $\Delta H^{\#} = 12\,0 \pm 1$ Kcal/mol $\Delta S^{\#} = 0\,3 \pm 0\,6$ e u

We became aware of the problem in the course of studying[8,9] hindered rotation in enamines, 2 Our interest was in the partial double bond character of the nitrogen to sp^2-carbon bond when the geometry is favourable, and we found substantial barriers to rotation about that bond In some compounds where the nitrogen atom or the double bond forms part of the framework of a ring, an effect on the barrier to ring inversion was observed, and we wanted to investigate this more fully We first

Table 2. Barriers (kcal/mol, Temp °K) to the two nmr-visible pseudorotation processes[a] of the twist-boat-chair conformations of 1-substituted cyclooctenes 3, results taken from reference 10

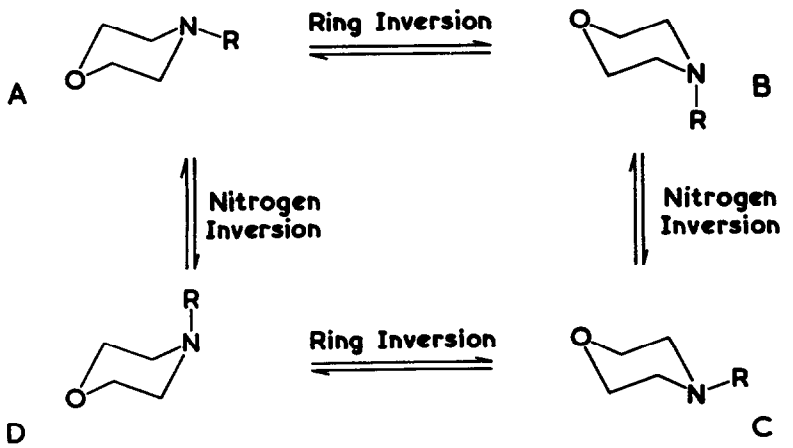
Substituent R	Barrier to pseudo-rotation through boat-boat conformation	Barrier to pseudo-rotation through chair-chair conformation
H[b]	5 3	8 2
$CH(CH_3)_2$	7 1 (153)	7 6 (168)
cyclopentyl	7 1 (144)	7 6 (168)
phenyl[c]	7 4 (159)	7 7 (170)
N-pyrrolidyl[c]	8 2 (74)	8 2 (174)

[a] The higher barrier pseudorotation process is conveniently called ring inversion[10]
[b] Results from reference 2 which does not cite a temperature
[c] It may be that the barriers to the two processes should be exchanged, see Text

considered the effect of conjugating substituents on ring inversion and pseudorotation of an unsaturated ring, 1-substituted-cyclooctenes 3, and found[10] that such substituents raise one pseudorotation barrier significantly compared with isosteric non-conjugating substituents, see Table 2, while a second pseudorotation process showed little effect of either conjugating or non-conjugating substituents These contrasting effects helped elucidate the different processes involved

In this paper we consider an inverse situation, that of a saturated ring whose framework contains a nitrogen atom bearing a conjugating substituent We extend the work of Sandstrom[4] on N-substituted morpholines to the series 1a and 1f-1j, where the substituents have similar size but different conjugating ability The equilibrium which can be probed by dynamic nmr spectroscopy is shown in the scheme The N-R-equatorial forms A and C are expected to be much more stable[11] than N-R-axial isomers, B and D

When A-C interconversion is slow on the nmr timescale there should be no change in the nmr spectrum of the R substituent, but axial and equatorial protons on the morpholine ring should be distinct



The nitrogen inversion barrier (A⇌D, B⇌C) is expected to be about 6kcal/mol[12] for 1a, R=H, and it is known that conjugation lowers such barriers[13], as the values for ammonia[14] and formamide[15], 5 77 and 1 1 kcal/mol respectively indicate As a result ring inversion is expected to be the rate-determining step in the interconversion of A with C in cases where barriers are greater than about 5kcal/mol

As substituents, we chose the set· non-conjugating cyclohexyl, conjugating cyclohexenyl, and similarly shaped conjugating para-substituted phenyl, 1f-1j The expectation based on Sandstrom's work[4] was that the increase in the double bond character of the exocyclic bond at nitrogen in morpholine should lower the ring inversion barrier of that ring, just as the ring inversion barriers in methylenecyclohexane[16] 8.4kcal/mol and in cyclohexanone[17], 4 0kcal/mol are lower than that of 10 2kcal/mol in cyclohexane[18] We also chose to investigate ring inversion in the parent morpholine more fully than previously using both saturation transfer[19] and classical lineshape methods at high field

The compound 1f R = 1-cyclohexenyl does not show changes in the carbon-13 nmr spectrum of the morpholine group which can be associated with hindered rotation about the C---N bond This indicates that the chemical shift difference is particularly small, something also found with 1-dimethylaminocyclohexene[8,9] Hindered rotation effects thus do not interfere with the ring inversion changes in the spectrum nor were changes associated with inversion of the cyclohexene ring observed

RESULTS AND DISCUSSION

The ring protons of an N-substituted morpholine appear as two triplets at room temperature, and as a complex ABCD spectrum when ring inversion is slow on the nmr timescale In this situation the signal of the protons next to the oxygen simplify to an AB-quartet on decoupling the NCH_2 protons and vice versa. The change of either of these quartets at intermediate rates of exchange allows the determination of ring inversion rates at a series of temperatures Rates determined for each of the compounds 1a and 1f to 1j lead to the free energies of activation shown in Table 1 In the case of 1a, rate constants for methylene chloride solutions were determined over a wider temperature range by saturation transfer techniques, and let to the enthalpy and entropy of activation shown

Each of the compounds 1g-1j with an N-substituent which is capable of conjugative interaction with the morpholine nitrogen atom shows a substantially lower barrier to ring inversion than the reference compound N-cyclohexylmorpholine 1g The importance of conjugation is confirmed by the barrier for phenylmorpholine lying between those of the 4-aminophenyl and 4-nitrophenyl derivatives In the latter compound, the electron-withdrawing nitro group increases the conjugative interaction of the morpholine with the phenyl ring and leads to the lowest ring inversion barrier of all in the set

Table 3 compares the effect of a para-substituent on the ring inversion of N-phenylmorpholine and on rotation of the methylaminogroup in N-methylaniline[20] As the electron- withdrawing conjugative effect of a para-substituted phenyl group increases along the series NH_2, H, NO_2 the double bond character

in the phenyl-nitrogen bond increases and appears as an increased rotational barrier and a decreased ring inversion barrier which is thus putatively linked to the double bond character in the exocyclic bond The higher ring inversion barrier for cyclohexenyl morpholine can thus be linked to the poorer conjugative effect of an ethylenic substituent compared to any substituted phenyl group. The ethylenic substituent has nonetheless some conjugative effect for the cyclohexyl-morpholine barrier is even higher

Table 3. Barriers (kcal/mol) to ring inversion in N-(para-substituted-phenyl)-morpholines and to rotation in para-substituted-N-methylanilines[20]

para-substituent	Ring inversion Barrier	phenyl--NMe rotational barrier
NO_2	5 5	11 1
H	7 2	7 25
NH_2	8 0	3 5[a]

[a] Deduced from a Hammett plot of barriers in other substituted N-methylanilines[20], and a sigma value for p-NH_2 of -0 66[21]

The entropy of activation for N-methyl morpholine is noticeably less positive than that of morpholine itself which suggests that the N-methyl-substituent makes some ways of crossing the barrier[5] so unfavourable enthalpically that they are little used The similarity of activation parameters for methylene chloride and for methanol solutions of morpholine suggest that nitrogen inversion plays almost no role in determining the rate of ring inversion

EXPERIMENTAL

Nmr measurements were made in different solvents reflecting the different temperature ranges which were used see Table 4 but it is not expected that ring inversion barriers are solvent dependent and this proved to be correct for morpholine itself as shown in Table 1 Results in Table 1 are for solutions in approximately 1 1 CD_2Cl_2 $CHClF_2$ for 1f and 1g, approximately 1 1 CF_2Cl_2·$CHClF_2$ for 1h and 1i, and $CHClF_2$ for 1j Other nmr procedures have been described previously[9] The experimentally determined frequency of chair chair interconversion is expected to be one half the frequencly of chair twist interconversion[6,7] Barriers in Table 1 are for chair - twist interconversion calculated on this basis Compounds 1a, 1g-1i are commercially available Literature methods [22,23] were used to prepare 1f and 1g

Table 4. H-1 NMR parameters used for determining the ring inversion barriers in **1a, 1f - 1j** The $\Delta G^{\ddagger}$ values (K cal mol^{-1}) were obtained by total line shape analysis The shifts refer to the axial and equatorial hydrogens of the group indicated in parentheses The spectra were taken at 200 MHz except for **1j** (400 MHz)

Compound	Solvent	Shifts (ppm)	J(Hz)	$\Delta G^{\ddagger}$
R=H(**1a**)	CH_3OD	3 78, 3 52(OCH_2 at -88°)	-11 2	10 05
	CD_2Cl_2	3 62, 3 38(OCH_2 at -95°)	-11 3	10 12
R = cyclohexyl (**1f**)	CHF_2Cl/CD_2Cl_2	2 64, 2 30(NCH_2 at -70°)	-11 5	10 6
R = cyclohexenyl (**1g**)	CHF_2Cl/CD_2Cl_2	3 00,2 33(NCH_2 at -100°)	-11 5	9 1
R = phenyl (**1h**)	CHF_2Cl/CCl_2F_2	3 22, 2 61(NCH_2 at -135°)	a)	7 2
R = 4-aminophenyl (**1i**)	CHF_2Cl/CCl_2F_2	3 10, 2 65(NCH_2 at -126°)	a)	8 0
R = 4-nitrophenyl (**1j**)	CHF_2Cl	3 62, 2 96(NCH_2 at -152°)	a)	5 5

a) Invisible under the broad linewidth

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