Barriers to rotation in *ortho*-alkylphenyl substituted 1,3-benzoxazines[1]

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Four 3,4-dihydro-3-*ortho*-alkylphenyl-2*H*-1,3-benzoxazines have been synthesized. Enthalpies and entropies of activation for rotation about the phenyl–nitrogen bond have been calculated from the temperature dependence of the proton resonance spectra for the *o*-isopropyl ($\Delta S‡ = -4$ e.u., $\Delta H‡ = 10.8$ kcal/mole) and *o*-*t*-butyl ($\Delta S‡ = 0.4$ e.u., $\Delta H‡ = 16.9$ kcal/mole) derivatives. The barrier to rotation for the *o*-methyl and 2,6-dimethyl derivatives was too low to be measured by this procedure.

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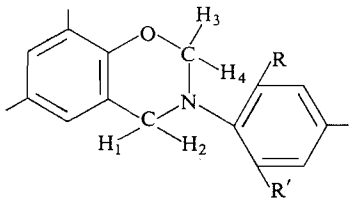
Introduction

There have been many high resolution magnetic resonance studies of hindered rotation about nominally single bonds (1–5). In most cases reported for hindered rotation about a carbon–nitrogen single bond the magnitude of the barrier to rotation has been attributed to partial double bond character. Thus far no studies have been reported in which changes in the barrier to rotation along a homologous series have been attributed solely to steric effects. In the present investigation proton resonance spectra were obtained for a series of substituted benzoxazines of the following general formula.



It was found that when R′ is a bulky substituent H-1 and H-2, and H-3 and H-4 were not equivalent on the nuclear magnetic resonance time scale.

In principle the non-equivalence of H-1 through H-4 could arise either by hindered rotation about the aryl carbon–nitrogen bond or by a barrier to inversion of the non-planar benzoxazine ring. Provided that R and R′ are not identical, H-1 through H-4 should remain non-equivalent even when ring inversion is rapid, provided that rotation about the carbon–nitrogen bond is slow. The non-equivalence arises from the closer proximity to R′ of, say, H-2 and H-4, compared with H-1 and H-3. If R = R′ this non-equivalence is removed.

When both hindered inversion and hindered rotation occur two different sets of non-equivalent proton signals can be expected. One set would arise from the isomer in which R′ is closest to H-1 and H-3 and the other set when R′ is closest to H-2 and H-4. However, if one of the R groups is more bulky than the other, one of the conformers may be present at a much lower concentration because steric repulsion between R and the benzoxazine ring will raise its potential energy. Therefore, although in principle two sets of non-equivalent proton signals can be expected, in fact only one set may be observable. If R = R′ the existence of two unique isomers would be removed and only one set of non-equivalent proton resonance signals would be observed. The possible situations are summarized in Table I.

In the preceding discussion it is implicitly assumed that there can be rapid inversion about the nitrogen atom. Because of the asymmetry of the benzoxazine ring, H-1 through H-4 will remain non-equivalent when inversion about nitrogen is fast, provided that ring inversion is slow. If ring inversion is rapid but rotation about the phenyl–nitrogen bond is slow, then ring inversion will probably be accompanied by nitrogen inversion to place the *o*-alkylphenyl ring in the conformation with minimum steric strain.

Experimental

Proton resonance spectra were obtained at 100 MHz on a "Varian Associates" HR 100 spectrometer. Probe temperatures were calibrated with a copper–constantan thermocouple in a dummy sample tube and should be accurate within 1 °C. Low temperature spectra were obtained using carbon disulfide as solvent while for the high temperature studies the solvent was *s*-tetrachloroethane. Tetramethylsilane was used as internal reference, and

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TABLE I

Relationship between motional freedoms and equivalency of benzoxazine ring protons

Inversion	Rotation	R = R′	R ≠ R′
Hindered	Hindered	Protons different	Two sets of different protons
Hindered	Free	Protons different	Protons different
Free	Hindered	Protons equivalent	Protons different
Free	Free	Protons equivalent	Protons equivalent

chemical shifts are reported as p.p.m. to low field. All melting points were determined on a Kofler hot stage using factory-calibrated thermometers. Infrared (i.r.) spectra were measured in carbon tetrachloride solution on a Perkin–Elmer model 621 spectrophotometer. The i.r. spectra of all the compounds showed no absorption in the 3700–3100 cm^{-1} region. The mass spectra were recorded on an Atlas CH 4 spectrometer. Microanalyses were carried out by Mr. J. R. H. Seguin of these laboratories.

*6-tert-Butyl-3,4-dihydro-3-o-tolyl-2H-1,3-benzoxazine (**1**)*

A solution of 1.5 g of barium hydroxide octahydrate in 25 ml (0.33 mole) of formalin was added to a mixture of 10.9 g (0.073 mole) of 4-*tert*-butylphenol and 7.8 g (0.073 mole) of *o*-toluidine and the mixture shaken at room temperature for 6 h. After the aqueous phase was decanted, the solid was dissolved in benzene and the solution washed with water. Benzene was removed after drying to give 18.8 g of crystalline product which recrystallized from 95% ethanol to produce 12.6 g of colorless crystals, m.p. 88–90°. An analytical sample was recrystallized from pentane, m.p. 90.9–92.0°. The i.r. spectrum showed no absorption in the 3700–3100 cm^{-1} region.

Anal. Calcd. for $C_{19}H_{23}ON$ (mol. wt., 281): C, 81.10; H, 8.24; N, 4.98. Found (mol. wt., mass spectroscopy, 281): C, 81.02; H, 8.21; N, 4.89.

*6-tert-Butyl-3,4-dihydro-3-(2,6-xylyl)-2H-1,3-benzoxazine (**2**)*

Treatment of 3.0 g of 4-*tert*-butylphenol and 2.4 g of 2,6-xylidine with alkaline formalin gave a product containing some starting materials (by thin-layer chromatography). The benzene solution was extracted with 2 *N* hydrochloric acid, with 10% sodium hydroxide solution, and then water. Drying and concentration left 3.8 g of yellow syrup, n_D^{25} 1.5592, pure by thin-layer chromatography.

Anal. Calcd. for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.08; H, 8.51; N, 4.89.

*6-tert-Butyl-3-o-cumyl-3,4-dihydro-8-methyl-2H-1,3-benzoxazine (**3**)*

The use of 4-*tert*-butylphenol with 2-*iso*-propylaniline in the reaction above produced a strongly acidic phenolic compound rather than a benzoxazine.

When 3.3 g of 4-*tert*-butyl-*o*-cresol and 2.7 g of purified 2-*iso*-propylaniline (n_D^{25} 1.5458) were condensed with alkaline formaldehyde the only product was the benzoxazine. After solution in hexane, extraction and concentration, the colorless crystals (2.8 g) melted 91–97°. Recrystallization from ethanol gave 2.4 g of a compound of melting point 93–96°. An analytical sample was obtained from pentane, m.p. 97.5–99.0°.

Anal. Calcd. for $C_{22}H_{29}NO$ (mol. wt., 323): C, 81.69; H, 9.04; N, 4.33. Found (mol. wt., mass spectroscopy, 323): C, 81.39; H, 9.11; N, 4.05.

*6,8-Di-tert-butyl-3-(2,4-di-tert-butylphenyl)-3,4-dihydro-2H-1,3-benzoxazine (**4**)*

A mixture of 0.56 g of 2,4-di-*tert*-butylaniline, 0.56 g of 2,4-di-*tert*-butylphenol and 10 ml of 37% formalin solution (no catalyst) was stirred and heated in a bath at 95° for 2 h. The cooled suspension was filtered, washed with water, and vacuum dried. The colorless crystalline product (1.08 g) after recrystallization from absolute ethanol gave 0.72 g of colorless felted needles, m.p. 173–175.6°. Further recrystallization gave an analytical sample, m.p. 174.7–176.0°.

Anal. Calcd. for $C_{30}H_{45}NO$ (mol. wt., 435): C, 82.70; H, 10.41; N, 3.21. Found (mol. wt., mass spectroscopy, 435): C, 82.24; H, 10.23; N, 3.46.

Results and Discussion

The structural formulae of the compounds studied and chemical shifts for the various types of protons are given in Fig. 1. Theoretical spectra were calculated by computer using a previously reported program (6). To utilize this program for an AB system it is necessary to specify the position, intensity and transition probability for each line. In all the compounds H-1 and H-2 gave significantly broadened lines both at the limits of rapid rotation and slow rotation. This is attributed to long range spin coupling to a proton or protons on the adjacent aromatic ring. To correct for this line broadening a convolution integral was introduced into the computer program to broaden the theoretical spectra by a Gaussian function whose width could be adjusted to that of the experimental line widths in the absence of exchange broadening. In Fig. 2 experimental spectra for H-1 and H-2 of compound **3** are presented along with approximately equivalent theoretical spectra. The rate constant for rotation at a given temperature was obtained by interpol-

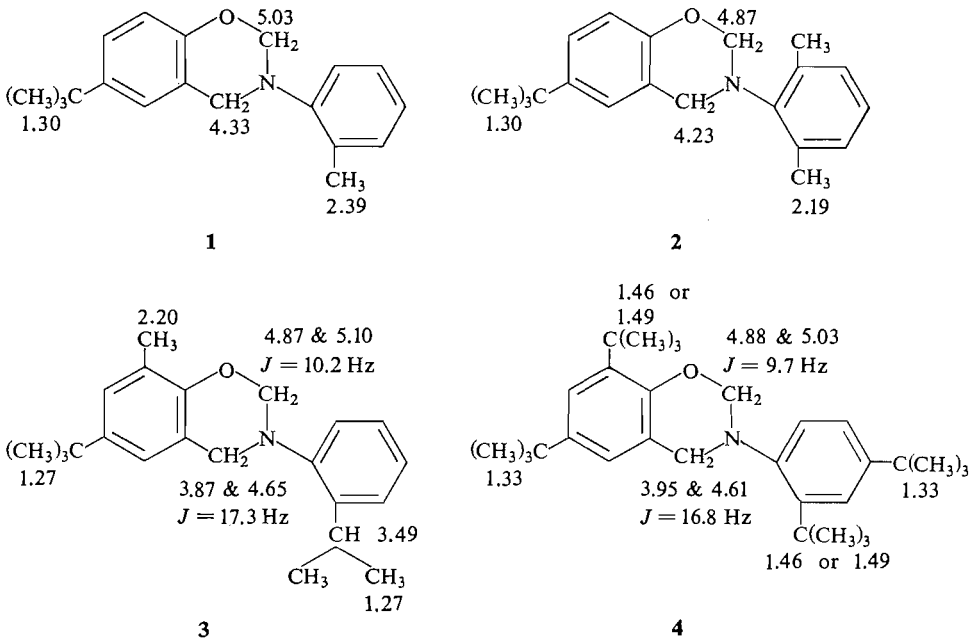

FIG. 1. Structural formulae and chemical shifts of some benzoxazines.

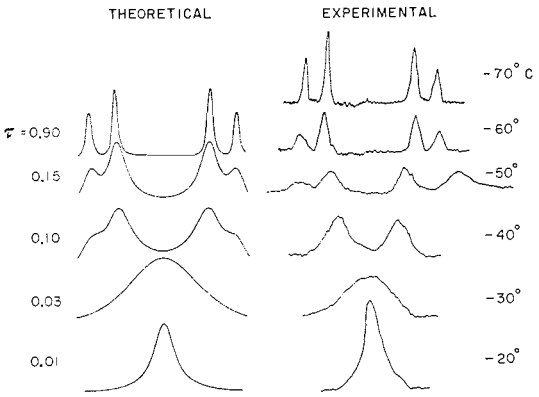

FIG. 2. Theoretical and experimental spectra for H-1 and H-2 of compound **3**.

ation of line widths and peak to trough ratios between theoretical spectra closely matching the experimental spectrum.

At room temperature the benzoxazine ring protons are equivalent, in pairs, for compounds **1**, **2**, and **3** but are non-equivalent in **4**. Lowering the temperature below 0 °C causes an observable non-equivalence in the proton resonance spectra for **3** but the protons in **1** and **2** remain equivalent down to the lowest temperatures studied (−60 °C). From the behavior of the proton resonance spectra of **3** and **4** it can be concluded that there is rapid inversion but that rotation about the carbon–nitrogen bond is slow on the n.m.r. time scale. Further evidence for this conclusion is obtained from the methyl resonances of R in compounds **3** and **4**. If ring inversion is slow there should be two different environments for R, i.e. with the *o*-alkyl substituted phenyl axial or equatorial, regardless of the rate of rotation about the carbon–nitrogen bond. Examination of a space filling molecular model suggests that there is considerable steric hindrance about the nitrogen of the benzoxazine ring. For a given conformation of the ring only one configuration of the benzene ring, relative to nitrogen, can be constructed. Therefore, the averaging effect of inversion about nitrogen alone need not be considered. Since only a single sharp signal is observed for R under conditions that yield non-equivalent benzoxazine ring protons, it is quite likely that ring inversion is a rapid process.

In Fig. 3 the logarithm of the rate constant for rotation about the carbon–nitrogen bond of compound **4**, averaged for results from *both* sets of ring protons, is plotted against the reciprocal temperature. From a least squares analysis of this

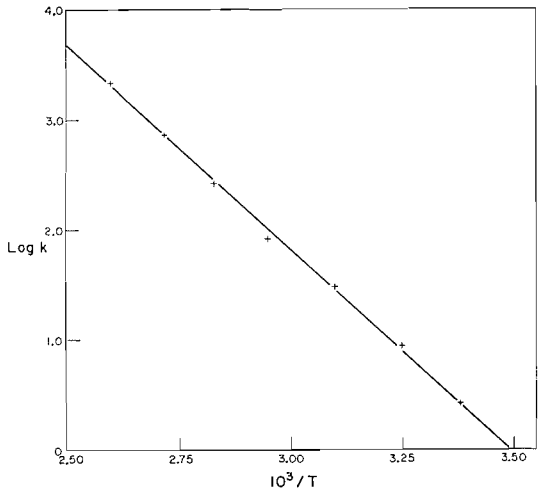

FIG. 3. The variation of rate of rotation with temperature for compound **4**.

data and similar data for compound **3** the following activation parameters were obtained.

$$\text{Compound } \mathbf{3}\ \Delta H^{\ddagger} = 10.8 \pm 0.6 \text{ kcal/mole}$$
$$\Delta S^{\ddagger} = -4 \pm 2 \text{ e.u.}$$
$$\text{Compound } \mathbf{4}\ \Delta H^{\ddagger} = 16.9 \pm 0.3 \text{ kcal/mole}$$
$$\Delta S^{\ddagger} = 0.4 \pm 0.2 \text{ e.u.}$$

The activation entropies are normal suggesting no unusual conformational requirement in the transition state for rotation. The failure to observe any line broadening arising from non-equivalent protons in compound **1** even at -60 °C implies that the rate constant for rotation in this compound is greater than 3.3×10^3 s^{-1} if we assume that all compounds have similar chemical shift differences. If we make the further assumption that $\Delta S^{\ddagger} = 0$ for compound **1** it can be calculated that $\Delta H^{\ddagger}$ for an *o*-methyl substituent is less than 8.9 kcal/mole. The barrier to rotation about the phenyl–nitrogen bond therefore increases by more than 1.9 kcal/mole on changing the *ortho* substituent from methyl to isopropyl and by 6.1 kcal/mole on changing from isopropyl to *t*-butyl.

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