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Synthesis and Structure Assignments of *cis*- and *trans*-2-(Diethylaminomethyl)cyclohexanols

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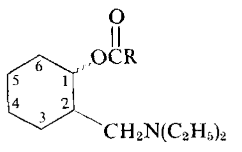
Abstract—The synthesis of *cis*- and *trans*-2-(diethylaminomethyl)-cyclohexanols and their structural assignments by NMR using the shift reagent Eu(dpm)$_3$ are described. The correlation of the induced shifts with the equation $\Delta\nu = K(3\cos^2\theta - 1)r^{-3}$, assuming an Eu—O distance of 2·4 Å and θ less than 30°, suggests that the interactions are pseudocontact. The values of K are 452 and 420 for the two cyclohexanols, respectively.

INTRODUCTION

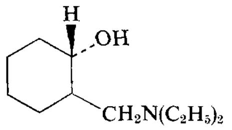
SINCE the discovery by Hinckley[1] and the subsequent studies of Sanders and Williams[2] of the effectiveness of tris-(dipivalomethanato)europium (III), [Eu(dpm)$_3$], as an NMR chemical shift reagent, much progress has been made both in the number of shift reagents developed and the sophistication of their applications,[3] e.g. the comparison of bond lengths and angles derived from NMR spectroscopy and crystal X-ray data. The earlier applications of shift reagents in the study of 4-substituted cyclohexanols[4] have been supplemented by more recent studies.[5]

We applied shift reagent techniques to the determination of the stereochemistry of 2-substituted cyclohexanol derivatives (**1**) where R is an aryl group. Although the first order analysis of the NMR data of the aryl derivatives in dimethylsulfoxide-d_6 (DMSO-d_6), permitted the characterization of the C-1 methine proton as either axial ($W\frac{1}{2} = 18$ Hz, δ (ppm) $\simeq 4{\cdot}6$) or equatorial ($W\frac{1}{2} = 8$ Hz, δ (ppm) $\simeq 5{\cdot}2$) nothing could be said about the conformation of the C-2 group. To make these assignments, the precursor cyclohexanols (**2** and **3**) were studied by NMR spectroscopy, utilizing the Eu(dpm)$_3$ shift reagent. The application of shift reagents to difunctional substrates is still very rare.

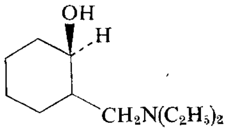
The compounds were prepared according to Scheme 1. An improved synthesis of **4** and **5**, and the separation of the isomers **2** and **3**, are described in the Experimental section.



(**1**)



(**2**)

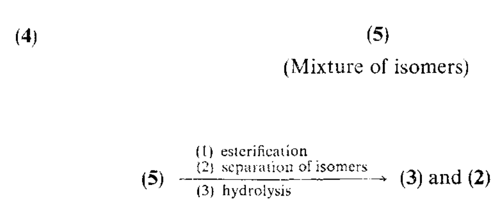


(**3**)

RESULTS AND DISCUSSION

The NMR data for **2** and **3**, obtained in deuterochloroform (CDCl$_3$) and deuterobenzene (C$_6$D$_6$) with TMS as internal standard, are listed in Table 1. On dilution of the CDCl$_3$ solution from 0·27 to 0·04 M, the resonance of the hydroxyl protons of **3** was shifted upfield from δ 5·67 to 4·65. On the other hand, under similar conditions, the resonance of the hydroxyl protons of **2** remained constant at δ 6·53. These observations suggest the occurrence of inter- and intramolecular hydrogen bonding for **3** and **2**, respectively. In C$_6$D$_6$ the resonance of the OH protons appeared at δ 6·10 (broad) and 4·95 sharp for **2** and **3**, respectively.

In dilute solutions in carbon tetrachloride, the infrared spectrum of **3** exhibited the stretching frequency of a nonbonded hydroxyl group at 3630 cm^{-1} and of a bonded hydroxyl band at 3240 cm^{-1}. At concentrations of 0·008 and 0·0008 M the ratios of absorbances of the free and bound hydroxyl bands are 0·18 and 0·42, respectively. This dependence on concentration of the infrared absorptions suggests that **3** bonds intermolecularly by a cyclic dimerization.[6] In the case of dilute



SCHEME 1

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TABLE 1. NMR DATA FOR 2-(DIETHYLAMINOMETHYL)CYCLOHEXANOLS[a]

Compound	Solvent	Chemical shifts					
		OH	C_1—H	C_6—H	C_5—H,C_4—H,C_3—H C_6—H,C_2—H	CH_2N=	CH_3
(**2**)	$CDCl_3$	6·5 b	3·4 s	2·0 m	1·7 m	2·8 q (1 H)	1·1 t
	(0·21M)		(10, 10, 4)		1·6	2·7 q (1 H)	
					1·4	2·4 m (3 H)	
					1·2	2·3 q (1 H)	
	C_6D_6	6·1 b	3·4 s	2·1 E	1·6 m	2·5 q	0·9 t
			(10, 10, 4)		1·5	2·4 q	
					1·4	2·1 m	
					1·2	2·0 q	
(**3**)	$CDCl_3$	5·7 b	3·8 n	2·1 m	1·7	2·9 m	1·0 t
	(0·27 M)		(7, 4, 4)		1·4	2·6 q	
					1·3	2·5 q	
						2·3 q	
	C_6D_6	5·0 s.s	3·9 n	2·3 E	1·7	2·6 m	0·9 t
			(7, 4, 4)		1·3	2·4 q	
						2·3 q	
						2·2 m	

[a] s = sextuplet; E = Estimated, hidden under the $CH_2N(CH_2—)_2$ protons resonances; b = broad; q = quartet (J = 7·0 Hz); t = triplet (7·0 Hz); m = multiplet; s.s = sharp signal; n = quintuplet.

solutions of **2** in carbon tetrachloride, no frequency ascribed to a nonbonded hydroxyl group was observed and the bonded hydroxyl band appeared at 3240 cm^{-1}.

In **2** the proton resonance at δ 3·38 (sextuplet, J = 10·0, 10·0, 4·0 Hz) [Fig. 1(b)] with two large couplings (ax–ax) and one small coupling (ax–eq) is assigned to the C_1—H_{ax} proton. Irradiation at δ 1·93 (C_6—H_{eq}) collapsed the sextuplet to a doublet of doublets (J = 10·0, 10·0 Hz) at δ 3·38 with loss of the ax–eq coupling of 4·0 Hz, and irradiation at δ 1·70 (C_6—H_{ax}) collapsed the sextuplet to a broad singlet (W½ = 7·0 Hz), indicating loss of ax–ax coupling. Irradiation at δ 1·54 (C_2—H_{ax}) collapsed the sextuplet at δ 3·38 to a broad singlet (W½ = 5·0 Hz) and also collapsed the multiplet at δ 2·38 (C_2—CH_2N = group). On the other hand, in **3**, the resonance at δ 3·82 (quintuplet, J = 7·0, 4·0, 4·0 Hz) [Fig. 1(a)], with two small and one large coupling constants, is assigned to the C_1—H_{eq} proton. Irradiation at δ 2·12 (C_6—H_{eq}) collapsed the quintuplet at δ 3·84 (C_1—H_{eq}) to a doublet of doublets (J = 7·0, 4·0 Hz), indicating loss of the 4·0 Hz coupling. Similar irradiations at δ 1·71 and 1·60 collapsed the quintuplet to a broad singlet (W½ = 8·0 Hz), and the proton resonances are assigned to C_6—H_{ax} and C_2—H_{ax} protons, respectively. These assignments are consistent with the 'chair' conformation of the cyclohexane, in which the $CH_2N(C_2H_5)_2$ group assumes a fixed equatorial position in both cases. It is not possible *a priori* to assign the other multiplets to methylene protons arising from the $CH_2N(C_2H_5)_2$ group. However, the use of the complexing reagent $Eu(dpm)_3$ simplified the spectra greatly.

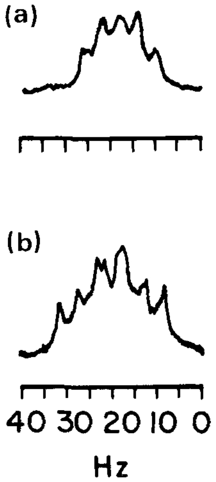


FIG. 1. 500 Hz expansion of (a) C_1—H_{eq} and (b) C_1—H_{ax} proton resonances of **3** and **2**, respectively, at 100 MHz frequency.

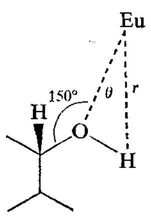
The quantitative additions of the shift reagent to $CDCl_3$ solutions of **2** and **3** are shown in Figs. 2(b) and 2(a), respectively. The assignments of the protons were made on the basis of decoupling experiments in the presence of the shift reagent. The slopes obtained from the linear plots of **2** and **3** are of the order C_1—OH_e(47)<C_1—H_a(17)<C_6—H_e(14)<C_6—H_a(10)<C_2—H_a(5)<C_2—CH_2N(2) and

$$C_1—OH_a(50)<C_1—H_e(21)<C_6—H_e(11)$$

$$\simeq C_6—H_a(11) \simeq C_2—H_a(11)<C_2—CH_2N(5),$$

respectively. The $-CH_2N(C_2H_5)_2$ group proton resonances are shifted the least, suggesting that nitrogen is not the coordinating site. The slopes of **2** and **3** are considerably smaller than those observed for *cis*- and *trans*-4-*t*-butylcyclohexanols,[4] presumably because of steric effects and/or hydrogen bonding. The induced shifts can be calculated from the McConnell and Robertson[7] equation, $\Delta\nu = K\ (3\cos^2\theta - 1)r^{-3}$, where θ is the O—Eu—H internuclear angle and r is the corresponding Eu—H distance.

Using molecular models the distances r of the protons from the europium ion in **2**, were calculated by placing Eu in the O—C_1—H_a plane with a Eu—O distance of 2·4 Å[8] and C_1—O—Eu angle of 150° as follows.



A plot of log $\Delta\nu$ vs log r gave a slope of $-3{\cdot}2$. Similar calculations for **3**, with the same Eu—O distance and C_1—O—Eu angle of 135° resulted in a slope of $-2{\cdot}8$. The substitution of r values in the above equation along with θ values between 20 to 30°, chosen to obtain a 'best fit,' resulted in K of 452 for **2**, whereas, θ values between 10 to 30° gave a K value of 420 for **3**. The range of values of K was about 3 %. The fit of the data suggests that the interactions are pseudo contact. In addition, the NMR data suggest that the approach of the $[Eu]^{3+}$ ion is from the C_1—C_6 bond in **2**, but it is from the axial side in **3**. The cyclohexanols may be represented as follows:

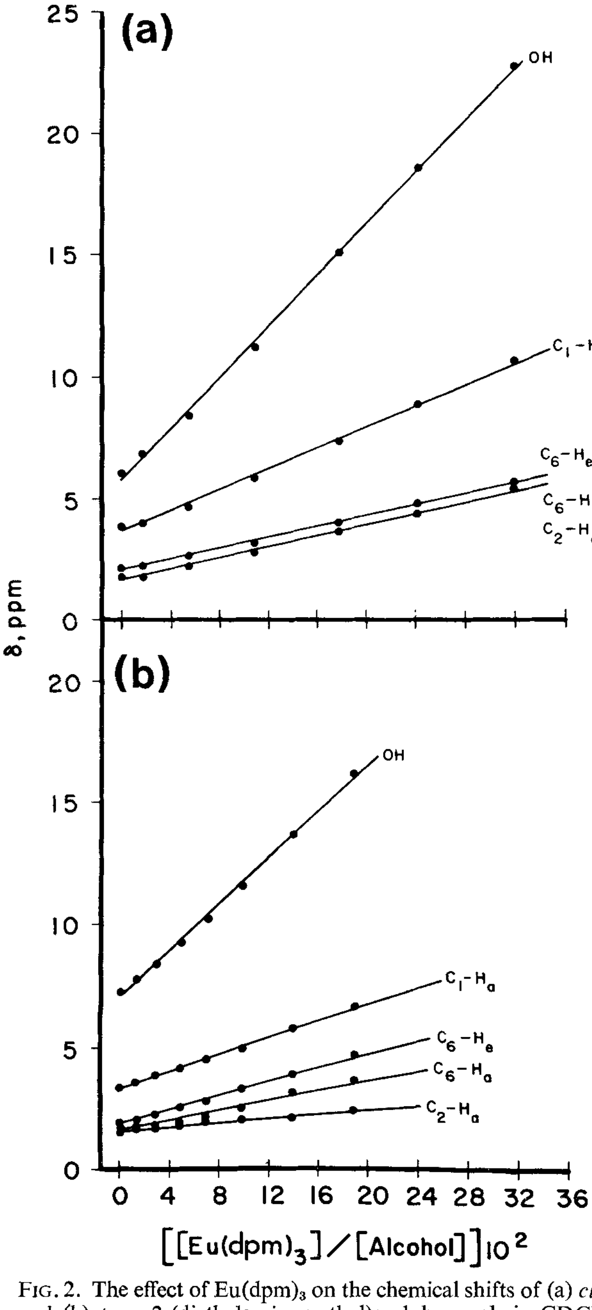
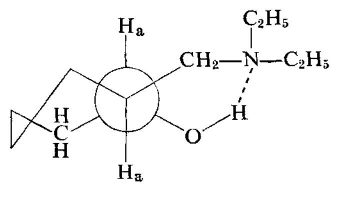
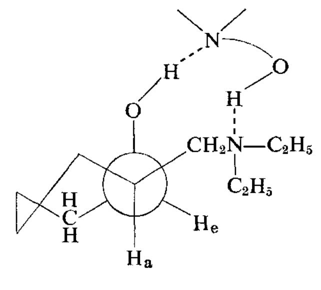


Fig. 2. The effect of $Eu(dpm)_3$ on the chemical shifts of (a) *cis*- and (b) *trans*-2-(diethylaminomethyl)cyclohexanols in $CDCl_3$.



(2)



(3)

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were obtained with a Perkin Elmer 621 spectrophotometer. The NMR spectra were recorded on a Varian XL-100-15 spectrometer internally locked to ^2H frequency of 15·4 MHz.

The lanthanide-induced shifts were determined by successive addition of the shift reagent ($Eu(dpm)_3$, Thompson-Packard, Little Falls, New Jersey) to the solution of substrate in $CDCl_3$. The solvent was dried over molecular sieve type 3A. Each NMR spectrum was recorded at approx. 32 °C, expanded and then decoupled.

The slope is defined as

$$\frac{\delta_1 - \delta_2}{[Eu(dpm)_3/\text{alcohol}]_1 - [Eu(dpm)_3/\text{alcohol}]_2}$$

The values are given in parentheses (page 509), estimated for the C_2—CH_2N group. No statistical analysis was performed.

2-(Diethylaminomethyl)cyclohexanone (4)

To a 3 l. flask was added 146 g (2·0 mol) of diethylamine and 600 g (6·0 mol) of cyclohexanone. This solution was stirred and treated portionwise with 170 ml (2·0 mol) of concentrated hydrochloric acid while the temperature was maintained below 40 °C. This mixture was cooled to 25°C, treated with 150 ml (162 g, 2·0 mol) of 37 % formaldehyde solution and heated slowly (30 min) to 80 °C. The temperature was maintained at 75 to 80 °C for 30 min, then the solution was cooled to room temperature, and treated with 500 ml of cold water and 500 ml of ether. The mixture was shaken and the layers were separated. The aqueous phase, after extraction with 500 ml of ether to remove unreacted cyclohexanone, was cooled and treated slowly with 400 g of K_2CO_3. The liberated base was extracted with 500 ml of ether (three times). The organic phases were combined and dried ($MgSO_4$), and the solvent was removed on a rotary evaporator to give 346 g (94 %) of an oily residue. This material[9] was kept cold prior to the reaction with $LiAlH_4$.

2-(Diethylaminomethyl)cyclohexanol, *cis* and *trans* Isomers (5)

In a 5 l. flask, 1·5 l. of THF was stirred and treated portionwise with 37·0 g (1·0 mol) of $LiAlH_4$ while the temperature was maintained below 30 °C. This slurry was stirred and treated dropwise with **4** (during 30 min) while the temperature was maintained at 20 to 25 °C. The mixture was stirred at room temperature for 30 min and refluxed for 4 h, then it was cooled and treated *dropwise* with 30 ml of water to destroy the excess $LiAlH_4$ (the quantity of this reagent could probably be decreased in this reaction). A solution of 20 g of NaOH in 50 ml was added, then ether to make the total volume 4·5 l. The mixture was allowed to stand overnight; most of the solids precipitated and were filtered through a sintered glass funnel and washed well with ether. The filtrate was dried ($MgSO_4$) and filtered and the solvent was removed on a rotary evaporator. The residue was fractionated to give 320 g (91%) of colorless liquid; b.p. 82 to 87 °C (2 mm).

Any large scale reaction of the ketone with $NaBH_4$ in CH_3OH should be avoided because H_2 is evolved vigorously at the reaction temperature (40 °C). This mixture of alcohols (**5**) was initially prepared by treatment of the ketone with Al—Hg.[9]

2-(Diethylaminomethyl)cyclohexyl-*p*-nitrobenzoate, hydrochlorides, *cis* and *trans* esters of 5

A solution of 298 g (1·6 mol) of *p*-nitrobenzoyl chloride in 1·5 l. of $CHCl_3$ was stirred and treated dropwise with 295 g (1·6 mol) of **5** (during 15 min) while the temperature was maintained at 20 to 25 °C. The solution was stirred at room temperature for 30 min and refluxed for 2 h, then was cooled and the solvent removed on a rotary evaporator. The partly crystalline residue (777 g) was dissolved in 500 ml of hot CH_3CN and the product was allowed to crystallize at room temperature for several h. After standing in the cold overnight, the crystalline solid was filtered and dried; wt 353·9 g, m.p. 174 to 182 °C. This material was dissolved in 700 ml of hot CH_3CN and the resulting solution was allowed to cool overnight at room temperature to give 236 g (42%) of the colorless *trans* isomer, m.p. 184 to 186 °C; λ max (Nujol) 4·1, 5·8, 6·2, 7·4 μ.

The first CH_3CN filtrate was diluted to 1·4 l. with ether to yield 133 g of the impure *cis* isomer (m.p. 165 to 168 °C). After recrystallization from CH_3CN and then from EtOH at room temperature, the *cis* isomer weighed 70 g (12%), m.p. 177 to 179 °C; λ max (Nujol) 3·8, 3·95, 5·8, 6·2, 7·4 μ.

trans-2-(Diethylaminomethyl)cyclohexanol (2)

A suspension of 100 g (0·27 mol) of the above *trans* ester in 500 ml of EtOH was treated with a solution of 66 g of KOH in 300 ml of H_2O. The mixture was refluxed for 3 h, then was cooled and filtered to remove the yellow solid. The filtrate was concentrated on a rotary evaporator to remove most of the EtOH. The residue was cooled and extracted with 250 ml of ether (four times). The ether phases were combined, dried ($MgSO_4$) and filtered, and the solvent was evaporated. Fractional distillation of the residue gave 44·9 g (90%) of colorless liquid, b.p. 78 to 80 °C (2 mm); λ max (Nujol) 3·0 μ.

cis-2-(Diethylaminomethyl)cyclohexanol (3)

Hydrolysis of 8·0 g of the *cis* ester according to the above procedure gave 3·5 g (87%) of colorless liquid, b.p. 85 to 86 °C (2 mm); λ max (Nujol) 2·8 μ.

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