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Conformational Analysis by LIS. II.[1] 2- and 3-Alkyl Substituted 1-Indanones

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The preferred conformations of the alkyl groups relative to the cyclopentenone ring of 2-ethyl-, 2-benzyl-, 2-isopropyl-, and 3-isopropyl-1-indanone were determined by means of the lanthanide-induced-shift technique (LIS). Two different models were used in the calculation of LIS. Coupling data — where available — were compatible with the conformations derived from LIS data.

(Keywords: Ketones, LIS-models; Lanthanide induced shifts)

Konformationsanalyse mittels Lanthaniden-induzierter Verschiebungen. II[1] 2- und 3-alkylsubstituierte 1-Indanone

Es wurden die bevorzugten Konformationen der 2-Ethyl-, 2-Benzyl-, 2-Isopropyl- und 3-Isopropylreste relativ zum Cyclopentenon-Ring von 2-, bzw. 3-Alkyl-1-indanonen mit Hilfe der LIS-Methode bestimmt; es wurden dabei zwei verschiedene Rechenmodelle herangezogen. In den Fällen, wo aus den Kopplungskonstanten auf die Konformation geschlossen werden konnte, waren diese Werte mit den Resultaten aus den Lanthaniden-induzierten Verschiebungen im Einklang.

Introduction

Conformational analysis of alkyl side chains in solution is a rather difficult task. In cases where the rotation is hindered (on the nmr scale) the commonly used vicinal coupling constants often lead to ambiguous results. One method to gain more information on the geometry of alkyl groups is offered by the LIS-technique[2,3].

In the present paper the conformations of alkyl side groups of the cyclopentenone part of 1-indanone are examined. Two common computational LIS models for ketones are used in the calculations: the one site model and the more recently recommended two site model[4]. In a

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preceding paper[5] it was demonstrated that the two site model offers no real advantages over the one site model which is much easier in handling. Nevertheless both models have been checked.

The conformations derived from LIS data are supported by the experimental coupling constants. In some cases the relevant coupling constants could only be determined from the lanthanide shifted spectra. All couplings remained constant over the whole range of reagent concentration thus indicating that no changes in conformation were introduced upon complexation. The coupling data alone did not suffice to deduce the preferred conformation of the alkyl groups but they were in no case contradictory to the LIS results. In one case interpretation of the ring current effect together with coupling constants and LIS data was necessary to clarify the situation.

Results

In all alkyl groups under consideration there are three LIS values which can be used to locate the positions of the protons of interest: ethyl (2 H, 1 *Me*), benzyl [2 H, 1 *para*-H; the latter is independent of the rotation of the phenyl ring and reflects therefore only the rotation about the C(cyclopentenone) — C(benzyl)-bond] and isopropyl (1 H, 2 *Me*). Note that the alkyl group is attached to a chiral center (C-2 or C-3) and that the two hydrogens of the CH_2 group in the ethyl and benzyl derivatives (and the two methyls of the isopropyl derivatives) are

Table 1. *Minimum R factors for all possibilities in assignment of positions A, B, and C to the experimental LIS (H and Me) for the one site model and the two site model* [ ]

Compounds and LIS[a, b] to be assigned	Minimum *R* factor in % ABC	BAC	BCA	CBA	CAB	ACB
2-*Et*	**6.4**	10	21	15	14	18
227 (H), 261 (H), 118 (*Me*)	**[9.0]**	[9.8]	[24]	[18]	[13]	[19]
2-*Bz*	**5.7**	9.5	21	15	17	23
245 (H), 271 (H), 18 (p-H)	**[3.9]**	[5.2]	[22]	[16]	[13]	[17]
2-*Isopr*	9.1	**5.9**	12	25	26	19
304 (H), 175 (*Me*), 119 (*Me*)	[8.2]	**[6.8]**	[17]	[27]	[24]	[14]
3-*Isopr*	7.9	7.6	**5.8**	**6.0**	7.4	7.7
90 (H), 61 (*Me*), 91 (*Me*)	[9.3]	[11]	**[6.6]**	**[7.0]**	[13]	[11]

[a] In Hz (60 Hz), $CDCl_3$ (*TMS*), $[Eu(dpm)_3]_0 : S_0 = 1:1$ extrapolated.

[b] Arrangement ACB for instance means for the 2-*Et* compound: 227 Hz, H, posit A; 261 Hz, H, posit. C; 118 Hz, CH_3, posit. B (see scheme).

therefore nonequivalent. Thus unique LIS values are obtained for each of the two hydrogens (or two methyls) in each case.

A complete permutation of positions attributed to the experimental LIS values then affords 6 different structure evaluations for each molecule. The analysis is based on the assumption that the staggered conformations (see scheme in *Newman* type projection) are adequate structural representations, an assumption justified by the observed couplings and some test calculations, where deviations of the purely staggered conformations did not improve the LIS fit of the minimum R assignments (Table 1).

Table 1 lists the R factors as a measure for the quality of the fit[2,6]. The results of both models are summarized in order to illustrate the essential agreement of both computational approaches for correct (lowest R factors) and incorrect assignments as well.

Discussion

2-Ethyl-1-indanone

No coupling constants between the C-2 proton and the ethyl CH_2 protons could be determined in this case. The results based on LIS allows a clear decision in favour of a conformation where the methyl points away from both the indanone ring system and the carbonyl group (type ABC, Tab. 1). The R factor ratio test[7,8] (meaningful only for the one site model[5]) results in a confidence level of 97.5% in favor of ABC over BAC which is the next best fit [R factor ratio 10:6.4 = 1.56; degrees of freedom = 6 (10—4); Tables in ref.[2,7]].

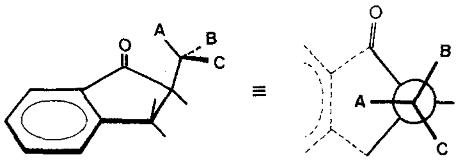
This implies that the C-3 CH_2 has a smaller steric interaction than the C-1 CO with the largest substituent of a freely roating alkyl group on C-2. The preferred conformation of a 2-benzyl substituent supports this conclusion.

2-Benzyl-1-indanone

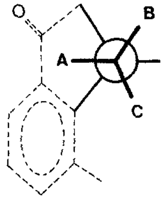
The two benzyl protons show coupling constants of 4.5 and 10 Hz to the proton at C-2. These values remain constant in the concentration range of $L_0:S_0 = 0.3$-1.0 (below 0.3 the corresponding proton signals are obscured by other resonances[9]; above 0.3 a simple first order analysis is possible). The proton exhibiting a 10 Hz coupling (LIS 245 Hz) is obviously in position A (*trans*-coplanar to the C-2 positioned proton in the cyclopentenone ring) the other could be either in B or C. Only types ABC (R 5.7 or 3.9; Tab. 1) or ACB (23 or 17) are able to account for the observed couplings. The LIS fit for ABC is much better (98% confidence level); the phenyl ring occupies an analogous position as the methyl group in 2-ethyl-1-indanone (i. e., position C).

2-Isopropyl-1-indanone

The coupling between the C-2 ring proton and the isopropyl proton is < 5 Hz (~ 4.5) the coupling pattern remaining constant between $L_0 : S_0 = 0.3$–0.8. The isopropyl proton may therefore occupy either positions B or C; BAC ($R = 5.9, 6.8$), BCA (12, 17), CBA (25, 27), and CAB (26, 24%) have to be taken into account to explain the coupling constant. Only BAC gives a good fit for the LIS data; confidence level 97% based on LIS and $> 99.5\%$ based on LIS *and* coupling data.



2- subst.



3-subst.

The proton occupies position B which is toward the carbonyl function which is therefore the sterically most unfavorable position for bulky substituents. The two methyl groups are directed to positions A and C. C is the sterically most unhindered position as is indicated by the results from 2-ethyl and 2-benzyl-1-indanone. The topology of position A differs from C by the interaction of the A substituent with the—relatively distant—phenyl ring of indanone. The main (non bonded) interaction between an A or C substituent with the *cis* proton at C-3 is the same in A and C.

2-Methyl- and 2-tert-Butyl-1-indanone

These two compounds show an average signal for *Me* and *tert-Bu*, giving an average LIS value as well. The assumption of an essentially equivalent Eu(III) position in the complexes of all 2-substituted 1-indanones (which is not completely correct but is a good approximation) allows the calculation of approximate LIS values for H and *Me* in positions A, B and C. H or *Me* in corresponding positions should exhibit similar LIS values in all compounds in the 2-substituted series. Table 2 shows these estimated LIS [based on the Eu(III) position in 2-methyl-1-indanone] together with the experimental LIS in the corresponding conformational positions (as assigned above). All of the 2-alkyl-1-indanones described here fit nicely into the scheme.

3-Isopropyl- (and 3-Methyl) 1-indanone

The coupling of the proton at C-3 with the isopropyl proton is 4 Hz and remains constant upon addition of shift reagent. This is consistent

Table 2. *Expected (based on calculations of the 2- and 3-methyl compounds, one site model) and experimental LIS for H and Me, positions A, B, and C (see scheme)*

		H			*Me*	
	A	B	C	A	B	C
2-subs. (calc.)	225	285	153	145	300	105
		averaged 221			averaged 183	
2-*Me*		av. 230		—	—	—
2-*Et*	227	261	—	—	—	118
2-*Bz*	245	271	—	—	—	—
2-*Isopr*	—	304	—	175	—	119
2-*tert-Bu*	—	—	—		av. 174	
		H			*Me*	
	A	B	C	A	B	C
3-subst. (calc.)	120	87	85	98	64	64
		averaged 97				
3-*Me*		av. 91		—	—	—
3-*Isopr*	—	—	90	91	61	—

with arrangements H/*Me*/*Me* in positions BAC (7.6, 11), BCA (5.8, 6.6), CBA (6.0, 7.0), and CAB (7.4, 13). No clear decision is possible based on the LIS calculations. The confidence level is only 50% for BCA in perference to CBA (and thus no decision between BCA or CBA is possible) but a choice in favor of either BCA or CBA versus CAB and BAC can be made at the 90% confidence level.

The chemical shifts of the two isopropyl methyl groups in the absence of shift reagent are δ 0.67 and 1.02 ppm. The former value is rather low and can be assigned to a methyl group in position A where the anisotropy of the phenyl ring (and carbonyl) can cause a significant shift to lower frequencies. This methyl in position A should suffer a higher LIS than the others (Tab. 2). This is again consistent with either CBA or BCA. However the other group absorbs at the "normal" value of 1.02 ppm and thus does not seem to be near the aromatic ring. This suggests that it occupies position B.

Therefore the combination of all data [the coupling constant, the chemical shifts (ring current effect) and the LIS data] indicate that only one type, namely CBA accounts for all the evidence. Position C seems therefore to be the sterically most unfavorable; this may result from larger steric requirements of the aromatic ring, including nonbonded interactions with the *ortho* hydrogen.

The expected LIS for H and *Me* in positions A, B, and C [based on the Eu(III) position calculated from 3-methyl-1-indanone] are shown in Tab. 2. The range of LIS (64–120 Hz) for the different positions is much narrower than for the 2-alkyl series (94–300 Hz), and reflects the difficulties encountered in the computational evaluation of the LIS for 3-alkyl-1-indanones.

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Experimental

The proper cartesian coordinates of the proton positions were calculated using the computer program COORD (QCPE program no. 136). The average proton position in freely rotating methyl groups was simulated either by "positional averaging" (one average position in the center of the three actual H) or by seperate calculation of geometrical factors for the individual protons (positioned in staggered conformation) with following averaging of the geometrical factors before scaling to the experimental LIS ("LIS averaging")[2]. The LIS for the 1-indanone part of the molecules are given in ref.[5].

Calculations using the "one site model" were performed with the computer program of *Willcott* and *Davis* (PDIGM)[8]. Details concerning the "two site model" are given in ref.[5] (TSM, modus II).

The nmr spectra were recorded with a Varian EM 360 spectrometer at constant substrate concentration ($CDCl_3$, *TMS*) and increasing amounts of tris(dipivalomethanato)europium(III)[5]. The normal 60 MHz spectra are listed below. The assignments of the H and *Me* in the alkyl branches (A, B, C) correspond to the notation used in the tables and in the scheme.

2-Methyl-1-indanone[10]: 7.67 (d, $H_{arom.}$), 7.40 (m, 3 $H_{arom.}$), 3.38 (q, $J_{gem.} = 17.5$ Hz, $J_{vic} = 8.5$ Hz), 2.73 (q, $J_{gem.} = 17.5$ Hz, $J_{vic.} = 3.8$ Hz), 2.7 (m, $J = 8.5$, 3.8, 6.8 Hz), 1.33 (d, CH_3, $J = 6.8$ Hz).

2-Ethyl-1-indanone[11]: 7.82 (d, $H_{arom.}$), 7.50 (m, 3 $H_{arom.}$), 3.35 (q, $J_{gem.} = 17$ Hz, $J_{vic.} = 8$ Hz), 2.85 (q, $J_{gem.} = 17$ Hz, $J_{vic.} = 3.5$ Hz, 2.62 (m), 1.88 (m, $\mathbf{CH_2}$—CH_3, posit. A), 1.67 (m, $\mathbf{CH_2}$—CH_3, posit. B), 1.00 (t, $J = 7$ Hz, CH_2—$\mathbf{CH_3}$).

2-Benzyl-1-indanone[9]: 7.82 (d, $H_{arom.}$), 7.50 (m, 3 $H_{arom.}$), 7,32 (5 $H_{arom.}$), 3.00 (pseudo d, 2 H), 2.67 (m), 3.42 (q, $J_{gem.} = 14.5$ Hz, $J_{vic.} = 4.5$ Hz, —$\mathbf{CH_2}$—*Ar*, posit. B), 2.92 (q, $J_{gem.} = 14.5$ Hz, $J_{vic.} = 10$ Hz, —$\mathbf{CH_2}$—*Ar*, posit. A): coupling constants could be evaluated from doped spectra only (L_0:S_0 > 0.3).

2-Isopropyl-1-indanone[12]: 7.83 (d, $H_{arom.}$), 7.55 (3 $H_{arom.}$), 3.2 (q, $J_{gem.} = 17$ Hz, $J_{vic.} = 8$ Hz), 3.00 (q, $J_{gem.} = 17$ Hz, $J_{vic.} = 3.5$ Hz), 2.67 (m, sum of $J = 16$ Hz $= 8 + 3.5 + 4.5$ Hz), 2.37 [m, —$\mathbf{CH}(CH_3)_2$, posit. B], 1.08 [d, —$CH(\mathbf{CH_3})_2$, $J = 6.8$ Hz, posit. C], 0.83 [d, —$CH(\mathbf{CH_3})_2$, $J = 6.8$ Hz, posit. A].

2-tert-Butyl-1-indanone[13]: 7.78 d, $H_{arom.}$), 7.50 (3 $H_{arom.}$), 3.10 (m, 2 H), 2.50 (m, 1 H), 1.07 (s, 9 H).

3-Methyl-1-indanone[10]: 7.78 (d, $H_{arom.}$), 7.58 (3 $H_{arom.}$), 3.46 (m, $J = 7, 7.3, 3.7$ Hz), 2.95 (q, $J_{gem.} = 18.7$ Hz, $J_{vic.} = 7.3$ Hz), 2.28 (q, $J_{gem.} = 18.7$ Hz, $J_{vic.} = 3.7$ Hz), 2.05 (d, CH_3, $J = 7$ Hz).

3-Isopropyl-1-indanone[14]: 7.74 (d, $H_{arom.}$), 7.52 (3 $H_{arom.}$), 3.41 (m, C-3—**H**, $J = 7, 4, 4$ Hz), 2.64 (q, $J_{gem.} = 18.5$ Hz, $J_{vic.} = 7$ Hz), 2.45 (q, $J_{gem.} = 18.5$ Hz, $J_{vic.} = 4$ Hz), 2.27 [m, C**H**(CH_3)$_2$, posit. C], 1.02 [d, —CH(C**H**$_3$)$_2$, $J = 7$ Hz, posit. B], 0.67 [d, —CH(C**H**$_3$)$_2$, $J = 7$ Hz, posit. A].

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