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Alkylation of carbonyl compounds in water: formation of C-C and C-O bonds in the presence of surfactants

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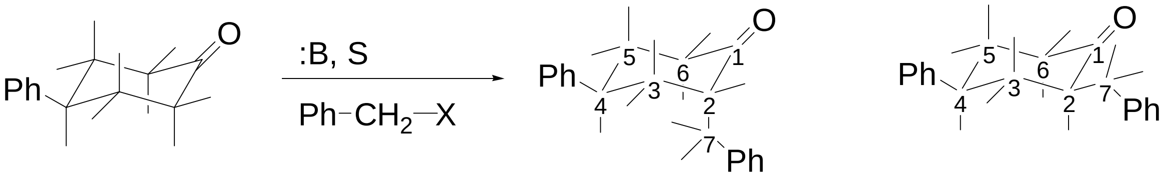
Structural analysis of α-benzyl-γ-phenylcyclohexanone

Since from the benzylation of γ-phenylcyclohexanone, we could obtain both the *cis*- and the *trans*-α-benzyl-γ-phenylcyclohexanone (Scheme S1), we wish to analyse the obtained compound.



:B = base, S = surfactant

Scheme S1. Benzylation of γ-phenylcyclohexanone

NMR data and theoretical calculations (Tables S1 and S2) suggest, as the major product, the *cis*-α-benzyl-γ-phenylcyclohexanone.

The chemical shift and spin-spin coupling constants are profoundly sensitive to the spatial arrangement of atoms in a molecule,[1] for this reason we have pointed the attention on the aliphatic portion of ^{1}H-NMR and also on the Haasnoot’s generalization of Karplus-equation[2] in order to estimate ^3J coupling constants, where the dihedral angles for both, the *cis*- and *trans*- isomer, were estimate using Spartan Plus software[3] (Wavefunction) with initial molecular mechanics minimization (MMFF) followed by ab initio treatments. We used the HF 6-31G level.

Spectral assignments (Table S1 and Experimental Section) were assisted by COSY and HETCOR 2D spectra. The axial and equatorial protons were assigned both on the basis that the chemical shift of an equatorial proton H_e at a given carbon atom in a homo-nuclear six-membered ring is at lower field than that of the axial hydrogen H_a at the same carbon atom[1b,4] (but for cyclohexanones normally an α-axial proton is more deshielded than the α-equatorial proton)[5] and by the equally well known observation that $J_{aa} >> J_{ae} \sim J_{ee}$,[1] from witch follows that the band width of the axial proton is appreciably greater than that of the equatorial proton. The method, although approximate, is sufficiently good to enable one to assign signals with confidence to equatorial and axial protons.[6]

The analysis to verify the hypothesis of *cis*- isomer, for the α-benzyl-γ-phenylcyclohexanone, was pointed on shape and multiplicity of H_2 (2.75ppm) and H_{3a} (1.63ppm) signals (Scheme S1). From a 1st order analysis (that is not necessarily strictly correct) the multiplicity of H_{3a} results from the spin-spin interaction with three H-nucleolus with similar coupling constants. The COSY experiment showed that the H_{3a} was coupled with the three hydrogens H_4, H_{3e} and H_2. From the line width and the splitting of H_4 we could hypothesise that the γ-phenyl group was equatorial, hypothesis confirmed by a previous conformational work on γ-Phenylcyclohexanone,[7] and so the H_4 was axial, and shared a $^3J_{aa}$ coupling with H_{3a} (Table S2). Literature data[8] show that the average of geminal coupling in cyclohexanones is about –13 Hz, follows that the third nucleolus, the H_2, should be axial with a coupling constant $\left|^3J_{aa}\right| \cong$ 13 Hz. From this analysis follows that if the H_4 and H_2 were axial the two substituents α-benzyl and γ-phenyl were in *cis* relation.

In support of the suggested isomer we have performed calculation in order to estimate the vicinal proton-proton coupling for the *cis-* and *trans-* isomers and compare those with the experimental data.

In this work we consider the Haasnoot's empirical generalization of the Karplus-equation (the results are shown in Table S2):

$$^3J_{HH} = P_1\cos^2\phi + P_2\cos\phi + P_3 + \sum\Delta\chi_i\{P_4 + P_5\cos^2(\xi_i\ \phi + P_6\ |\Delta\chi_i|\} \qquad \text{(S1)}$$

using the dihedral angles ϕ estimated by *ab initio* calculations.

As a results the parameters estimated for the *cis-* isomer agree with the experimental ones whereas a poorly agreement was found between the calculated and the estimated parameters for the *trans-* isomer (Table S1 and S2).

We would like to stress the evidence that for the *trans-* isomer the calculated coupling $^3J_{H2e\text{-}H3a}$ is much lower than the experimental data (compare 5.23 Hz with 12.85 Hz; Table S2) and also the calculated signal line width for the H_{2e} proton ($LW_C = {}^3J_{H2e\text{-}H3a} + {}^3J_{H2e\text{-}H3e} + {}^3J_{H2e\text{-}H7}$) is lower than the experimental one (experimental LW at ¼ height[6] 33.4 Hz, calculated 20.9 Hz; Table S1). The same analysis for the *cis-* isomer comes with an unexpected agreement between the calculated and the experimental vicinal coupling, actually the difference lies within one r.m.s. deviation of 0.5 Hz estimated for the Equation (S1) by Haasnoot.[2] The larger (2-6 Hz) difference between the calculated and the experimental LW comes because we neglected all long rang coupling, and also each calculated coupling for the H_7 were different from the experimental data because the free rotation along the C_2-C_7 bond, however the sum are within 1 Hz.

In conclusion both, the experimental data and the calculated one, agree with *cis*-α-benzyl-γ-phenylcyclohexanone.

Table S1. Chemical shift and line width for selected proton signals.

	H_{3a}	H_{5a}	H_7	H_2	H_4	$H_{7'}$
δ[a] (ppm)	1.63 (q)	1.92 (m)	2.41 (dd)	2.75 (m)	3.00 (tt)	3.32 dd)
LWexp.[b] (Hz)	39.7	45.6	25.4	33.4	32.64	21.46
LWc[c] (Hz)	37.7[d] *cis* 30.6 *trans*			27.8 *cis* 20.9 *trans*		

[a] Measured chemical shift (ppm) from the TMS as the internal reference; [b] Experimental line width at ¼ height;[4] [c] LWc = $\sum J_{HH}$ where J were the coupling constants calculated from Equation (S1) (see Table S2); [d] Estimated with $J_{gem}=13$

Table S2. Comparison between the experimental coupling constants and the values calculated by the Equation S1 for *cis*-and *trans*-isomer.

H-H	ϕ_{cis}[a] (°)	$^3J_{cis}$[b] (Hz)	ϕ_{trans}[a] (°)	$^3J_{trans}$[b] (Hz)	$^3J_{exp}$[c] (Hz)
H_2 - H_7	163.83	11.44	-171.92	12.11	9.0
H_2 - $H_{7'}$	-80.3	1.16	72.55	1.70	4.6
		12.60[d]		13.81[d]	13.6[d]
H_2 - H_{3a}	178.82	12.36	45.66	5.23	12.85
H_2 - H_{3e}	62.74	2.82	69.68	1.81	
H_{3a} - H_{4a}	-178.05	12.36	-177.70	12.35	12.45

[a] Dihedral angles in degree from the ab initio calculation (see text); [b] Values estimated using the Equation (S1), we follow the Haasnoot's rules[2] Definition for ξ and $\Delta\chi_i$, the parameters P_1-P_6 were from set D;[2] [c] Experimental coupling constants. [d] $J_{H2\text{-}H7'} + J_{H2\text{-}H7}$

References

[1] a) J. P. Aycard, H. Bodot, *Org. Magn. Resonance,* **1975**, *7*, 35-40; b) H. Booth, *Progress in nuclear magnetic resonance spectroscopy*, *Vol. 5*, Pergamon Press, New York, **1969**, pp.149-381; c) M. Barfield, D. M. Grant, *Advances in Magnetic Resonance*, *Vol 1*, Academic Press, New York, **1965**, pp. 149-193; d) A. A. Bothner-By, *Advances in Magnetic Resonance*, *Vol 1*, Academic Press, New York, **1965**, pp. 195-210; e) H. Günther, *NMR Spectroscopy 2nd ed.*, J. Wiley, West Sussex England, **1995**.

[2] C. A. G. Haasnoot, F. A. A. M. De Leeuw, C. Altona, *Tetrahedron*, **1980**, *36*, 2783-2792.

[3] W. J. Hehre, J. Yu , P. E. Klunzinger, L. Lou. *A Brief Guide to Molecular Mechanics and Quantum Mechanical Calculations*, Wavefunction: Irvine, **1998**.

[4] H. Feltkamp, N. C. Franklin, M. Hanack, K. W. Heinz, *Tetrahedron Lett.*, **1964**, 3535-3540.

[5] K. M. Wellman, F. G. Bordwell, *Tetrahedron Lett.*, **1963**, 1703-1708.

[6] E. W. Garbisch jr, *J. Am. Chem. Soc.*, **1964**, *86*, 1780-1782.

[7] R. J. Abraham, H. A. Bergen, D. J. Chadwick, *Tetrahedron Lett.*, **1981**, *22*, 2807-2810.

[8] R. Cahill, R.C. Cookson, T. A. Crabb, *Tetrahedron*, **1969**, *25*, 4711-4735.