Synthesis of a Mesogenic Compound with a Defined Conformation

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Abstract: The synthesis of the bicyclohexyl derivative 2 has been attained in 4 steps by bi-directional elaboration of bicyclohexanone 3. Due to the specifically placed methyl substituents, 2 populates a single conformation at the inter-ring bond, resulting in improved material properties.

Key words: carbocycles, conformation, fluorine, liquid crystals

Increased use of liquid crystal displays in electronic devices led to a constantly growing demand of new liquid crystalline materials with optimal properties, such as high clearing temperature, low rotational viscosity or high dielectric anisotropy ($\Delta\varepsilon$). Recent studies on liquid crystalline compounds of the type 1 demonstrated a remarkable dependence of the dielectric anisotropy of these axially fluorinated bicyclohexyl derivatives on the conformation of the molecular backbone. AM1-calculations indicated that the dielectric anisotropy vanishes when the dipole moments of the C-F bonds point in opposite directions and cancel each other, i.e. if the conformation at the bicyclohexyl bond is trans ($\Phi = \text{dihedral angle H-C-C-H} = 180^\circ$), cf. Scheme 1. In conformations with smaller dihedral angles the dipoles reinforce each other: the smaller $\Phi$ the more negative will be the dielectric anisotropy $\Delta\varepsilon$. The actual value of $\Delta\varepsilon$ is then the population weighted average over the conformer population.

Compound 1 populates two types of conformation: The gauche conformation 1b (58%, calculated $\Delta\varepsilon = -2.7$) and the trans conformation 1a (42%, calculated $\Delta\varepsilon = -0.4$). A Boltzmann distribution over the two conformations 1a and 1b predicts an averaged $\Delta\varepsilon$-value of $-1.7$, which is slightly lower than the experimentally determined value of $\Delta\varepsilon = -2.5$. Obviously, if the conformer equilibrium can be shifted in the direction of 1b, the compounds should possess larger negative $\Delta\varepsilon$-values. A shift in the conformer population toward 1b could be attained by rational placement of substituents, i.e. by rational conformation design. We therefore targeted the C$_2$-symmetric compound 2, which has two additional methyl groups compared to compound 1. While maintaining free rotation about the inter-ring bond the two equatorial methyl groups should destabilize both the trans conformation 2a as well as one of the two possible gauche conformations (2c) by two syn-pentane interactions to the point that these arrangements are no longer minima on the rotational energy profile (a comparison of the calculated rotational profiles for 1 and 2 is given in Figure 1). The calculations show for 2 only two minima on the rotational energy profile: 2b ($\Phi = -60^\circ$) and, substantially (+4.9 kcal mol$^{-1}$) higher, another conformer which reduces syn-pentane interactions by increasing the dihedral angle $\Phi$ to 80$^\circ$. Compound 2 should therefore populate exclusively the strain-free gauche conformation 2b (cf. Scheme 2) which, due to the small dihedral angle at the inter-ring bond should lead to a significantly larger negative $\Delta\varepsilon$-value.
The synthesis of compound 2 originated from 4,4'-dicyclohexanone 3. In a bi-directional approach, 3 was converted to the bis-silylenolether, which was transformed into the bis-enone 4 using the Saegusa protocol. This led to a 1:1 mixture of the meso- and d/l-diastereomers. Subsequent addition of Me₂CuLi introduced the two methyl groups selectively trans to the cyclohexyl substituent furnishing a mixture of meso-5 and d/l-6. The diastereomers were both crystalline compounds. X-ray crystal structure analysis of 5 showed that this is the diastereomer which has the proper relative configuration for the synthesis of 2. Wittig reaction of 5 with pentyldiene-phosphorane led to an E/Z-mixture of the bisalkene 7. Following earlier precedent, the bis-alkene was converted with HF/pyridine (Olah’s reagent) into the target compound 2, which was recrystallized to diastereomeric purity.

Conformational analysis of the bicyclohexyl derivatives rests on a determination of the $3J_{H-H}$ coupling constant across the inter-ring bond. In the case of compound 2, this was prevented by severe signal overlap. We therefore turned to conformational analysis of the precursor ketone 5, which should display a similar conformational behavior to that of 2. The SELINCOR technique without proton decoupling permitted the determination of the $3J_{H-H}$ coupling constant across the inter-ring bond to $J \approx 3.0$ Hz. This value documents the predominance of a gauche conformation but does by itself not differentiate between the two possible gauche conformations to 5b and 5c. Since the conformation 5b is the only one free of syn-pentane interactions, the latter is likely the predominant conformation. This is indeed the conformation found in the solid state, as the X-ray crystal structure of 5 shows (Scheme 4).

The high conformational preference found for the ketone 5 should also prevail in the difluoro compound 2, a fact that should be reflected in the dielectric anisotropy of compound 2. With a $\Delta \varepsilon$-value of $-4.2$, compound 2 possesses indeed a much improved dielectric anisotropy compared to compound 1.

We showed in this study that conformation design, i.e. the selective destabilization of undesired conformers by rational placement of substituents, led the way from 1 to compound 2 with an attendant improvement in the conformation-dependent material properties.
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References and Notes


(3) The energy profile for the rotation about the inter-ring bond was calculated using the MMFF94 force field. The structures corresponding to the minima were optimized by AM1-calculations and used as input for the calculations of the A-values.


(7) Tsuzuki, S.; Schä...bicyclohexyl-2,2´-dien-4,4´-dione (4)

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(11) 2,2´-Dimethyl-bicyclohexyl-4,4´-dione (5,6). Methyllithium (1.3 M in Et2O, 15.5 mL, 20.1 mmol) was added at 0 °C to a suspension of CuI (1916 g, 10.06 mmol) in Et2O (50 mL). The solution was cooled to ~78 °C and a solution of the diene 4 (598 mg, 3.14 mmol) in Et2O (10 mL) was added dropwise. After warming to 0 °C over 5 h it was saturated aqueous NH4Cl solution (50 mL) and concd. aqueous NH3 (25 mL) were added. The phases were separated and the aqueous phase was extracted with tert-butyl methyl ether (3 × 40 mL). The combined organic phases were washed with brine (10 mL), dried (Na2SO4) and concentrated. Purification by flash chromatography (pentane/tert-butyl methyl ether 1:1) afforded d)-diketone 5 (246 mg, 36%) and meso-diketone 6 (261 mg, 36%) as colorless solids. 5: R1,0.50 (petroleum ether/tert-butyl methyl ether 1:1) mp: 92 °C; 1H NMR (500 MHz, CDCl3): 6 = 1.03 (6, d, J, = 6.4 Hz), 1.40 (dq, 2H, J, = 4.3 Hz, J, = 13.5 Hz), 1.72-1.78 (m, 2H), 1.87-1.91 (m, 4H), 2.14 (t, J, = 13.5 Hz), 2.30 (3d, 2H, J, = 13.5 Hz), 2.39-2.43 (m, 4H); 13C NMR (75 MHz, CDCl3), 7 = 19.7 (2C), 24.6 (2C), 35.1 (2C), 41.1 (2C), 42.5 (2C), 49.2 (2C), 210.7 (2C); Anal. Calcd for C12H14O2: C 75.63; H 9.97; Found: C 75.50; H 9.88. 6: R2,0.44 (petroleum ether/tert-butyl methyl ether 1:1) mp: 99 °C; 1H NMR (500 MHz, CDCl3): 6 = 0.75 (d, 6H, J, = 6.6 Hz), 1.20-1.24 (m, 2H), 1.27 (dd, 2H, J, = 4.2, 12.6 Hz), 1.34-1.42 (m, 2H), 1.50-1.59 (m, 2H), 1.78 (dd, 2H, J, = 1.0, 10.7, 11.7 Hz), 1.95-2.00 (m, 2H), 2.23 (dd, 2H, J, = 2.1, 4.5, 14.1 Hz), 2.27-2.31 (m, 2H); 13C NMR (75 MHz, CDCl3), 7 = 21.2 (2C), 28.6 (2C), 34.9 (2C), 40.7 (2C), 44.6 (2C), 49.4 (2C), 211.1 (2C); Anal. Calcd for C14H22O2: C 75.63; H 9.97; Found: C 75.92; H 10.06.

(12) Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-157219. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

(13) 1R,2R*,1R*,2R*,4S*,1R*,4R*,4S*,1R*,4R*,4S*,-Dimethyl-4,4´-dipentylidenedibicyclohexyl (7). Potassium tert-butoxide (168 mg, 1.50 mmol) was added at 0 °C to a suspension of n-pentyltriphenylphosphonium bromide (620 mg, 1.50 mmol) in Et2O (4 mL). The mixture was stirred for 1.5 h and then diketone 5 (98 mg, 0.44 mmol) was added. After stirring for 8 h at room temperature, silica gel (1.5 g) was added and the solvent was removed in vacuo. The residue was purified by flash chromatography (pentane) to afford an E/Z-mixture of the diolefin 7 (139 mg, 95%) as a colorless oil. R2,0.81 (petroleum ether/tert-butyl methyl ether 1:1); 1H NMR (500 MHz, CDCl3); 6 = 0.88-0.95 (m, 26H), 1.29-1.36 (m, 28H), 1.48 (t, 2H, J, = 12.6 Hz), 1.60-1.66 (m, 6H, 1H), 1.80 (t, 2H, J, = 11.6 Hz), 1.95-2.07 (m, 8H), 2.14-2.20 (m, 4H), 2.57 (d, 2H, J, = 13.2 Hz), 2.62 (d, 2H, J, = 12.6 Hz, J, = 1.8 Hz), 5.05-5.08 (m, 4H); 13C NMR (125 MHz, CDCl3), 7 = 14.0 (4C), 19.5 (2C), 19.9 (2C), 20.0 (2C), 22.2 (2C), 26.0 (2C), 26.2 (2C), 28.6 (2C), 32.4 (2C), 34.9 (2C), 35.9 (2C), 37.5 (2C), 37.8 (2C), 37.9 (2C), 38.4 (2C), 44.3 (2C), 44.4 (2C), 44.5 (2C), 46.3 (2C), 121.1 (2C), 121.3 (2C), 138.9 (2C), 139.1 (2C); Anal. Calcd for C14H22O2: C 78.79; H 12.81; Found: C 78.07; H 12.58.


(15) 1R,2R*,1R*,2R*,4S*,1R*,4R*,4S*,-Difluoro-2,2´-dimethyl-4,4´-dipentylidenedibicyclohexyl (2). A solution of an E/Z-mixture of the diolefin 7 (165 mg, 0.50 mmol) and HF-pyrindine complex (1 mL, 70% w/w) in THF (1 mL) was stirred for 12 h. The mixture was poured on ice and neutralized with solid NaHCO3. The phases were separated and the aqueous phase was extracted with pentane (3 × 3 mL). The combined organic phases were dried (Na2SO4) and concentrated. Purification by flash chromatography (pentane/tert-butyl methyl ether 1:3) furnished 2 (59 mg, 32%) along with monofluorinated product (42 mg, 24%) and residual diolefin 7 (46 mg, 28%). Further purification of the obtained product by crystallisation (n-heptane) afforded 2 (52 mg, 28%) as a single isomer. R1,0.11 (pentane); mp: 70 °C; 1H NMR (400 MHz, CDCl3); 6 = 0.83 (6H, J, = 6.6 Hz), 0.89 (t, 6H, J, = 6.6 Hz), 1.01 (dd, 2H, J, = 12.5, 13.7 Hz), 1.11-1.19 (m, 2H), 1.29-1.58 (m, 22H), 1.74-1.93 (m, 6H); 13C NMR (100 MHz, CDCl3); 7 = 14.0.
(2C), 19.2 (2C), 20.3 (2C), 22.6 (2C), 22.8 (d, 2C, \( J = 4.7 \) Hz), 28.8 (2C), 32.3 (2C), 35.2 (d, 2C, \( J = 22.9 \) Hz), 41.1 (d, 2C, \( J = 22.8 \) Hz), 43.3 (2C), 44.6 (d, 2C, \( J = 22.6 \) Hz), 96.0 (d, 2C, \( J = 167.2 \) Hz); \(^{19}\text{F} \) NMR (188 MHz, CDCl\(_3\)): \( \delta = -157.5 \); Anal. Calcd for C\(_{24}\)H\(_{44}\)F\(_2\): C 77.78; H 11.97; Found: C 77.79; H 12.26.


(18) The \( \Delta \rho \) -values were determined by linear extrapolation from a 10% w/w solution in the commercially available Merck mixture ZLI-2857 (\( T_{\text{N}} = 82.3 \) °C, \( \Delta \rho = -1.42, \Delta n = 0.0776 \)) as a standard host.

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