Novel Synthesis and Crystal Structures of Two $\alpha$, $\alpha'$-bis-Substituted Benzylidene Cyclohexanones: 2,6-Bis-2-nitro(benzylidene)cyclohexanone and 2,6-Bis-4-methyl(benzylidene)cyclohexanone

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Abstract Two $\alpha$,$\alpha'$-bis-substituted benzylidene cycloalkanones have been synthesized in presence of SnCl$_4$ and their crystal structures have been determined by means of X-ray diffraction. The bis(para-methyl) derivative, 2,6-bis-4-methyl(benzylidene)cyclohexanone 1 crystallizes in the orthorhombic space group Pbc$a$ with $a = 9.413(2)$ Å, $b = 10.787(2)$ Å, and $c = 33.702(5)$ Å, while bis(ortho-nitro) derivative, 2,6-bis-2-nitro(benzylidene)cyclohexanone in monoclinic $P2_1/n$ space group with $a = 8.482(2)$ Å, $b = 13.435(2)$ Å, $c = 15.377(3)$ Å, and $\beta = 92.96(2)^\circ$. In both compounds the olefinic bonds are in $E$-configuration, and the cyclohexyl rings adopt a sofa conformation. The phenyl rings are not coplanar with the planes of C=C–C(=O)–C=C fragments; the dihedral angles between these planes are 14.25(11) and 19.37(11)° in 1 and 60.50(6) and 63.26(6)° in 2. This twist might be regarded as the effect of the repulsive interactions between the hydrogen atoms from phenyl and cyclohexyl rings, and much larger values in 2 are certainly connected with the presence of nitro group in ortho-positions of the phenyl ring. It seems that, because of the lack of specific interactions the close packing requirements and the van der Waals forces are main factors determining the crystal packing.

Keywords Cyclohexanone · Conformation · Crystal packing · Crystal structure

Introduction

Bis(substituted-benzylidene) cycloalkanones are very important synthetic precursors for synthesis of biologically active pyrimidine derivatives [1, 2]. These compounds have gained lots of attention due to their uses as agrochemical, pharmaceutical, and perfume intermediates and as liquid crystal polymer units [3–5]. Many of these methods suffer, however, from side reactions giving the corresponding products in low yields [6]. Recently some new kinds of Lewis acids have been used but in some cases the yields are less than 38% [7]. We have recently described the use of poly(ethylene) glycol/AlCl$_3$ as a green and reusable system for the synthesis of $\alpha$, $\alpha'$-bis(substituted-benzylidene) cycloalkanones [8]. In recent study, the versatility of SnCl$_4$ and the environmentally benign nature of ethanol as a green, inexpensive, and accessible solvent encouraged us to couple them together and study their utility for aldol condensation. Comparing the other methods, our synthetic procedure for preparation of different $\alpha$, $\alpha'$-bis(substituted-benzylidene) cycloalkanones (Scheme 1) provides good yields for a vast variety of substituted aromatic aldehydes with both electron withdrawing and electron releasing groups furthermore. Also the simplicity of operation, lack of unexpected by-products and mild condition of temperature are the others advantages of this method [9]. In recent study for the first time we have used SnCl$_4$ as a mild, inexpensive and efficient catalyst for the synthesis of different $\alpha$, $\alpha'$-bis(substituted-benzylidene) cycloalkanones (Scheme 1). Use of ethanol as a green solvent helped us to improve total yields and this new combination for the first time provided excellent conditions to obtain good single crystals for X-ray studies of some obtained $\alpha$, $\alpha'$-bis(substituted-benzylidene) cyclohexanones. Here we report the results of the X-ray
crystallographic studies for \((2E,6E)-2,6\text{-bis}(4\text{-methylbenzylidene})\text{cyclohexanone (1, Scheme 1)}\) and \((2E,6E)-2,6\text{-bis}(2\text{-nitrobenzylidene})\text{cyclohexanone (2)}\). Structures of some similar compounds have been reported earlier, for instance bis(3-nitro) [10] and bis(4-nitro) derivatives [11]. Interestingly, even for the very similar compounds there are no indications of isomorphism what can suggest that very weak interactions are responsible for crystal packing.

## Results and Discussion

Figures 1 and 2 show the perspective views of molecules 1 and 2, respectively. Table 1 lists the relevant bond lengths, bond angles and torsion angles.

The overall conformation of the molecule might be described by the dihedral angles between the planar fragments: two phenyl rings, A (C8–C13) and B (C15–C20), and the planar fragment of the cyclohexanone (C7=C6–C1=O1–C2=C14; referred to as C). The appropriate values are listed in Table 1, and Fig. 3 shows the comparison of both the molecules. As it is evident from Fig. 3, compound 1 is significantly flatter than 2 as a consequence of ortho-positions in 2. In the Cambridge Structural Database ([12] version 5.31 of November 2009, updated August 2010) there are 24 compounds of similar, 3,5-diaryl-6-monosubstituted-cyclohex-2-enone, structure (with no additional substituents in the cyclohexanone ring and on bridging C-atoms). There are no clear trends in the overall conformation of the molecules. For instance, for the derivatives with the single substituents at 4,4′ positions the spread of dihedral angles is quite big, the twist between the terminal rings ranges from \(0.3^\circ\) in 4-methyl-4′-nitro derivative [13] to \(51.4^\circ\) in one of three symmetry-independent molecules of 4,4′-dibromo compound [14]. Even in unsubstituted 2,6-bis(benzylidene)cyclohexanone the angles between the planar fragments are quite large, \(38.3^\circ\) between the phenyl rings [15]. This lack of coplanarity which originates from the twist between the aryl rings and adjacent olefinic groups is regarded as the result of the repulsive interactions between the hydrogen atoms of the aryl rings and equatorial hydrogen atoms from cyclohexyl ring [e.g., 13]. This steric repulsion causes also the increase in the bond angles at the C-atoms joining the rings i.e., C6–C7–C8 and C2–C14–C15 (cf. Table 1). The intra-annular angles in phenyl rings show the influence of the substituents (cf. for instance [16]), which is close to additivity in 1.
As expected in case of \( \text{2} \) with ortho-substitution the additivity is hardly visible.

In both compounds the olefinic bonds are in \( E \)-configuration (torsion angles \( \text{O1–C1–C6–C7} \) and \( \text{O1–C1–C2–C14} \) are \( 11.5(2) \) and \( -9.0(2) \) in \( \text{1} \), and \( -20.3(3) \) and \( 12.8(3) \) in \( \text{2} \)). It might be noted that in both cases the dihedral angles have opposite signs, as it is in majority—but not all, actually in 22 out of 31 fragments—structures from the CSD.

The cyclohexanone rings are in sofa conformations. The asymmetry parameters [17], which in principle show the deviation from the ideal symmetry of six-membered ring, in this case \( \text{C}_2 \), have the values of \( 3.2^\circ \) in \( \text{1} \) and \( 8.6^\circ \) in \( \text{2} \), what suggests the much more distorted conformation in this latter case. Also the calculations of the least-squares planes through five ring atoms (\( \text{C}1, \text{C}2, \text{C}3, \text{C}5, \text{and} \text{C}6 \)) show that the ring in \( \text{2} \) is more deviated from the ideal sofa conformation (maximum deviation is \( 0.064(2) \ \text{Å} \) in \( \text{1} \) and \( 0.095(2) \ \text{Å} \) in \( \text{2} \)). The sixth atom, \( \text{C}5 \) is significantly out of the mean plane, by \( 0.729(3) \ \text{Å} \) in \( \text{1} \) and \( 0.605(3) \ \text{Å} \) in \( \text{2} \).

In the crystal structures virtually no specific interactions are present. Some potential \( \text{C–H} \cdots \text{O} \) contacts are listed in Table 2. What is quite puzzling, there are also no indications for either \( \pi \cdots \pi \) or \( \text{C–H} \cdots \pi \) interactions which quite often play significant role in determination of crystal packing of similar compounds. Therefore, in both the structures probably the close packing requirements and the van der Waals contacts determine the packing (Fig. 4).

### Table 1

| Substituents in mutual para positions. | A and B are phenyl rings (A: C8–C13, B: C15–C20), and C is the planar fragment of the cyclohexanone (C7=C6–C1(=O1)–C2=C14) |
|--------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| | |
| C1–O1 | 1.2311(19) | 1.227(2) |
| C2–C14 | 1.336(2) | 1.329(2) |
| C6–C7 | 1.345(2) | 1.336(2) |
| C2–C1–C6 | 118.60(16) | 118.97(18) |
| C1–C6–C7 | 116.48(15) | 116.21(17) |
| C6–C7–C8 | 130.90(16) | 130.04(17) |
| C1–C2–C14 | 117.41(16) | 116.11(17) |
| C2–C14–C15 | 131.69(16) | 126.69(18) |
| C4–C3–C2–C14 | 154.71(17) | 148.45(19) |
| C4–C5–C6–C7 | -159.46(17) | -135.42(17) |
| C1–C2–C14–C15 | -177.06(16) | -178.67(18) |
| C1–C6–C7–C8 | 176.45(16) | 175.0(2) |
| C2–C14–C15–C20 | 27.1(3) | 50.2(3) |
| C6–C7–C8–C9 | -23.8(3) | -41.7(3) |
| A/B | 5.24(10) | 21.60(10) |
| A/C | 14.25(11) | 60.50(6) |
| B/C | 19.37(11) | 63.26(6) |
| A/NO2 | 26.4(3) | |
| B/NO2 | 10.3(3) | |

### Table 2

| Short C–H–O contacts geometry (Å, °) |
|-------------------------------------|
| D–H–A | D–H | H–A | D–A | D–H–A |
| C111–H11C–O1 | 0.96 | 2.57 | 3.508(3) | 165 |
| C3–H3A–O91 | 0.97 | 2.70 | 3.620(3) | 159 |
| C5–H5A–O1 | 0.97 | 2.66 | 3.417(3) | 135 |
| C7–H7–O162 | 0.93 | 2.60 | 3.321(3) | 135 |
| C11–H11–O161 | 0.93 | 2.59 | 3.429(3) | 151 |
| C12–H12–O91 | 0.93 | 2.56 | 3.287(3) | 135 |
| C17–H17–O1 | 0.93 | 2.75 | 3.668(3) | 168 |
| C18–H18–O92 | 0.93 | 2.56 | 3.476(3) | 168 |
| C20–H20–O162 | 0.93 | 2.66 | 3.476(3) | 146 |

Symmetry codes

- \( a \): \( x + \frac{1}{2}, y, \frac{3}{2} - z \)
- \( b \): \( -x, -y, 1 - z \)
- \( c \): \( 1 - x, -y, 1 - z \)
- \( d \): \( \frac{1}{2} + x, \frac{1}{2} - y, -\frac{1}{2} + z \)
- \( e \): \( \frac{1}{2} - x, -\frac{1}{2} + y, \frac{1}{2} - z \)
- \( f \): \( -\frac{1}{2} + x, \frac{1}{2} - y, \frac{1}{2} + z \)
- \( g \): \( x, y, 1 + z \)
- \( h \): \( \frac{1}{2} - x, -\frac{1}{2} + y, 3/2 - z \)

**Fig. 3** Least-squares fit of molecules \( \text{1} \) and \( \text{2} \); the cyclohexanone fragments of the molecules were fitted one onto another [22]
Experimental

Preparation

A mixture of aldehyde (2 mmol) and ketone (1 mmol) and SnCl₄ (0.3 mmol) in EtOH (2 mL) was stirred at 45 °C for an appropriate time. After completion of the reaction (Scheme 2) monitored by TLC, the reaction mixture was cooled in ice bath to precipitate the desired product. Colourless single crystals suitable for X-ray of compounds 1 and 2 were obtained by slow evaporation of an ethanol solution. 1: Yellow needles: Yield: 89%; mp 171–172 °C; IR (KBr) m: 2938, 2914, 1660, 1600 cm⁻¹; 2: Yellow needles: Yield: 75%; mp 157–159 °C; IR (KBr) m: 1638, 1617, 1519 cm⁻¹.

Crystallography

Colourless transparent plate-like crystals (0.5, 0.4, 0.15 mm; 0.3, 0.3, 0.05 mm for 2) were used for data collection. Diffraction data were collected at room temperature by the ω-scan technique, on an Xcalibur Eos diffractometer [18] with graphite-monochromatized MoKα radiation (λ = 0.71073 Å). The data were corrected for Lorentz-polarization and absorption effects [18]. Accurate unit-cell parameters were determined by a least-squares fit of 3533 (1) and 1991 (2) reflections of highest intensity, chosen from the whole experiment, and then the. Precision of the diffractometer was also taken into account in order to avoid unphysically small standard uncertainties [19]. The structures were solved by direct methods with SIR92 [20] and refined with the full-matrix least-squares procedure on F² by SHELXL97 [21]. Scattering factors incorporated in SHELXL97 were used. The function Σw(Fo²–|Fc²|²) was minimized, with w⁻¹ = [σ²(Fo²)² + (AP)²] (where P = [Max {Fo², 0} + 2Fc²]/3). All non-hydrogen atoms were refined anisotropically, hydrogen atoms were put in the calculated positions difference Fourier map, and refined as a “riding” model with the isotropic displacement parameters set at 1.2 (1.5 for methyl groups) times the Ueq value for appropriate non-hydrogen atom. Relevant crystal data are listed in Table 3, together with refinement details.

Table 3 Crystal data, data collection, and structure refinement

| Compound | 1          | 2          |
|----------|------------|------------|
| Formula  | C₂₂H₂₂O    | C₂₀H₁₆N₂O₃ |
| Formula weight | 302.40 | 364.35 |
| Crystal system | Orthorhombic | Monoclinic |
| Space group | Pbca | P2₁/n |
| a (Å) | 9.413(2) | 8.482(2) |
| b (Å) | 10.787(2) | 13.435(2) |
| c (Å) | 33.702(5) | 15.377(3) |
| β (°) | 90 | 92.96(2) |
| V (Å³) | 3422.0(11) | 1750.0(6) |
| Z | 8 | 4 |
| Dₓ (g/cm³) | 1.17 | 1.38 |
| F(000) | 1296 | 760 |
| μ (mm⁻¹) | 0.07 | 0.10 |
| θ range (°) | 3.12–25.00 | 3.06–25.00 |
| hkl range | −11 ≤ h ≤ 7 | −10 ≤ h ≤ 9 |
|          | −12 ≤ k ≤ 11 | −15 ≤ k ≤ 9 |
|          | −39 ≤ l ≤ 40 | −18 ≤ l ≤ 17 |

Reflections

Collected | 7696 | 6293 |
Unique (Rint) | 3002 (0.017) | 3068 (0.030) |
With I > 2σ(I) | 1869 | 1433 |
No. of parameters | 210 | 245 |
Weighting scheme

A | 0.067 | 0.0381 |
R(F) [I > 2σ(I)] | 0.047 | 0.044 |
wR(F²) [I > 2σ(I)] | 0.114 | 0.061 |
R(F) [all data] | 0.083 | 0.114 |
wR(F²) [all data] | 0.122 | 0.066 |
Goodness of fit | 1.014 | 1.013 |
Max/min Δρ (e Å⁻³) | 0.14/−0.17 | 0.21/−0.21 |

SHELXL97 were used. The function Σw(Fo²–|Fc²|²) was minimized, with w⁻¹ = [σ²(Fo²)² + (AP)²] (where P = [Max {Fo², 0} + 2Fc²]/3). All non-hydrogen atoms were refined anisotropically, hydrogen atoms were put in the calculated positions difference Fourier map, and refined as a “riding” model with the isotropic displacement parameters set at 1.2 (1.5 for methyl groups) times the Ueq value for appropriate non-hydrogen atom. Relevant crystal data are listed in Table 3, together with refinement details.

Supplementary Material

CCDC-800799 (1) and CCDC-800800 (2) contain supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.
ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

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References

1. Guilford WJ, Shaw KJ, Dallas JL, Koovakkat S, Lee W, Liang A, Light DR, McCarrick MA, Whitlow M, Ye B, Morrissey MM (1999) J Med Chem 42:5415
2. Deli J, Lóránd T, Szabó D, Földesi A (1984) Pharmazie 39:539
3. Dimmock JRA, Padmanilayam MP, Zello GA, Nienaber KH, Allen TM, Santos CL, Clercq E, De Balzarini J, Manavathu EK, Stables JP (2003) Eur J Med Chem 38:169
4. Gangadharana KK (1995) Polymer 36:1903
5. Artico M, Di Santo R, Costi R, Novellino E, Greco G, Massa S, Tramontano E, Marongiu ME, De Montis A, La Colla P (1998) J Med Chem 41:3948
6. Nakano T, Iriyune S, Umano S, Inada A, Ishii Y, Ogawa M (1987) J Org Chem 52:2239
7. Watanabe K (1980) Bull Chem Soc Jpn 53:1366
8. Amoozadeh A, Nemati F (2009) S Afr J Chem 62:44
9. Motiur Rahman AFM, Jeong B-S, Kim DH, Park JK, Lee ES, Jahng Y (2007) Tetrahedron 63:2426
10. Li Z-H, Li J-J, Wang P (2007) Z Kristallogr New Cryst Struct 222:73
11. Quail JW, Das U, Dimmock JR (2005) Acta Cryst E61:o1150
12. Allen FH (2002) Acta Cryst B58:380
13. Quail JW, Doroudi A, Pati HN, Das U, Dimmock JR (2005) Acta Cryst E61:o1795
14. Zhou LY (2007) Acta Cryst E63:o3113
15. Jia Z, Quail JW, Arora VK, Dimmock JR (1989) Acta Cryst C45:285
16. Domenicano A, Murray-Rust P (1979) Tetrahedron Lett 24:2283
17. Duax WL, Norton DA (1975) Atlas of steroid structures. Plenum, New York, pp 16–22
18. Oxford Diffraction (2009) CrysAlis PRO (version 1.171.33.36d). Oxford Diffraction Ltd, Oxfordshire
19. Herbstein FH (2000) Acta Cryst B56:547
20. Altomare A, Casarano G, Giacovazzo C, Gualardi A (1993) J Appl Cryst 26:343
21. Sheldrick GM (2008) Acta Cryst A64:112
22. Siemens (1989) Stereochemical workstation operation manual, Release 3.4. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin
23. Macrae CF, Bruno IJ, Chisholm JA, Edgington PR, McCabe P, Pidcock E, Rodriguez-Monge L, Taylor R, van de Streek J, Wood PA (2008) J Appl Cryst 41:466