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Crystal structures and isometricity comparison of methylated bisphenol F derivatives

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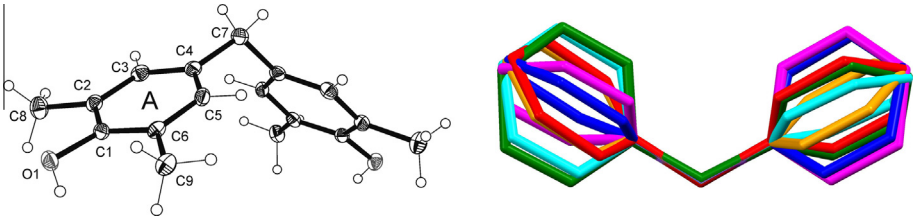
HIGHLIGHTS

- The X-ray structure of four bisphenol F derivatives are determined.
- Four methyl groups at bisphenol F do not disturb the strong hydrogen bond network.
- Methyl groups have a higher structural influence than H donors or acceptors.
- Isometricity comparison reveals the degree of relationship between the structures.

GRAPHICAL ABSTRACT



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ABSTRACT

The syntheses and X-ray structures of three methylated bisphenol F derivatives and one respective analogue are reported. A special emphasis lies on the influence of methyl groups on the conformation of the common diphenylmethane scaffold. The introduction of four methyl groups to bisphenol F was found not to disturb its typical strong hydrogen bond network, and yet, to change the pattern of the aromatic interactions in the overall packing. According to the isometricity comparison, the addition of methyl groups to the diphenylmethane core has a greater influence on the conformation of the individual molecules, than the presence or absence of hydrogen bonding donors or acceptors.

1. Introduction

The term 'bisphenol' is used for a class of chemical compounds bearing two hydroxyphenyl moieties connected via a carbon or sulfur bridge [1]. For many decades, they are widely used in the manufacturing of epoxy resins and polycarbonates to produce different everyday objects like water bottles, coatings or electronic devices [2]. Though these polymers are more or less uncritical in connection with human health, they are believed to disintegrate liberating harmful bisphenol monomers [3]. One prominent member is bisphenol F featuring a bridging methylene group between the two aromatic units. In this respect, 'F' stands for 'formaldehyde' from which the actual molecule is synthesized by reaction with phenol. It is believed to interfere with environmental processes and human health, e.g. was found to establish estrogenic activity in *in vitro* bioassays [4]. Humans can be exposed to bisphenol F and its derivatives as environment and food contaminants [5].

By adding electron donating methyl groups to the aromatic rings of bisphenols they become more lipophilic and sterical demanding. Their respective solubility, bioavailability and biological activity are directly connected to the molecular structure and intermolecular interactions of the particular derivative in the solid state and in solution [6]. Though some compounds of this type were studied according to their medicinal activity [7], the knowledge of methylated bisphenols and their analogues is rather limited [8]. Here we discuss in detail the crystal structures and solid

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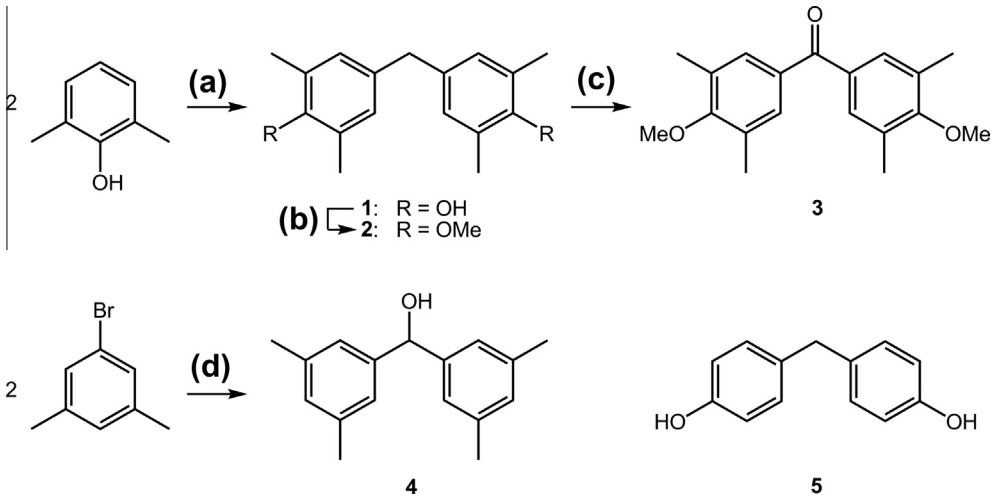

Scheme 1. Synthesis of bisphenol derivatives **1**–**4**.(a) HCHO, NaOH/H_2O, EtOH; (b) CH_3I, K_2CO_3, acetone; (c) CrO_3, AcOAc; and (d) 1. Mg, THF, 2. ethyl formate, THF.

state behaviour of three bisphenol F derivatives and one respective analogue (**1**–**4**). To the best of our knowledge, specifics on the molecular structure of these compounds are missing [9]. In this paper, we present the X-ray structures and deliver an extensive conformational analysis including isometricity comparison. Of special interest in this respect is the influence of different phenyl substituents on the relative position of the aromatic units.

2. Experimental

2.1. Synthesis

Compounds **1**–**3** (Scheme 1) were prepared analogously to literature protocols, starting with commercially available 2,6-dimethylphenol, which was dimerized by reaction with formaldehyde [10], followed by etherification with methyl iodide [11] and oxidation with CrO_3 [12]. Benzhydrol **4** was obtained from 1-bromo-3,5-dimethylbenzene and ethyl formate via a Grignard reaction [13].

2.2. X-ray structure determination

Crystals of the title compounds suitable for X-ray diffraction were obtained by slow evaporation of respective solutions of **1** in ethyl acetate, **2** in *n*-hexane, **3** in ethanol and **4** in ethanol, respectively. The X-ray structure of bisphenol F (**5**) has been published by Lim and Tanski [14] and was included in our discussion for comparison.

The single crystal X-ray diffraction data of compounds **1**–**4** were collected at 100 K on a Bruker Kappa diffractometer equipped with an APEX II CCD area detector and graphite-monochromatized Mo Kα radiation (λ = 0.71073 Å) employing φ and ω scan modes. The data were corrected for Lorentz and polarization effects. Semiempirical absorption correction was applied using the SADABS program [15]. The SAINT program [15] was used for the integration of the diffraction profiles. The crystal structures were solved by direct methods using SHELXS-97 [16] and refined by full-matrix least-squares refinement against F^2 using SHELXL-97 [16]. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were generated at ideal geometrical positions and refined with the appropriate riding model. Geometrical calculations were performed using PLATON [17] and molecular graphics were generated using SHELXTL [16]. The crystallographic data collection and refinement parameters are given in Table 1. Relevant angles and crucial intermolecular contacts are presented in Tables 2 and 3, respectively.

Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre (CCDC 954338 to CCDC 954341). Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/datarequest/cif, by e-mailing data-request@ccdc.com.ac.uk or by contacting the Cambridge CB21 EZ, UK; fax: +44 1223 336033.

2.3. Isometricity calculation

The Molecular Isometricity Indeces $I(m)$ [24] for the X-ray structures of **1**–**4** were calculated by the following equation by least-squares fitting of the positions occupied by the identical atoms of the two superimposed molecules:

$$I_i(n) = \left| \left[\frac{\Sigma(\Delta R_i)^2}{n} \right]^{1/2} - 1 \right| * 100$$

where n is the number of distance differences between the crystal coordinates (ΔR_i) of identical non-H atoms within the same section of the related structures. The higher the $I(m)$ value, the higher the similarity of the compounds.

While the Isostructurality Index $I(s)$ takes into account both the differences in the geometry of the molecules and the positional differences caused by rotation and translation, the Molecular Isometricity Index $I(m)$ represents solely the differences in the geometry of the molecules neglecting to the placement of the molecule in the asymmetric unit.

3. Results and discussion

3.1. X-ray single crystal analysis

In the structure of tetramethylated bisphenol F **1** the two phenolic moieties are related by a crystallographic twofold rotational symmetry with the two phenyl rings varying clearly from perpendicularity (67.1°) (Table 2, and Fig. 1). The two angles between the planes of each aromatic unit and the plane defined by C_{aryl}–C_{bridge}–C_{aryl}, the so-called pitch angle, are identical (82.4°) because of the molecular symmetry. In contrast, mother bisphenol **5** [14] displays two different pitch angles (40.7 and 45.7, resp.), as molecular symmetry is not realised in the absence of tetramethylation. Despite the two phenolic groups in **1**, the polar solvent, ethanol, used for