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# CRYSTAL AND MOLECULAR STRUCTURE, AND CYTOTOXIC ACTIVITY OF DIETHYL ETHER OF 2-[(PHENYL-(PHENYL-*O*-CARBORANYL)-METHYL]MALONIC ACID

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The crystal and molecular structure of diethyl ether of 2-[(phenyl-(phenyl-*o*-carboranyl)-methyl]malonic acid is determined by single crystal X-ray diffraction and NMR spectroscopy for the first time. The cytotoxic activity of the molecule is analyzed.

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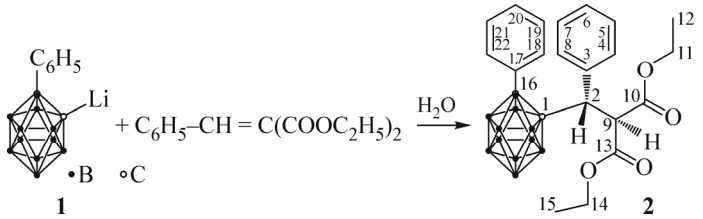
With the aim to continue the research in the chemistry of *o*-carboranes, we have determined for the first time the crystal structure and obtained the NMR spectral data of diethyl ether of 2-[(phenyl-(phenyl-*o*-carboranyl)-methyl]malonic acid **2**.

Compound **2** was synthesized by the interaction of lithium phenyl-*o*-carboranyl **1** with benzylidenemalonic ester according to the following scheme [1]:




Scheme of the synthesis of compound **2** and atomic numbering.

## RESULTS AND DISCUSSION

The $^1$H NMR spectra show two triplets at 0.66 ppm and 1.23 ppm (3H), corresponding to methyl groups, two quartets at 3.56 ppm and 4.23 ppm (2H), corresponding to methylene groups, and two doublets at 3.92 ppm and 4.12 ppm

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(1H), corresponding to hydrogen atoms at C9 and C2 atoms in the *trans*-position relative to each other (spin-spin coupling constant of 10 Hz). The signals of hydrogen atoms of the benzene rings (at C3–C8 and C17–C22) produce a complicated multiplet in the range 6.65-7.80 ppm.

The $^{13}$C NMR spectrum displays signals corresponding to the ester moiety of the molecule of **2** (C15, C12, C14, C11, C13, C10), which are in the following regions: 13.52 ppm, 14.13 ppm, 61.84 ppm, 62.67 ppm, 166.94 ppm, and 165.62 ppm respectively. The signals of the C9 and C2 carbon atoms are observed at 47.33 ppm and 59.02 ppm. The disappearance of signals at 85.46 ppm, 85.75 ppm, 129.49 ppm, and 137.13 ppm in the $^{13}$C NMR Dept. spectrum confirms their correspondence to the C16, C1, C17, and C3 atoms. The signals at 128.92 ppm, 132.17 ppm, and 129.89 ppm belong to the carbon atoms of benzene rings.

The structure of compound **2** is determined by a single crystal X-ray diffraction analysis.

Compound **2** crystallizes in an centrosymmetric orthorhombic space group *Pbca*. The asymmetric unit of the crystal contains one molecule of diethyl ether of 2-[(phenyl-(phenyl-*o*-carboranyl)-methyl]malonic acid. The substituents at carbon atoms of the carborane moiety (C(16) and C(1)) are in the *syn-peri*-planar (*cis*) conformation; the torsion angle C(2)–C(1)–C(16)–C(17) = 3.1(2)°; a synclinal (*gauche*) conformation is implemented along the C(1)–C(2) bond (the torsion angle $C(16)_{cage}$–$C(1)_{cage}$–C(2)–C(3) = –74.35(15)°), as a result of which the phenyl rings are at a short distance and slightly inclined to each other.

Both C10–O1 and C13–O3 bond lengths of the ester moiety are 1.204(2) Å, which corresponds to the typical values of double bonds, while the C10–O2 (1.3305(17) Å) and C13–O4 (1.3370(17) Å) bond lengths indicate an ordinary bond. The geometric parameters of the carborane core are typical (the B–C distances vary within 1.712(2) Å and 1.739(2) Å, and B–B distances are within 1.763(2)-1.790(3) Å). The bond length $C(1)_{cage}$–$C(16)_{cage}$ = 1.709(2) Å, which is comparable with the $C_{cage}$–$C_{cage}$ bond in *bis*-(2-benzyl-*o*-carborane-1-yl)-benzene [2], *bis*-((2-phenyl-*o*-carborane-1-yl)methyl)-benzene [3], and 1-phenyl-2-(4-vinylbenzyl)-*o*-carborane [4].

Fig. 1 shows the geometry of the molecule of **2**.

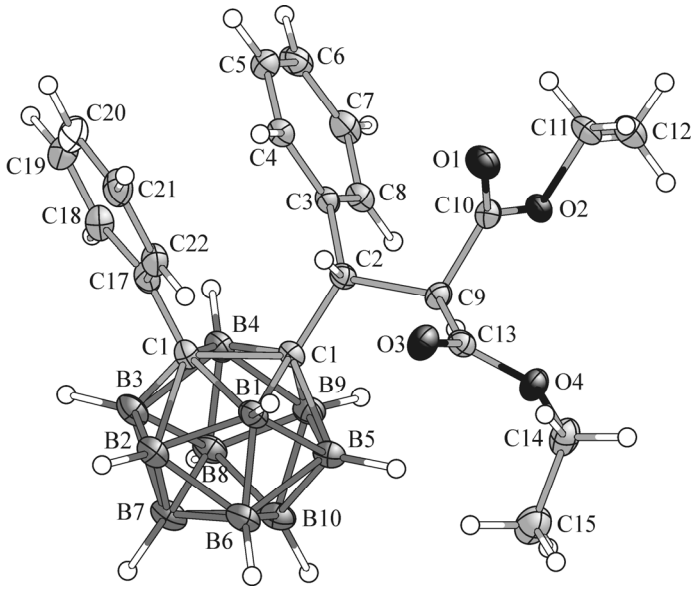


**Fig.1.** Geometry of the molecule of compound **2** in the crystal and numbering of non-hydrogen atoms. Thermal ellipsoids are drawn at the 50% probability level.

## EXPERIMENTAL

The NMR spectra were recorded on an Avance III Bruker DRX-500 spectrometer (with the operating frequency of 500.13 MHz for $^1$H, and 125.76 MHz for $^{13}$C, δ-scale) using the following standard programs for the measurement of two-dimensional spectra: COSY $^1$H–$^1$H, HMBC, HSQC, Dept.

The IR spectra were recorded on an IR-Fourier Cary 600 Series spectrometer (Agilent Technologies, USA) using Gladiatr single reflection ATR accessories with a diamond crystal (PIKE, USA). All the measurements were carried out with the resolution of 4.0 cm$^{-1}$; the number of scanning was 40.

The reaction course was controlled by TLC. Sorbfil plates in the ethyl acetate–hexane system were used for TLC.

**Diethyl ether of 2-[(phenyl-(phenyl-*o*-carboranyl)-methyl]malonic acid 2.** Compound **2** is readily soluble in DMSO, DMFA, chloroform, ethyl acetate, and hexane and poorly soluble in alcohol and water. The melting point is 109.7-111.9°C (103-104°C [1]).

$^1$H NMR (500 MHz, DMSO, δ, ppm, *J*, Hz): 0.66 (3H, t, *J* = 7.0), 1.23 (3H, t, *J* = 7.0), 3.56 (2H, quint), 4.23 (2H, quint), 3.92 (1H, d, *J* = 10), 4.12 (1H, d, *J* = 10), 6.65-7.80 (10H, m).

$^{13}$C NMR (125.76 MHz, DMSO): 13.52 (q, C-15), 14.13 (q, C-12), 47.33 (d, C-9), 59.02 (d, C-2), 61.84 (t, C-14), 62.67 (t, C-11), 85.46 (s, C-16), 85.75 (s, C-1), 128.92 (d, C-5, C-7, C-19, C-21), 129.49 (s, C-17), 129.89 (d, C-4, C-8, C-18, C-22), 132.17 (d, C-6, C-20), 137.13 (s, C-3), 166.94 (s, C-13), 165.62 (s, C-10).

IR spectrum (KBr, ν, cm$^{-1}$): 3064 (C–H$_{aryl}$), 2984 (C–H$_{alkyl}$), 2605 (B–H), 1756 (C=O ester group, intens.), 1725 (C = O), 1496, 1455, 1370, 1341, 1302, 1278, 1249, 1205, 1183, 1143, 1093, 1025, 1007, 977, 864, 754, 723, 694, 633, 578, 540.

**Single crystal X-ray diffraction analysis.** The unit cell parameters and reflection intensities of the crystal of compound **2** were measured at 100 K on a SuperNova, Dual, Cu at zero, Atlas diffractometer (Agilent, USA), equipped with a CCD detector, with Mo$K_\alpha$ (λ = 0.71073 Å) radiation and ω-scanning. The images were integrated using the CrysAlisPro program [5]; the intensities (scale-up, absorption correction and LP corrections) were processed using the Olex2 program [6]. The structure was solved by the direct method using the ShelXS program and refined by the least-squares technique on $F^2$ using the ShelXL program [7, 8]. Non-hydrogen atoms were refined in the anisotropic approximation; all hydrogen atoms were placed in the calculated positions and refined in a riding model with isotropic temperature factors, with 1.2$U$(eq) for the corresponding carbon atoms and 1.52$U$(eq) for the methyl groups.

**Crystallographic data of compound 2** at $T$ = 100 K. $C_{22}H_{32}B_{10}O_4$, $M$ = 468.58, orthorhombic, space group *Pbca* (no. 61), $a$ = 13.3238(3) Å, $b$ = 15.9244(4) Å, $c$ = 24.5816(5) Å, $V$ = 5215.6(2) Å$^3$, $Z$ = 8, $T$ = 100 K, $\rho_{calc}$ = 1.194 g/cm$^3$, μ(Mo) = 0.072 mm$^{-1}$, $F$(000) = 1968, 30999 reflections measured, 6555 independent reflections ($R_{int}$ = 0.0543), which were used in all calculations. The final divergence factors were $R_1$ 0.0521 (for 4919 observed reflections with $I > 2\sigma(I)$) and $wR_2$ 0.137 (for all data).

The results of the X-ray diffraction analysis of the crystal of compound **2** have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1531811), and can be easily obtained by request *via* the website: www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; or deposit@ccdc.cam.ac.uk).

**Cytotoxic activity.** In order to study the cytotoxic activity of compound **2,** we have carried out tests by the known method using brine shrimps *Artemia salina* [9]. It is found that in all the tested concentrations (1-10 mg/ml) compound **2** exhibits acute lethal toxicity; the larval mortality is 65-70%.

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