



Dedicated to Professor Bogdan C. Simionescu  
on the occasion of his 70th anniversary

## SYNTHESIS AND INVESTIGATION OF 2-(HYDROXYBENZYLIDENE)-5-METHYLCYCLOHEXAN-1-ONE\*\*

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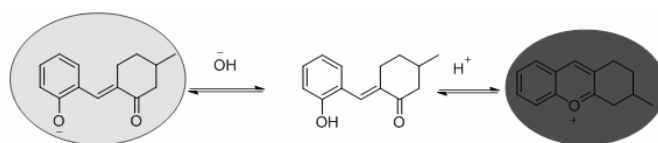
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The 2-(2-hydroxybenzylidene)-5-methylcyclohexan-1-one (**BMC**) was synthesized in basic solution and the structure was confirmed by single crystal X-ray diffraction and <sup>1</sup>H NMR. **BMC** crystallizes in the monoclinic space group *P*2<sub>1</sub>/*c*, with cell dimensions *a* = 6.1146(14), *b* = 10.9437(15), *c* = 17.529(7) Å, β = 94.09(3)°. The **BMC** behaviour was investigated at different pH values. Upon a pH jump from 7 to 1, **BMC** undergoes cyclisation and forms xanthylium cation (**MTX**) with a maximum absorption band at 515 nm. In the case of reverse pH jump, the **BMC** converted instantaneously into deprotonated **BMC** with the maximum absorption at 390 nm.



### INTRODUCTION

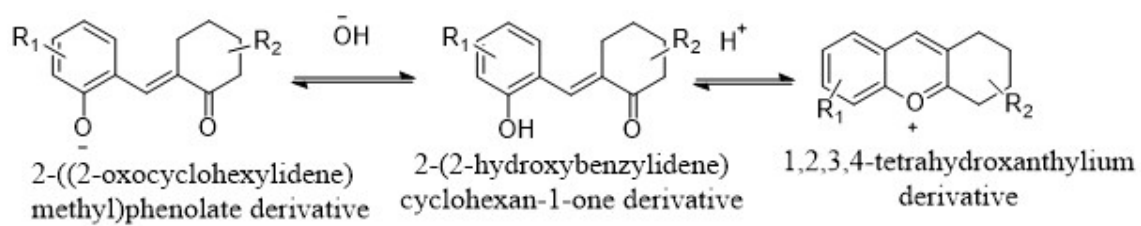
The derivatives of 2-(benzylidene)cyclohexan-1-one are an important class of compounds in the field of biology,<sup>1</sup> medicine,<sup>2,3</sup> photochemistry,<sup>4,5</sup> food chemistry<sup>6,7</sup> and art.<sup>8</sup> The derivatives with hydroxylic group in *ortho* position towards ethylenecyclohexanone moiety showed halochromic behavior: in basic pH they exist as 2-((oxocyclohexylidene)methyl)phenolate species, whereas at lower pH they form 1,2,3,4-tetrahydroxanthylium derivatives by elimination of one molecule of water (Scheme 1).<sup>5,9-11</sup> Thus, the color and properties of these compounds are strongly related to the molecular form

(unprotonated/open/close form) and the nature of substitution pattern of benzene and/or cyclohexanone rings.

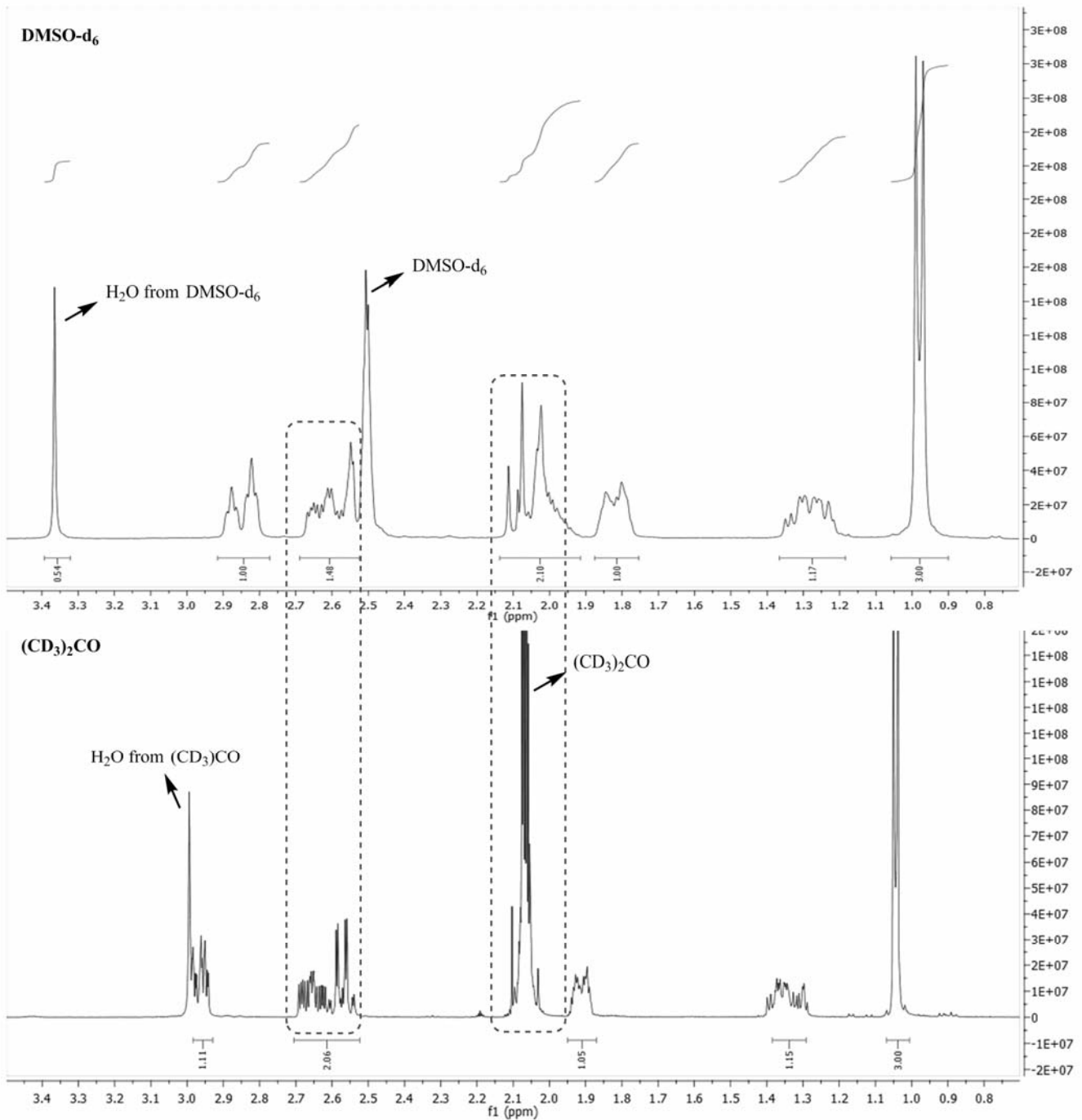
Nowadays, the system capable of existing in more than two forms (multistates) and that can be interconverted by more than one type of external stimulus (multifunctions) like pH, temperature, light, solvent, etc.<sup>12-15</sup> are of great interest in both fundamental and application fields. However, only few derivatives of 2-(2-hydroxybenzylidene)cyclohexan-1-one are known and studied.<sup>16-21</sup> In order to understand the relation between external stimuli and complexity of network of chemical reactions, the synthesis and investigation of new compounds from this class are compulsory.

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\*\* Supplementary Information on <http://web.icf.ro/rrch/> or <http://revroum.lew.ro>



Scheme 1 – Network of chemical reactions.

Fig. 1 –  $^1\text{H}$ -NMR spectra of BMC in DMSO- $d_6$  and acetone- $d_6$ .

As a continuous work in the frame of multistate/multifunctional systems we report herein the synthesis, X-ray structure, spectral properties of 2-(2-hydroxybenzylidene)-5-methylcyclohexan-1-one (**BMC**) and its behavior as a function of pH.

## RESULTS AND DISCUSSION

The **BMC** compound was obtained by condensation reaction in basic alcoholic solutions<sup>16</sup> from 2-hydroxybenzaldehyde and 3-methylcyclohexanone. Due to the presence of methyl group on cyclohexanone fragment it was obtained mono-condensate compound (**BMC**), even by using an excess of aldehyde, instead of di-condensate structure (2,6-bis(2-hydroxybenzylidene)-5-methylcyclohexan-1-one), as it has been obtained in our previously work.<sup>5,9</sup> This behavior can be explained by a lower reactivity of the methylene group from  $\alpha$  position between keto group (C=O) and methyl (-CH<sub>3</sub>) and/or the steric hindrance provided by the methyl moiety. The <sup>1</sup>H NMR experiments for **BMC** were recorded in DMSO-*d*<sub>6</sub> and CD<sub>3</sub>OD<sub>3</sub> and proved the structure. The signals assigned to protons of aromatic ring

are better resolved in acetone than in DMSO-*d*<sub>6</sub> (Figure S1 and S2). The signal assigned to residual peak of acetone covers the area between 1.95-2.08 ppm, where signal/signals corresponding to two protons of cyclohexanone moiety is/are expected (Figure 1). The spectrum in DMSO-*d*<sub>6</sub> revealed the signals of protons from this area because the residual peaks assigned to DMSO-*d*<sub>6</sub> appear at 2.5 ppm (Figure S2).

X-ray single crystal study demonstrated the compound **BMC** has a molecular crystal structure built up from neutral units, as shown in Figure 2. Bond distances and angles are quoted in Table 1. The molecule is essentially planar except for the atoms C10 and C11 of the cyclohexanone part with the largest deviation from the mean plane of 0.61 Å for C11 atom.

The analysis of the crystal structure indicated the absence of  $\pi$ - $\pi$  stacking interactions between the aromatic rings and the packing motif can be characterized as parallel supramolecular ribbons (Figure 3) formed to O-H...O hydrogen-bonding between hydroxyl group as donor and carbonyl oxygen O<sub>2</sub> as acceptor of protons.

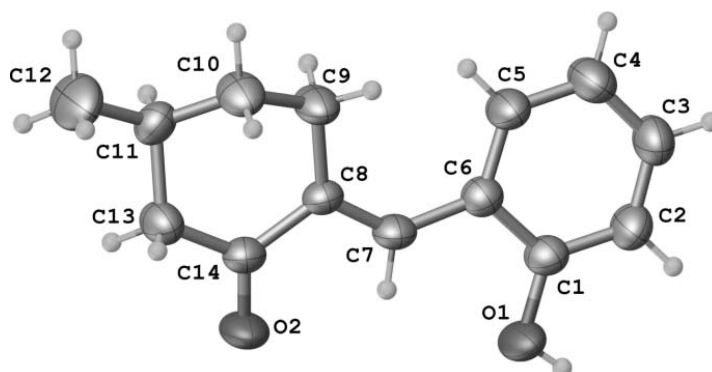


Fig. 2 – X-ray molecular structure of **BMC** with atom labeling scheme and thermal ellipsoids at 50% probability level. Only the major component of disordered fragment is shown.

Table 1

Bond distances (Å) and angles (°)

O1-C1	1.362(3)	C6-C7	1.461(3)	O1-C1-C2	121.4(2)	C7-C8-C14	116.5(2)
O2-C14	1.228(2)	C7-C8	1.339(3)	O1-C1-C6	117.6(2)	C14-C8-C9	118.2(2)
C1-C2	1.386(3)	C8-C9	1.514(3)	C2-C1-C6	121.0(2)	C8-C9-C10	113.2(2)
C1-C6	1.410(3)	C8-C14	1.484(3)	C2-C3-C4	120.7(2)	C11-C10-C9	109.9(3)
C2-C3	1.365(3)	C10-C11	1.503(5)	C5-C4-C3	119.0(2)	C10-C11-C12	111.2(3)
C3-C4	1.383(3)	C11-C12	1.542(5)	C4-C5-C6	122.8(2)	C10-C11-C13	106.8(3)
C4-C5	1.375(3)	C11-C13	1.530(4)	C1-C6-C7	117.8(2)	C13-C11-C12	109.5(3)
C5-C6	1.393(3)	C13-C14	1.503(3)	C5-C6-C1	116.4(2)	C14-C13-C11	115.6(2)
				C5-C6-C7	125.8(2)	O2-C14-C8	121.7(2)
				C8-C7-C6	132.8(2)	O2-C14-C13	118.0(2)
				C7-C8-C9	125.3(2)	C8-C14-C13	120.3(2)

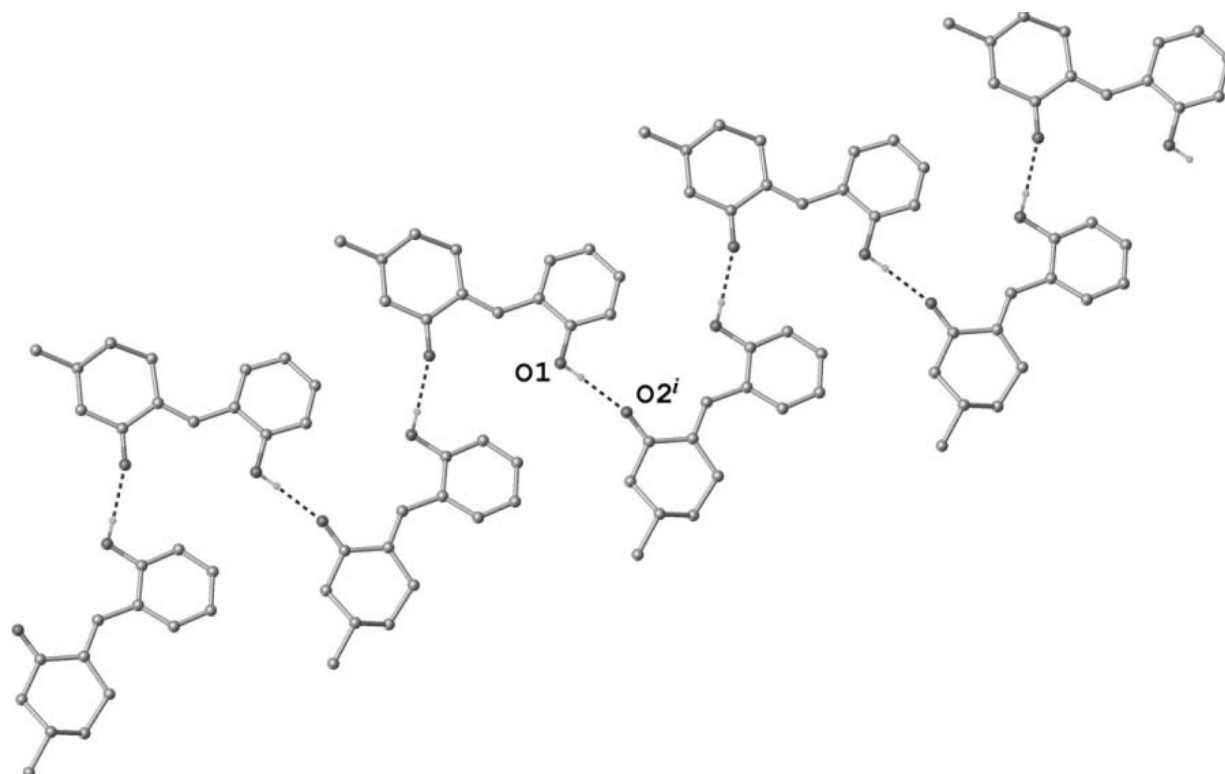


Fig. 3 – View of the supramolecular ribbon in the crystal structure of **BMC**. Only H-atoms involved in hydrogen bonding are shown. H-bond parameters: O1-H $\cdots$ O2 [O1-H 0.82 Å, H $\cdots$ O2 1.93 Å, O1 $\cdots$ O2 (2 - x, 0.5 + y 1.5 - z) 2.744(2) Å, O1-H $\cdots$ O2 174.4°].

By adding a few drops of HClO<sub>4</sub> 70% to a solution of **BMC** in methanol, the color changed from pale yellow to red due to the formation of the cationic form **MTX** (Figure 4) with a maximum absorption at 515 nm (Figure S3). The reversibility of the system was tested many times during one week proving the stability of the system in alcohol solvent. After water addition the solution became colorless in 20 hours. This behavior showed the instability of **MTX** in the presence of water, probably due to the formation of a side-product (bixanthene derivative), as in the case of 2-(2-hydroxybenzylidene) cyclohexan-1-one reported previously.<sup>11</sup>

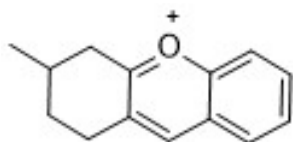


Fig. 4 – Chemical structure of 3-methyl-1,2,3,4-tetrahydroxanthylum (**MTX**).

**BMC** in basic pH turns into the unprotonated form (**BMC**<sup>-</sup>) with yellow color, which exhibits a broad absorption band at 390 nm. The UV-Vis spectra of **BMC** in aqueous solutions on pH range

between 7.5 and 12.9 are presented in Figure 5. The intensity of the absorption band characteristic to the **BMC**<sup>-</sup> anion was gradually increased with the pH and the saturation was observed around pH 13 ( $\epsilon = 7767.5 \text{ M}^{-1} \text{ cm}^{-1}$ ), as the acido-basic equilibrium presented in Scheme 1 is drastically shifted to the left.

## EXPERIMENTAL

2-hydroxybenzaldehyde, 3-methylcyclohexan-1-one and hydrochloric acid were purchased from Merck & Co. Sodium hydroxide was from Lach-Ner (CZ). All the other reagents and solvents were of analytical grade.

Elemental analysis was performed using VarioMICRO cube system from Elemental Analyses. The NMR spectra were recorded on a Bruker Advance III 500 spectrometer at 298 K. The FTIR spectra were recorded on a Cary 630 FTIR from Agilent Technologies, recorded using KBr pellets. The UV-VIS absorption spectra were recorded on an Agilent Cary 60 spectrophotometer. The pH of the solutions was measured using an Oakton pH/°C meter pH 10 series. Spectroscopic experiments in basic conditions were carried out in buffer/methanol (29 : 1, v/v) by adding 0.1 mL of a solution of **BMC** in methanol (4.8 mM) to 2.9 mL of buffer solution (pH previously adjusted) in order to obtain the final desired pH value. For these measurements two different buffer solutions were used: Na<sub>2</sub>HPO<sub>4</sub>/KH<sub>2</sub>PO<sub>4</sub> (pH 7 – 9) and glycine/NaOH (pH 9 – 13).

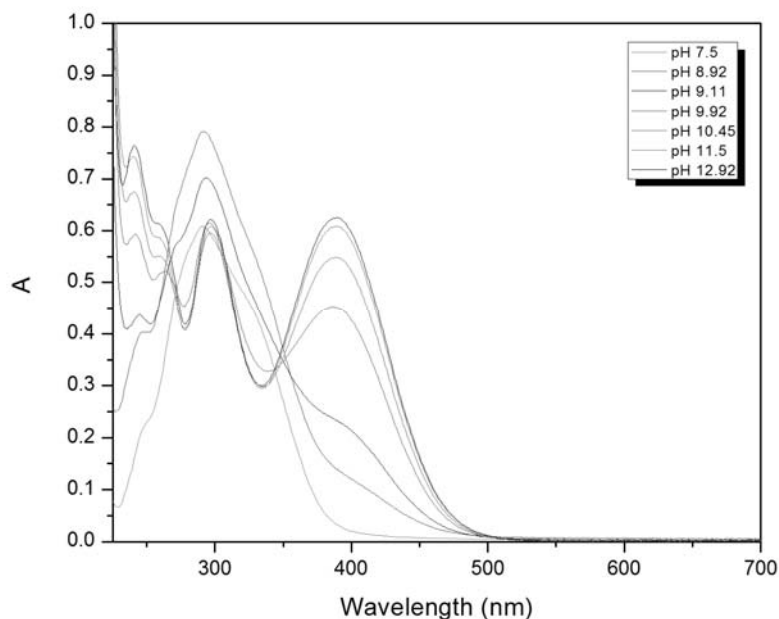


Fig. 5 – UV-Vis spectra of **BMC** aqueous solutions in basic pH ( $8 \times 10^{-5}$  mol L<sup>-1</sup>).

Table 2

Crystallographic data, details of data collection and structure refinement parameters

Empirical formula	C <sub>14</sub> H <sub>16</sub> O <sub>2</sub>	Z	4
Formula weight	216.27	$D_{\text{calc}}/\text{mg}/\text{mm}^3$	1.228
Temperature/K	293	$\mu/\text{mm}^{-1}$	0.081
Crystal system	monoclinic	Crystal size/ $\text{mm}^3$	$0.40 \times 0.30 \times 0.20$
Space group	$P2_1/c$	$\theta_{\text{min}}, \theta_{\text{max}}(^{\circ})$	4.4 to 50.04
$a/\text{\AA}$	6.1146(14)	Reflections collected	4384
$b/\text{\AA}$	10.9437(15)	Independent reflections	2062 [ $R_{\text{int}} = 0.0561$ ]
$c/\text{\AA}$	17.529(7)	Data/restraints/parameters	2062/4/153
$\alpha/^{\circ}$	90.00	GOF <sup>c</sup>	1.074
$\beta/^{\circ}$	94.09(3)	$R_1^a$ ( $I > 2\sigma(I)$ )	0.0649
$\gamma/^{\circ}$	90.00	$wR_2^b$ (all data)	0.1505
$V/\text{\AA}^3$	1170.0(5)	Largest diff. peak/hole/ $e \text{\AA}^{-3}$	0.15/-0.15

<sup>a</sup> $R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|$ . <sup>b</sup> $wR_2 = \{ \sum [w(F_o^2 - F_c^2)^2] / \sum [w(F_o^2)^2] \}^{1/2}$ . <sup>c</sup> GOF =  $\{ \sum [w(F_o^2 - F_c^2)^2] / (n - p) \}^{1/2}$ , where  $n$  is the number of reflections and  $p$  is the total number of parameters refined.

The **BMC** crystals were obtained by slow evaporation from acetone/hexane (1:1, v/v). X-ray diffraction data were collected with an Oxford-Diffraction XCALIBUR E CCD diffractometer equipped with graphite-monochromated MoK $\alpha$  radiation. Single crystals were positioned at 40 mm from the detector, and 104 frames were measured each of 20 s over 1 $^{\circ}$  scan. The unit cell determination and data integration were carried out using the CrysAlis package of Oxford Diffraction<sup>22</sup>. The structures were solved by direct methods using Olex2<sup>23</sup> software with the SHELXS structure solution program and refined by full-matrix least-squares on  $F^2$  with SHELXL-97.<sup>24</sup> Hydrogen atoms attached to carbon were placed in fixed, idealized positions and refined as rigidly bonded to the corresponding non-hydrogen atoms. Positional parameters of the H attached to O atom were obtained from difference Fourier syntheses and verified by the hydrogen bond parameters. Positional parameters of two disordered carbon atoms were refined in combination with PART and SADI restraints and the displacement parameters for paired components were constrained to be equivalent. Crystal data

and further details of data collection and structure refinement are given in Table 2. CCDC: 1571002.

#### Synthesis of **BMC**

A solution of 4.2 mL 2-hydroxybenzaldehyde (4.88 g, 40 mmol) in 5 mL ethanol was stirred at room temperature for 10 minutes. Then, 2.5 mL of 3-methylcyclohexan-1-one (2.24 g, 20 mmol) were added and the mixture was stirred vigorously for 30 minutes. 24 g of a NaOH 20% (w/w) solution were added dropwise, slowly, by maintaining the temperature below 40  $^{\circ}$ C and the reaction was carried out at room temperature for 24 h. 30 mL of distilled water were then added and the mixture was neutralized to pH 5.0 using a solution of HCl 6 M. A yellowish precipitate was formed which was filtered, dried and recrystallized from acetone/water. The yield of reaction was 50 %. Elemental analysis Calcd for C<sub>14</sub>H<sub>16</sub>O<sub>2</sub>: C 77.75, H 7.46, Found: C 77.63, H 7.53 %. m.p = 136.5-138  $^{\circ}$ C.

<sup>1</sup>H-NMR (300 MHz, DMSO- $d_6$ )  $\delta$  (ppm): 9.90 (s, 1H, -OH), 7.50 (s, 1H, -CH=C bridge), 7.26 (d,  $J = 7.6$  Hz, 1H, H<sub>ar</sub>), 7.23

– 7.12 (m, 1H, Har), 6.89 (d,  $J = 7.7$  Hz, 1H, Har), 6.83 (t,  $J = 7.4$  Hz, 1H, Har), 2.85 (dt,  $J = 16.3, 3.5$  Hz, 1H, H<sub>al</sub>), 2.69 – 2.58 (m, 1H, H<sub>al</sub>), 2.54 (d,  $J = 2.0$  Hz, 1H, H<sub>al</sub>), 2.14 – 2.05 (m, 1H, H<sub>al</sub>), 2.01 (d,  $J = 6.3$  Hz, 1H, H<sub>al</sub>), 1.89 – 1.75 (m, 1H, H<sub>al</sub>), 1.36 – 1.19 (m, 1H, -HC-CH<sub>3</sub>), 0.98 (d,  $J = 6.1$  Hz, 3H, -CH<sub>3</sub>). (Figure S2)

<sup>13</sup>C-NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ (ppm): 200.72 (C=O), 157.20 (C-OH), 135.23 (CH=C bridge), 130.65 (CH=C bridge), 130.53 (CH<sub>ar</sub>), 122.59 (C<sub>ar</sub>), 119.04 (CH<sub>ar</sub>), 115.92 (CH<sub>ar</sub>), 48.50 (CH<sub>2</sub>), 31.84 (CH<sub>2</sub>), 30.04 (CH), 27.87 (CH), 22.01 (CH<sub>3</sub>). (Figure S4) and Figure S5 DEPT.

FT-IR (KBr) cm<sup>-1</sup>: 3347, 2952, 2925, 2868, 1655, 1601, 1558, 1453, 1361, 1305, 1255, 1143, 940, 752 (Figure S6).

<sup>1</sup>H-NMR in basic medium (500 MHz, 700 μL DMSO-*d*<sub>6</sub> + 40 μL of 40 wt% NaOD in D<sub>2</sub>O), δ (ppm): 7.84 (s, 1H, CH=C bridge), 7.06 (d,  $J = 9.0$  Hz, 1H, Har) 6.86 (t,  $J = 7.7$  Hz, 1H, Har), 6.34 (d,  $J = 7.7$  Hz, 1H, Har), 6.12 (t, 1H, Har), 2.67-2.90 (m, 1H), 2.39-2.63 (m, 3H), 1.65-1.98 (m, 2H), 1.08-1.34 (m, 1H), 0.92 (d, 3H, CH<sub>3</sub>). (Figure S7)

## CONCLUSIONS

2-(2-hydroxybenzylidene)-5-methylcyclohexan-1-one was synthesized in basic solutions. The product of condensation reaction is not affected by an excess of carbonylic component due to the low reactivity of the α methylene position and steric hindrance. The X-ray diffraction shows a monoclinic packing of crystal system with 4 molecules/ unit cell. BMC resulted to be a halochromic material: BMC forms 1,2,3,4,- tetrahydroxy xanthilium salt (MTC) in an acidic pH, but the fatigue of the system is low in the presence of water. In a basic pH, BMC switches to unprotonated species and this process is pH reversible.

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