# MALTOL VERSUS THIOMALTOL. THEORETICAL COMPARISON OF SELECTED PROPERTIES.

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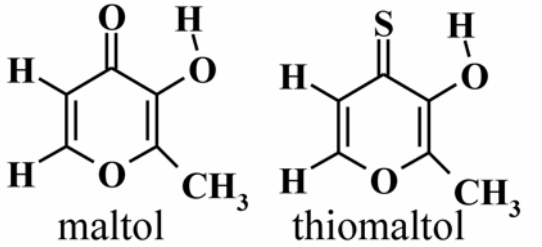
Derivatives of the pyromeconic acid (3-hydroxy-4H-pyran-4-one) are family of the ligands widely used in coordination chemistry. Among them, the importance of maltol (3-hydroxy-2-methyl-4H-pyran-4-one) as the most important member of this class of compounds must be underlined [1]. Maltol complexes with different metal ions possess strong biological activity and are tested as new medicines in diabetes and anaemia therapy as well as new radiopharmaceutical agents. In order to obtain new useful ligands several modifications of the hydroxypyrone system have been attempted. From several years, thiomaltol, ligand in which oxygen atom from the keto group is replaced by sulphur (see Fig. 1) is widely investigated [2]. Such mixed oxygen – sulphur ligands can be for example useful as efficient scavengers of lead ions, a serious contaminant [3].

Fig.1. Molecular structures of maltol and thiomaltol.




Ligands investigations are of crucial importance for prediction and interpretation of the properties of their complexes with metal ions. In this study geometries of tautomeric structures, equilibrium constants among them and aromaticity properties of the most stable tautomers are presented. Data for both, neutral and charged forms (anion and cation, created by deprotonation or protonation, respectively) of thiomaltol are included. Thiomaltol properties are compared with those reported previously for maltol (tautomeric equilibria [4], heteroaromaticity in the pyran rings [5], and π-electron delocalisation in the OCCO molecular fragment [6]). Studying the SCCO molecular fragment properties is very important because this group is responsible for metal ions binding in the studied ligand.

All quantum-chemical calculations have been executed at the B1LYP[7]/6-3111++G(d,p)[8] level as implemented in the GAUSSIAN-03 package [9]. In order to select the most probable conformations of studied thiomaltol species their potential energy surfaces have been scanned and the lowest minimum has been located for every tautomer. These lowest energy conformations have been fully optimized and the nature (minimum or saddle point) of them have been checked by frequency calculations at the

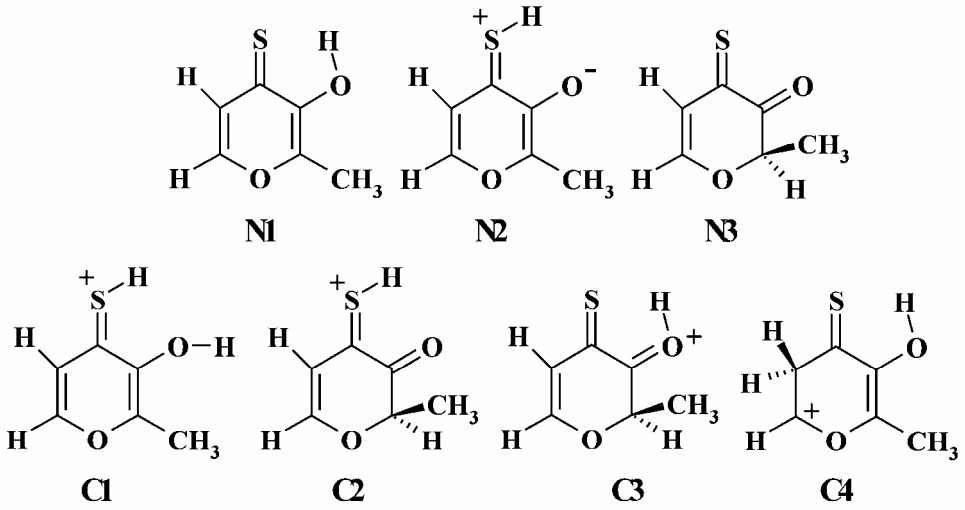
same computational level. All molecular energies have been corrected by the zero point energies (ZPE) of vibrational motions.

Statistical thermodynamic treatment has been used for tautomeric equilibrium constans determination [10]. In this method equilibrium constant ($K_T$) is related to the standard change of the Gibbs energy, $\Delta G^0$, by the following equation: $\Delta G^0 = - RT \ln K_T$. $\Delta G^0$ values have been estimated by GAUSSIAN from the total partition function given as a product of translational, rotational and vibrational partition functions evaluated within the rigid motor – harmonic oscillator – ideal gas approximation.

HOMA (Harmonic Oscillator Model of Aromaticity) and NICS (Nuclear Independent Chemical Shift) indices have been employed to determine aromaticity/π-electron delocalization properties of studied compounds. HOMA [11] is a geometry-based index calculated on the base of bond lenghts of the potential aromatic system using the equation: $HOMA = 1 - [\alpha/N \Sigma(R_{opt} - R_i)^2$. $R_{opt}$ and $R_i$ are optimal bond lengths and bond lengths in the real system, respectively. Empirical factor, $\alpha$, sets the HOMA value equal to 0 for the Kekule structure of benzene and 1 for real benzene structure. N is the number of bonds in the studied system. The HOMA index was splitted i two parts, GEO and EN [12]. $HOMA = 1 - \alpha(R_{opt} - R_{ave})^2 - \alpha/N \Sigma(R_{ave} - R_i)^2 = 1 - EN - GEO$. GEO and EN are two effects that can decrease the aromaticity of the molecular system, namely: bond lengths alternation (GEO) and bond elongation (EN). The NICS index was originally defined as the negative value of the magnetic shielding computed at the aromatic ring center or at another point of the molecule[13]. From that time other NICS technics were introduced. Two of them are employed in this work. The NICS(1) index is the negative magnetic shielding calculated 1 Å above the ring (or another point) center [14] while $NICS(1)_{zz}$ is the out of plane component of the NICS(1) magnetic tensor [15]. Highly negative NICS values denote aromaticity whereas systems with positive values are antiaromatic.

A lot of tautomeric structures are possible for neutral thiomaltol and its cation. Tautomerism cannot occur for the anion, due to the lack of labile proton (the labile proton of the hydroxyl group dissociates during the anion formation). In this work only the most stable types of tautomers (determined previously for pyromeconic acid, maltol, and ethylmaltol [4] and kojic acids family [16]) are considered. Their structures are presented in Fig. 2.

Fig. 2. Studied neutral and cationic tautomers.



Relative energies and equilibrium constants of neutral and protonated thiomaltol tautomers are collected in Table 1 (for comparison maltol data are also presented). Only two neutral thiomaltol tautomers (N1 and N3) are stable. In the case of N2 tautomer, during geometry optimization procedure, proton from the –SH group migrates toward exocyclic oxygen. As a result, tautomer N2 tranforms into N1. Like in maltol the N1 structure is the most stable neutral form. The energy gap between N1 and N2 for thiomaltol and corresponding tautomeric equilibrium constant are similar to their maltol counterparts. In the case of the thiomaltol cation protonation occurs in the same place as for native maltol molecule (protonation on the sulphur atom of the thioketo group in thiomaltol and protonation of the oxygen atom of the keto group in maltol). But in contrary, the energy gap between the tautomer with the lowest energy, C1, and others is much more lower, see Table1. Because of that, C2 and C3 maltol cation tautomers are much less possible than the same types of tautomers in the case of thiomaltol. Tautomer C4 possess one imaginary frequency and all attempts to obtain a minimum have not given satisfactory results.

Table 1. Relative Energies (kJ/mol, ZPE included) and tautomeric equilibrium constants (B1LYP/6-311++G(d,p) calculations).

| Tautomers | Maltol [4] | | Thiomaltol | |
|---|---|---|---|---|
| | Relative Energy | $K_T$ | Relative Energy | $K_T$ |
| Neutral molecules | | | | |
| N1 ↔ N2 | 49.53 | $3.46 \cdot 10^{-9}$ | ----- | ----- |
| N1 ↔ N3 | 62.23 | $4.27 \cdot 10^{-11}$ | 68.23 | $7{,}31 \cdot 10^{-13}$ |
| Cations | | | | |
| C1 ↔ C2 | 230.70 | $3.83 \cdot 10^{-41}$ | 77.38 | $3.17 \cdot 10^{-14}$ |
| C1 ↔ C3 | 310.92 | $3.37 \cdot 10^{-55}$ | 130.08 | $1.17 \cdot 10^{-23}$ |
| C1 ↔ C4 | 266.55 | $2.00 \cdot 10^{-47}$ | ----- | ----- |

Aromaticity data for thiomaltol and maltol are presented in Table 2 (heterocyclic pyran ring) and 3 (XCCO group). The HOMA index predicts a bit stronger aromatic character of thiomaltol than maltol. This is true for both, the XCCO molecular fragment and for the heterocyclic pyran ring. The same (except aromaticity of the cation in the pyran ring) is true for the NICS(1) index. In contrary, behaviour of the NICS(0) is different. Here, maltol structures are slightly more aromatic. In general differences between maltol and thiomaltol are not big and for these three indices mentioned above the aromaticity order determined previously for maltol and other hydroxypyrones (aromaticity of cation > aromaticity of neutral molecule > aromaticity of anion) is still valid. Different results are obtained for the $NICS(1)_{zz}$. In this case the aromaticity order is different in every case, i.e. one aromaticity order is observed for heterocyclic ring in maltol, another one for heterocyclic ring in thiomaltol, etc. The reason, why the results provided by the $NICS(1)_{zz}$ method are so different than data from other indices is unknown so far. This problem will be studied in the future for the biggest set of hydroxypyrones and tiohydroxypyrones. In general, weights of GEO and EN sub-indices calculated for thiomaltol are similar to those determined for maltol.

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Table 2. Aromaticity indices values for various maltol and thiomaltol species – heterocyclic pyran rings.

| | HOMA | GEO | EN | NICS(0) | NICS(1) | $NICS(1)_{zz}$ |
|---|---|---|---|---|---|---|
| Maltol [5] | | | | | | |
| Neutral | 0.02 | 0.68 | 0.30 | -2.63 | -4.58 | -9.02 |
| Cation | 0.55 | 0.40 | 0.06 | -7.15 | -7.84 | -17.14 |
| Anion | -0.46 | 0.70 | 0.76 | -1.38 | -3.81 | -8.62 |
| Thiomaltol | | | | | | |
| Neutral | 0.27 | 0.50 | 0.23 | -1.93 | -4.63 | -9.10 |
| Cation | 0.62 | 0.26 | 0.12 | -5.79 | -7.36 | -15.97 |
| Anion | -0.03 | 0.46 | 0.57 | -0.79 | -3.89 | -9.40 |

Table 3. Aromaticity indices values for various maltol and thiomaltol species – XCCO group. (X=O maltol, X=S thiomaltol)

| | HOMA | GEO | EN | NICS(0) | NICS(1) | $NICS(1)_{zz}$ |
|---|---|---|---|---|---|---|
| Maltol [6] | | | | | | |
| Neutral | 0.05 | 0.55 | 0.40 | -4.37 | -3.20 | -3.96 |
| Cation | 0.45 | 0.07 | 0.48 | -7.83 | -3.38 | -2.65 |
| Anion | -0.40 | 1.12 | 0.28 | -0.54 | -2.04 | -2.19 |
| Thiomaltol | | | | | | |
| Neutral | 0.36 | 0.21 | 0.43 | -3.86 | -3.90 | -5.09 |
| Cation | 0.49 | 0.06 | 0.45 | -7.00 | -3.88 | -3.50 |
| Anion | 0.05 | 0.63 | 0.32 | 0.73 | -2.76 | -3.78 |

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