JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2005; **18:** 250–254

Theoretical studies on the aromaticity of selected hydroxypyrones and their cations and anions. Part 1—Aromaticity of heterocyclic pyran rings

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Received 3 March 2004; revised 18 May 2004; accepted 26 May 2004

ABSTRACT: The aromaticity of heterocyclic pyran rings in selected hydroxypyrones and their anions and cations was studied using three aromaticity indices, HOMA, I_6 and NICS. These values were determined for theoretical geometries obtained at the HF, SVWN, B3LYP and B1LYP levels of calculations with the 6–311 + + G(d,p) basis set. The data obtained show that the aromaticity for the hydroxypyrones under investigation increases in the order: anion < neutral molecule < cation. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: hydroxypyrones; aromaticity; HOMA; NICS; I_6

INTRODUCTION

Aromaticity is a basic concept in explaining the structure and reactivity of many chemical compounds, and experimental and theoretical studies on this phenomenon constitute one of the most popular topics in chemistry.[1] Its precise definition is still under heated dispute but there are certain criteria of aromaticity.[2] According to these criteria, aromatic compounds are more stable than their analogues with localized double and single bonds (energetic criterion of aromaticity), their bond lengths are between those typical for the single and double bonds (geometric criterion), they possess a π-electron ring current induced in the magnetic field (magnetic criterion) and they prefer substitution over addition reactions (reactivity criterion). Aromaticity is not restricted to carbocyclic and heterocyclic compounds only. It can be also considered in systems with intramolecular hydrogen bonding (quasi-aromaticity)[3] and in metal complexes, where metal ion is part of the ring (metalloaromaticity).[4]

The hydroxypyrones studied here are made up of two different rings (Fig. 1): a six-membered heterocyclic pyran ring and a five-membered quasi-ring with an intramolecular hydrogen bond. The aim of this work was to study the aromaticity of the heterocyclic ring. The ligands investigated were pyromeconic acid (3-hydroxy-4*H*-pyran-4-one), maltol (3-hydroxy-2-methyl-4*H*-pyran-4-one) and ethylmaltol (3-hydroxy-2-ethyl-4*H*-pyran-4-one). These compounds are of interest owing to their potentially strong biological activity while forming complexes with metal ions.[5] Some of them have been tested as new drugs. The most promising ones are maltol complexes with vanadium(III, IV) (insulin mimetic properties[6,7]) and iron(III) (iron deficiency anaemia[8]) ions.

In a solution, the hydroxypyrones under investigation form cations and anions by protonation or deprotonation, respectively.[9] The pKa$_1$ and pKa$_2$ values for maltol are 2.28 and 8.62, respectively. The changes in aromaticity on proton release or acceptance were also studied in this work. Owing to their chemical structures, tautomeric equilibria are expected in neutral and positively charged hydroxypyrones. We have shown previously that only enolic tautomers of the studied compounds exist as neutral molecules and protonation occurs on the oxygen atom of the keto group.[10] The ligands studied here consist of a flat pyran ring with keto and hydroxyl substituents (see Fig. 1). Owing to the presence of the conjugated π-electron system, they may be considered in terms of varying aromaticity.

It is expected that the aromaticity of the hydroxypyrone metal complexes will strongly influence their molecular properties. It has been suggested that metalloaromaticity is responsible for increasing the stability of chelate compounds (energetic criterion of aromaticity).[11] The aromaticity of heterocyclic and metallocyclic rings in complexes of hydroxypyrones may also give information about the reactivity of these compounds (reactivity criterion of aromaticity). Hence we believe that aromaticity studies of hydroxypyrones have not only a theoretical but also a strong practical meaning. Studies on the

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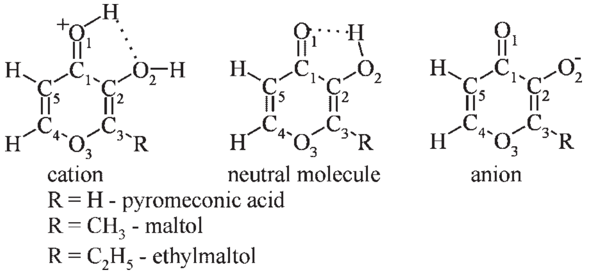

Figure 1. Structures and atom numbering scheme for the investigated forms of hydroxypyrones

properties of ligands usually constitute the first step in research on their metal complexes. Therefore, in this work, we determined the aromaticity of various forms of three biologically active hydroxypyrones. These data will be used as a starting point to the discuss aromaticity of their complexes with various metal ions.

COMPUTATIONAL DETAILS

Three aromaticity indexes are used, among which the HOMA (Harmonic Oscillator Model of Aromaticity) index[12,13] is the most popular in aromaticity studies. Its concept is based on the optimal interatomic distance for an aromatic molecule with full π-electron delocalization. The HOMA index is calculated according to the equation:

$$\mathrm{HOMA} = 1 - \left[\frac{\alpha}{n}\sum\left(R_{\mathrm{opt}} - R_i\right)^2\right] \tag{1}$$

where α is an empirical factor that determines HOMA = 0 for the Kekulé structure of benzene and HOMA = 1 for benzene with optimal 'aromatic' bond lengths, R_{opt} and R_i are optimal bond lengths and bond lengths in the real system, respectively, and n is the number of bonds taken into the summation. A few years ago the HOMA index was divided into two parts:[14,15]

$$\begin{aligned}\mathrm{HOMA} &= 1 - \alpha\left(R_{\mathrm{opt}} - R_{\mathrm{ave}}\right)^2 - \frac{\alpha}{n}\sum\left(R_{\mathrm{ave}} - R_i\right)^2\\ &= 1 - \mathrm{EN} - \mathrm{GEO}\end{aligned} \tag{2}$$

where R_{ave} is the average bond length in the system studied. Two effects that can decrease the aromaticity of the molecules are incorporated into this equation, namely bond length alternation (GEO) and bond elongation (EN).

I_6 is another geometry-based index of aromaticity.[16] Bond orders N are estimated from bond lengths according to the Gordy rule;[17] thus, I_6 values are obtained from the equations

$$V = \frac{100}{\overline{N}}\sqrt{\frac{\sum\left(N - \overline{N}\right)^2}{6}} \tag{3}$$

$$I_6 = 100\left(1 - \frac{V}{33.3}\right) \tag{4}$$

where $\overline{N}$ is the arithmetic mean of the calculated bond orders. The constant value of 33.3 is set based on the assumption that the aromaticity of benzene is equal to 100.

The last probe of aromaticity used in this study is the NICS (Nucleus Independent Chemical Shift) index. It is a magnetic index defined as the negative absolute magnetic shielding computed in the center of the ring.[18] The NICS value depends on the quantum chemical method and the basis set used in computation. It is also sensitive to the method used in the NMR shielding tensor calculation. In this work, we use the GIAO (Gauge-Independent Atomic Orbital)[19] method combined with all the methods employed in geometry calculations. The NICS value for the aromatic reference molecule, benzene, is about −10, and for the antiaromatic reference system, cyclobutadiene, it is about 28.[18] The NICS index has been the most common method used in aromaticity studies during the last few years.[20]

For precise aromaticity determination, good-quality geometric parameters are required. Generally, there are two sources of these, namely experimental values and theoretical calculations. In the case of the hydroxypyrones studied, not all experimental data needed are available. Geometries of the neutral molecules of pyromeconic acid,[21] maltol[22] and ethylmaltol[23] are available. So far, however, diffraction experiments have been done only for the maltol cation chloride.[24] No such data for hydroxypyrone anions have been found in the literature. Therefore, in this work we decided to use the theoretically optimized structures of the studied compounds. Some structural quantum chemical calculations on various forms of pyromeconic acid, maltol and ethylmaltol were performed. In these calculations, the HF method[25] and some DFT functionals with the 6–311++G(d,p) basis set were employed. Within the DFT methods, local (SVWN[26]) and two hybrid (B3LYP[27] and B1LYP[28]) functionals were used. The determinations of the most stable structures of maltol, ethylmaltol and pyromeconic acid and their anions and cations were published previously.[10] Here we use these geometries to evaluate the aromaticity indices for various forms of the compounds under investigation.

RESULTS AND DISCUSSION

Comparisons of the experimental and theoretical bond lengths of pyromeconic acid are given in Table 1. In order to test the influence of the theoretical methods on the bond length calculations, we include the results obtained from four methods: HF, SVWN, B3LYP and B1LYP. As can be seen, by comparison with the experimental results, all of the theoretical methods calculate the geometry of the studied ligand with acceptable quality. The best

Table 1. Comparison between experimental and calculated [6–311++G(d,p) basis set] bond lengths for pyromeconic acid

Bond	Experimental[21]	HF	SVWN	B3LYP	B1LYP
O(1)—C(1)	1.248	1.201	1.241	1.234	1.232
C(1)—C(2)	1.448	1.471	1.455	1.469	1.469
C(2)—O(2)	1.350	1.338	1.319	1.345	1.346
C(2)—C(3)	1.343	1.327	1.351	1.350	1.348
C(3)—O(3)	1.354	1.349	1.349	1.364	1.363
O(3)—C(4)	1.341	1.324	1.329	1.344	1.343
C(4)—C(5)	1.328	1.332	1.353	1.351	1.350
C(5)—C(1)	1.427	1.454	1.422	1.446	1.447

Table 2. Comparison between experimental and calculated (B1LYP method) [6–311++G(d,p) basis set] bond lengths for various forms of maltol

	Cation		Neutral		Anion
Bond	Exp.[22]	B1LYP	Exp.[24]	B1LYP	B1LYP
O(1)—C(1)	1.307	1.310	1.245	1.234	1.236
C(1)—C(2)	1.408	1.418	1.444	1.465	1.513
C(2)—O(2)	1.346	1.350	1.353	1.352	1.263
C(2)—C(3)	1.368	1.375	1.358	1.353	1.406
C(3)—O(3)	1.337	1.344	1.363	1.372	1.392
O(3)—C(4)	1.329	1.334	1.342	1.344	1.330
C(4)—C(5)	1.345	1.359	1.344	1.348	1.345
C(5)—C(1)	1.404	1.406	1.440	1.447	1.456

Table 3. Aromaticity data for pyromeconic acid [all calculations with the 6–311++G(d,p) basis set]

Species	Aromaticity index	HF	SVWN	B3LYP	B1LYP
Neutral molecule					
	HOMA	−0.04	0.36	0.04	0.04
	GEO	0.90	0.49	0.67	0.68
	EN	0.14	0.15	0.29	0.28
	I_6	37.87	49.71	41.73	41.33
	NICS	−2.62	−2.75	−2.75	−2.75
Cation					
	HOMA	0.67	0.72	0.64	0.55
	GEO	0.31	0.24	0.26	0.40
	EN	0.01	0.04	0.10	0.05
	I_6	60.04	61.43	58.46	51.83
	NICS	−7.71	−6.81	−7.30	−7.36
Anion					
	HOMA	−0.55	−0.05	−0.49	−0.48
	GEO	1.04	0.53	0.71	0.72
	EN	0.51	0.52	0.78	0.76
	I_6	34.20	50.34	42.04	41.41
	NICS	−1.42	−1.02	−1.45	−1.49

agreement is found for the B3LYP and B1LYP methods, and the worst for the HF method. The latter is understandable, as the HF treatment does not take into account electron correlation. We think that the observed discrepancies between the theoretical and calculated geometries are due to the fact that the comparison is made between the experimental data obtained for single crystals (where intermolecular hydrogen bonds are created) and those calculated for free molecules in the gas phase.

In Table 2, the experimental and theoretical (B1LYP) bond lengths for cationic, anionic and neutral maltol molecules are compared. Again, the agreement between the theoretical and experimental values is satisfactory. In addition, the theoretical methods describe fairly well the structural changes among the various maltol forms. Good examples are the elongation of the O(1)—C(1) bond after protonation of the keto oxygen atom in the cation and the shortening of the O(2)—C(2) bond after deprotonation of the O(2) atom in the anion.

Aromaticity data for the pyran ring in the pyromeconic acid molecule are given in Table 3 and are also shown in Fig. 2. The data obtained for the HOMA index strongly suggest that relative aromaticity decreases from cation to neutral molecule to anion. The same is true for the NICS data obtained. In the case of the I_6 index, the results

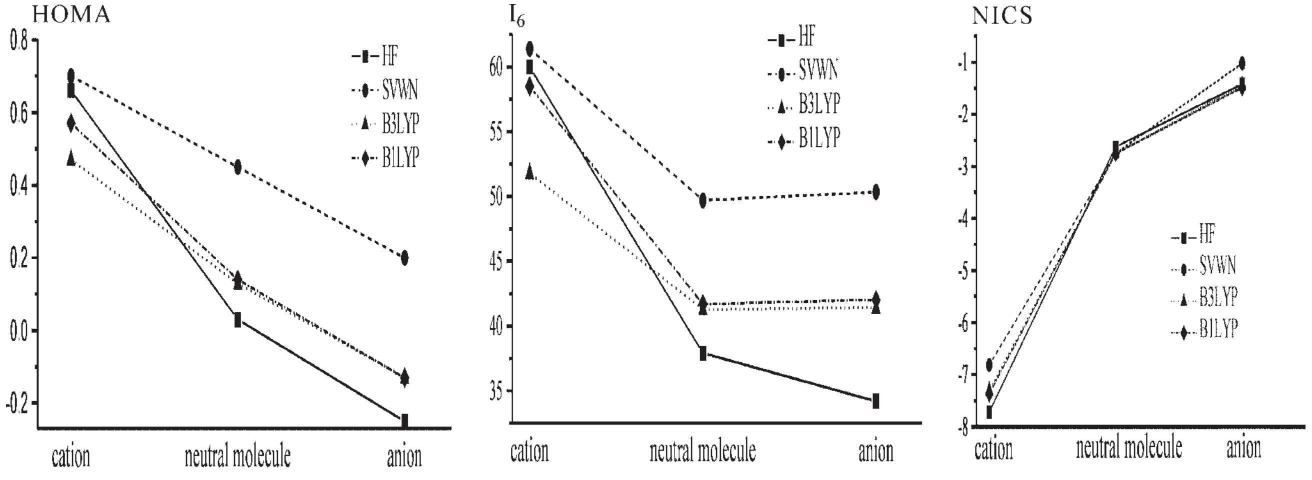

Figure 2. Changes in aromaticity indexes for various forms of the pyromeconic acid molecule. Calculations with the 6–311++G(d,p) basis set

obtained are slightly different. This method, except for the Hartree–Fock data, predicts only small differences between the aromaticity of the anion and neutral molecule. Other than for the other indexes, the aromaticity of the anion is here even slightly stronger than that of neutral molecules. These data clearly indicate that one has to be cautious when interpreting aromaticity results calculated with the I_6 index. This index, like the GEO part of the HOMA index, depends only on bond alternation in the molecule. As seen from Table 3, the values of the GEO part for the anion and the neutral pyromeconic acid molecule are similar. However, additional dearomatization of the anions occurs and is associated with the EN part. The EN values are much greater for anions than for neutral molecules. This effect cannot be observed in the I_6 index. This is the main source of erroneous data obtained while using the I_6 index in such calculations. According to the data presented in Table 3, the GEO term is much greater than the EN term for cations and neutral molecules. In the case of the pyromeconic acid anion, this is found only with the HF method. The GEO and EN values obtained for anion geometries calculated with the DFT methods are very close. The GEO values are shown to be somewhat smaller than the EN values when calculated using the B3LYP and B1LYP functionals.

Similar results obtained for maltol and ethylmaltol are presented in Tables 4 and 5. From these data one can conclude that the decreasing order of relative aromaticity, mentioned above, is the same for all of the hydroxypyrones studied. In the case of the DFT methods and the I_6 index, this order differs from that for the other data. This behaviour has been explained above. Similarly to the pyromeconic acid, the GEO term plays a major role for cations and neutral molecules, while its values are close to the EN values for anions (except for the HF method).

Table 4. Aromaticity data for maltol [all calculations with the 6–311++G(d,p) basis set]

Species	Aromaticity index	HF	SVWN	B3LYP	B1LYP
Neutral molecule					
	HOMA	−0.04	0.36	0.08	0.02
	GEO	0.88	0.48	0.63	0.68
	EN	0.16	0.15	0.28	0.30
	I_6	37.56	48.91	41.51	40.53
	NICS	−2.43	−2.70	−2.63	−2.63
Cation					
	HOMA	0.76	0.75	0.67	0.55
	GEO	0.23	0.20	0.22	0.40
	EN	0.01	0.05	0.11	0.06
	I_6	63.48	62.68	59.80	57.22
	NICS	−6.73	−6.60	−7.09	−7.15
Anion					
	HOMA	−0.53	−0.01	−0.47	−0.46
	GEO	1.03	0.49	0.68	0.70
	EN	0.50	0.51	0.79	0.76
	I_6	33.61	50.68	41.78	41.35
	NICS	−1.36	−0.84	−1.32	−1.38

Table 5. Aromaticity data for ethylmaltol [all calculations with the 6–311++G(d,p) basis set]

Species	Aromaticity index	HF	SVWN	B3LYP	B1LYP
Neutral molecule					
	HOMA	−0.03	0.36	0.03	0.03
	GEO	0.88	0.48	0.66	0.67
	EN	0.15	0.16	0.31	0.30
	I_6	37.67	48.85	40.98	40.62
	NICS	−2.58	−2.86	−2.82	−2.82
Cation					
	HOMA	0.69	0.71	0.61	0.62
	GEO	0.30	0.25	0.28	0.28
	EN	0.01	0.04	0.11	0.10
	I_6	59.56	59.76	56.76	56.96
	NICS	−6.86	−6.35	−6.98	−7.04
Anion					
	HOMA	−0.53	−0.02	−0.47	−0.47
	GEO	1.03	0.50	0.68	0.70
	EN	0.50	0.52	0.79	0.77
	I_6	33.47	50.63	41.78	41.21
	NICS	−1.44	−0.80	−1.40	−1.44

It was observed for RNA and DNA bases[29] that aromaticity decreases with increase in the number of the C═X (X = O, N) groups attached to the ring. The same effect is observed with hydroxypyrones. There are two single-bonded exocyclic CO groups in the cation, one single- and one double-bonded CO group in the neutral molecule and one double- and one partially double-bonded CO group in the anions. Hence our calculations support the expected changes in the aromaticity of the pyran ring, which decreases with increasing number of exocyclic C═O groups.

From the results obtained, it is easy to compare the aromaticities for the same (cation, anion or neutral) forms of pyromeconic acid, maltol and ethylmaltol calculated at a particular level of theory. Generally, our calculations show that the differences among neutral molecules and anions are negligible. For example, the HOMA indexes obtained from the HF geometries are −0.04, −0.04 and −0.03 for neutral molecules of pyromeconic acid, maltol and ethylmaltol, respectively. Hovewer, small differences are found for cations, especially when the NICS method is applied.

It should be emphasized that the same basis set [6–311++G(d,p)] was used for all computations. Nevertheless, some disagreement in the results obtained for different theoretical geometries is observed, as shown in Fig. 2. Both hybrid DFT functionals (B3LYP and B1LYP) give nearly the same results. Usually the HF calculations show the same level of aromaticity. Some discrepancies are obtained for the SVWN method and geometric aromaticity indexes (HOMA and I_6). Thus, the SVWN method shows greater aromaticity for HOMA and I_6. In contrast, the aromaticities estimated with the NICS index are generally smaller than those obtained for the other methods (HF, B3LYP and B1LYP). In our opinion, supported by the data obtained, the HF method, despite its weak point (lack of electron correlation), can still be useful for aromaticity calculations.

CONCLUSIONS

The geometry of the compounds studied here predicted by theoretical methods is in good agreement with the available experimental data. These methods have been shown to be suitable for describing of structural changes during cation and anion formation. The best geometric parameters were obtained using the B3LYP and B1LYP methods.

We have shown that the relative aromaticity in the heterocyclic rings of the three hydroxypyrones studied decreases in the order cation > neutral molecule > anion. We have also demonstrated that different theoretical methods lead to different values of aromaticity indexes, as is clearly shown for the SVWN method. In some cases, aromaticities determined from the SVWN geometries differ from other data, but the relative behaviour of this method is similar to that of the other theoretical methods used in this work. The data obtained here show that there is no influence of the aliphatic substituents on the aromaticity of the heterocyclic pyran ring. The aromaticity order of hydroxypyrones evaluated in this work is consistent with the published HOSE data for these compounds.[30]

Our work strongly supports the view that the HOMA and NICS indices should be preferred in aromaticity calculations, as the I_6 index sometimes differs significantly. For the HOMA and NICS computations, the B3LYP or B1LYP geometries seem to be the most reliable.

Acknowledgements

We thank the Warsaw University Interdisciplinary Centre for Mathematical and Computational Modelling ICM for allowing us to use their computers (project number G17-8). K.Z. is the recipient of a Jagiellonian University Rector's Fund award for an outstanding researcher. The authors thank Professor T. M. Krygowski (Warsaw University) for reading the text and helpful suggestions.

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