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Guanidinium Cation – An Acyclic Analogue of Benzene?

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Guanidinium cation fragment plays a very important structural role in chemistry of biologically active compounds. Hence, there is no surprise that the Science Citation Database [1] gives more than 1000 examples of the use of this term as a key word in the titles or in abstracts in the last 6 years. Also, Cambridge Structural Database [2] reports more than four hundred crystal structures with the guanidinium sub-unity, if only the highest precision data are concerned. The guanidine containing molecules are considered to be a critical part of many biological processes [3,4]. Because of its strongly basic character, with pK_a in water at the level of around 14 [5] the guanidine group is fully protonated under the physiological conditions and exists mostly in a cationic form as guanidinium salts [6]. The positive charge mediates the interactions between enzyme and substrate or receptor and ligand by electrostatic interactions.

In the structural inorganic chemistry it is a well-known and often encountered observation that molecular anions of Y-shape exhibit an increased stability. This phenomenon is sometimes called the Y-delocalization [7]. Guanidinium itself and molecules with a guanidinium fragment also belong to this category [8,9]. The purpose of this paper is to report some kind of analogy between the structural stability of Y-shaped guanidinium cation and its derivatives and the benzene derivatives. In the latter case it was shown that the π-electron delocalization measured by the geometry based HOMA index of aromaticity [10] is only little perturbed by substituents [11] in comparison with the changes due to the topological effects observed in the benzene ring in benzenoid hydrocarbons [12]. Application of the same methodology may allow us to answer to the question – how far the guanidinium cation moieties embedded in diversified molecular environments may be perturbed by various factors.

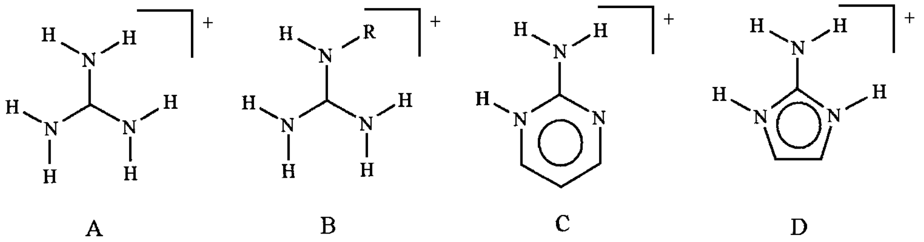
The estimation of the delocalization in the system with use of the HOMA index has been performed in two ways: (i) by use of molecular geometries retrieved from Cambridge Structural Database [2], (ii) applying MP2/6-311+G** optimized geometries [13] for five model compounds: the guanidinium cation, its symmetrically trisubstituted derivatives with CN and OH as the substituents, and two cases in which the guanidinium moiety included six and five membered π-electron rings (as shown in Scheme 1). The formula for HOMA reads [10]:

$$\mathrm{HOMA} = 1 - \tfrac{\alpha}{n}\Sigma\left(\mathrm{R}_{\mathrm{opt}} - \mathrm{R}_{\mathrm{i}}\right)^2$$

where R_{opt} is assumed for the bond length in the case of optimal delocalization, whereas α is a normalization factor to get HOMA = 1 for the case when all bonds in question are equal to R_{opt}, and HOMA = 0 for cases when single and double bonds in a molecule in question are equal to the reference single and double bonds of a given kind. The model constants, α and R_{opt} for CN bonds are equal to 93.52 and 1.334 Å, respectively [10].

The guanidinium skeleton exists in many molecular moieties and for the purpose of this study four sub-samples (A – D) were built up as presented in Scheme 1:

Scheme 1



The mean HOMA for sub-sample A is 1.011 [14]. This sub-sample consists of 37 guanidinium derivatives [2], which differ only by means of the variation of the counter anions. This group of systems is characterized by the highest delocalization of π-electrons that was numerically measured by means of HOMA index. This index for theoretically (MP2/6-311+G*) determined geometry of guanidinium cation is 1.00.

Sub-sample B consists of a guanidinium skeleton, in which the structural changes may exist not only as a result of the varying counteranion but also due to the changes in the structure closest to the guanidinium skeleton itself (R – group). The mean HOMA for the sample of 29 derivatives [2] gives 0.999. This means that the delocalization is still very high, the perturbations in the structure close to the guanidinium skeleton is sufficient to decrease the delocalization only in a minor way. The same is found for a theoretically (MP2/6-311+G*) determined geometry of symmetrically trisubstituted derivatives with CN or OH as substituents for which HOMA is 0.990 and 0.995, respectively.

In two other sub-samples, C and D the guanidinium skeleton is part of the six- or five-membered heterocyclic rings, respectively, the decrease of delocalization is greater. The mean values of HOMA are for these two cases 0.978 and 0.988, respectively. Theoretical values for HOMA for 2-aminopyrimidinium and 2-aminoimidazolium cations are here 0.981 and 0.973, respectively.

All the experimental results are based on the highest precision molecular geometry (with mean standard deviation not exceeding 0.005 Å) and hence may be considered as very reliable.

HOMA values obtained for the theoretically optimized geometry of model compounds are practically identical with those for the data from experimental measurements. This means that intermolecular interactions, which always are present in the crystalline state, practically do not affect bond lengths being in Y-delocalization and used for calculations of HOMA values.

Low variation of the very high values of HOMA index resembles the situation found for the polysubstituted benzene derivatives [11] and implies a very strong resistance against the perturbation,*i*. . a substantial π-electron delocalization. Fig. 1 presents a histogram of the distribution of HOMA values for the whole sample indicating a very low dispersion of the data,*i*. . supporting the above presented statement.

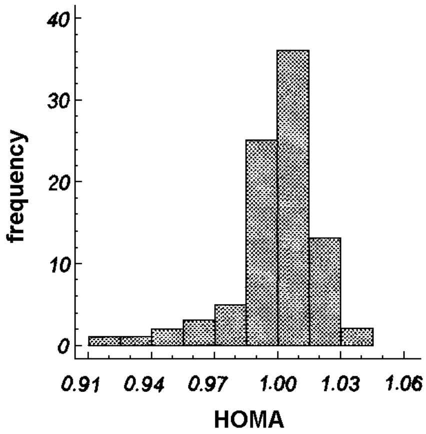


Figure 1. Histogram of the distribution of HOMA values for the whole sample, frequency of cases plotted against the HOMA values in 0.03 ranges.

These results may be compared with those for benzene derivatives [11]. In variously substituted benzene derivatives the range of the mean HOMA values was found between the highest value equal to 0.995 (for 1,3,5-trisubstituted species; 22 element sample) and the lowest one equal to 0.866 (for 1,2,3-trisubstituted species, 217 element sample). This comparison shows that guanidinium moiety may probably exhibit even a stronger resistance to the perturbations than those observed for benzene.

From the above-presented data it results that there may be accepted a strong analogy between the aromatic system, like *g* . benzene- and guanidinium moieties, as far as the π-electron delocalization is concerned and resistence to the perturbations. Moreover, it is also shown that the HOMA model, usually applied to study the aromaticity of the cyclic π-electron systems, may also be successfully applied to estimate the π-electron delocalization in non-cyclic π-electron systems.

As a general conclusion we may answer the title question: the values of the geometry-based aromaticity index HOMA, which measures the degree of the π-electron delocalization, supports the statement that guanidinium cations behave in some way similarly as the typical aromatics – benzene – following both, the most modern criteria of aromaticity [15] as well as the older statement by Hafner *a* . [16]: "one of the most striking phenomena related to aromaticity is the unusual tendency of aromatic system to remain so". Undoubtedly, the guanidinium moiety follows this principle well, but being in acyclic systems like A or B cannot be called aromatic. Nevertheless it may be named as an acyclic analogue of aromatic systems since like benzene contain 6π-electrons [9]. It should be noted, that in the case of conjugated polyene dications, the Y shaped trimethylenmethane dication, $C_4H_6^{2+}$ is also more stable than the linear structure but in the higher polyene dications the linear topology is favored over the respective Y-shaped systems [17].

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