STRUCTURE ANALYSIS OF CATECHOL-LIKE MOLECULAR FRAGMENTS

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A system of a rigid benzene ring and two variable torsion angles ϕ(C–C–OH) in catechol-like molecular fragments was studied. A scattergram of the two torsion angles taken from the Cambridge Structural Databank is in a good agreement with the potential energy map calculated with the AMBER compatible energy minimizer ORAL. Symmetry operations and point symmetry domains used during the analysis are described in detail. Results are interpreted in accord with the catchment region theory and the structure–correlation principle.

Molecules of three dihydroxybenzene isomers (catechol, resorcinol, hydroquinone) were studied recently in connection with their energy–geometrical and chemical properties relationships. Comparison of their potential energy maps and molecular shape invariance maps has been published by Arteca et al.[1]. Arteca and Mezey[2] discussed the shapes of these systems, undergoing rigid rotations from stationary point geometries. Particularly, catechol (1,2-dihydroxybenzene) was considered in more detail to elucidate the theorems on symmetry relations between ground- and excited-state configurations[3].

This article is dedicated to the analysis of the distribution of geometry of catechol-like molecular fragments (CLMF) retrieved from the Cambridge Structural Databank[4] and is a part of conformational study of simple compounds in our laboratory[5,6]. Final scattergram of two torsion angles ϕ(C–C–OH) defined in Fig. 1 is confronted with the potential energy surface calculated by a molecular mechanics method. Molecular symmetry of the fragment under study was respected in all calculations using the procedures introduced by Bauder et al.[7] and generalized by Soldán[8].

METHODS

Symmetry Determination

Determination of the molecular symmetry enables us to reflect an inherent property of the matter and, furthermore, it reduces significantly all the computational efforts. Our considerations will be focused on isometric configurations of the CLMF which will also be assumed to be isoergonic. The full isometric group leads to all isometric configurations with respect to the same kind of atoms. The group is given by combination of a point symmetry group (covering group) and an internal isometric group of the molecule. This procedure corresponds to the method of Bauder et al.[7-9] which is a general approach to these problems and reflects the nuclear configurations with higher point symmetry. Catechol-like fragment was selected to demonstrate this method because of its relatively simple geometry. In the general case the point symmetry group of CLMF is a trivial group C_1. The internal isometric group is more complicated and will be discussed in detail.

Nuclear Configuration

The natural way of visualization of the molecular geometry is a set of N points in the 3-dimensional real space, $\mathcal{R}_3$, where N is the number of atoms constituting the molecule.

Alternatively, molecular geometry can be defined by a set of $3N - 6$ internal structural parameters (internal coordinates[9,10])

$$\Phi\{\phi_1, \phi_2, \ldots, \phi_{3N-6}\}.$$

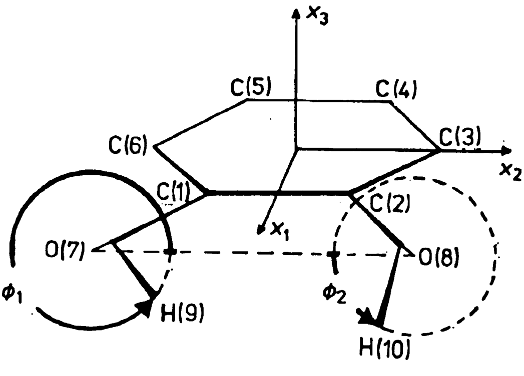

FIG. 1
Numbering scheme and Cartesian coordinate system for catechol molecule. Positive sense of torsion angles ϕ_1 and ϕ_2 corresponds to the standard convention[26]. The situation when both H(9) and H(10) are in the closest interaction corresponds to $\varphi_1 = \varphi_2 = 0°$

The corresponding pair (ϕ, $P(\phi)$), where the range of possible values of ϕ will be denoted by $P(\phi)$, is called the internal nuclear configuration space, the INCS, (spanned by ϕ) of a given molecule.

Knowing $\varphi \in P(\phi)$, we can define the relative nuclear configuration

$$\mathrm{RNC}\{\varphi, Z(n), M(n);\ n = 1, 2, \ldots, N\}$$

as a set of informations determining a nuclear configuration

$$\mathrm{NC}\{\boldsymbol{X}(n,\varphi), Z(n), M(n);\ n = 1, 2, \ldots, N\}$$

up to the translation and rotation of the whole molecule as a rigid body in $\mathcal{R}_3$. The position vectors $\boldsymbol{X}(n,\varphi)$ of the atomic nuclei will be referred to a properly chosen Cartesian system (Fig. 1). $Z(n)$ and $M(n)$ are the charge number and mass, respectively, $n = 1, 2, \ldots, N$.

The $3N$-dimensional space spanned by the N atom coordinates $\boldsymbol{X}(n,\phi)$ is known as the nuclear configuration space (NCS). If some internal coordinates vary only very little in the chemical process under study, they do not have to be condsidered explicitly and we can investigate the system only in a section of the INCS.

Parameterization of the CLMF

To simplify our problem we have assumed the CLMF to be planar with the C_{2v} point symmetry group with the only exception of hydroxyl hydrogens H(9) and H(10) which can rotate along the O(7)–C(1) and O(8)–C(2) axes, respectively (Fig. 1). Therefore, only two torsion angles $\phi_1(2,1,7,9)$ and $\phi_2(1,2,8,10)$ define the free (active) internal structural parameters of the CLMF.

The corresponding section of the INCS can be written as (ϕ,$Q(\phi)$), where $\phi = (\phi_1,\phi_2)$ and $Q(\phi) = (D \bmod 360°) \times (D \bmod 360°)$, $D = (-180°, 180°\rangle$.

The Internal Isometric Group

The internal isometric group of CLMF is

$$F = \{\mathrm{F}_1, \mathrm{F}_2, \mathrm{F}_3, \mathrm{F}_4\},$$

where F_i, $i = 1, 2, 3, 4$, are one-to-one mappings operating on $P(\phi)$ and leading to new configurations of the CLMF which are isometric with the original configuration. We can write the mappings as

$$\mathrm{F}_1, \mathrm{F}_2, \mathrm{F}_3, \mathrm{F}_4 : D \times D \rightarrow D \times D$$

and

$$F_1(\varphi_1,\varphi_2) = (\varphi_1,\varphi_2),$$

$$F_2(\varphi_1,\varphi_2) = (-\varphi_1,-\varphi_2),\ \text{if}\ \varphi_1 \neq 180°,$$

$$F_2(180°,\varphi_2) = (180°,-\varphi_2),\ \text{if}\ \varphi_2 \neq 180°,$$

$$F_2(\varphi_1,180°) = (-\varphi_1,\ 180°),\ \text{if}\ \varphi_1 \neq 180°,$$

$$F_2(180°,180°) = (180°,180°),$$

$$F_3(\varphi_1,\varphi_2) = (\varphi_2,\varphi_1),$$

$$F_4(\varphi_1,\varphi_2) = (-\varphi_2,-\varphi_1),\ \text{if}\ \varphi_i \neq 180°,$$

$$F_4(180°,\varphi_2) = (-\varphi_2,180°),\ \text{if}\ \varphi_2 \neq 180°,$$

$$F_4(\varphi_1,180°) = (180°,-\varphi_1),\ \text{if}\ \varphi_1 \neq 180°,$$

$$F_4(180°,180°) = (180°,180°),$$

where $(\varphi_1,\varphi_2) \in D \times D$.

Representation of the Internal Isometric Group

Due to the trivial point symmetry group of the CLMF we can define a representation h of a group F in the following way:

$$h\colon F \rightarrow S(10) \times O(3)\,,$$

where $S(10)$ is a permutation group of a set $\{1, 2, \ldots, 10\}$, $O(3)$ is a group of orthogonal 3 × 3 matrices and "×" means the Cartesian product.

Explicitly, we have

$$h(F_1) = (P_1,I)$$

$$h(F_2) = (P_1,K_1)$$

$$h(F_3) = (P_2,K_2)$$

$$h(F_4) = (P_2,K_1K_2)\,,$$

where P_1 is an identity permutation,

$$P_2 = \begin{pmatrix} 1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 \\ 2 & 1 & 6 & 5 & 4 & 3 & 8 & 7 & 10 & 9 \end{pmatrix},$$

$$I = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}, \qquad K_1 = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & -1 \end{pmatrix}, \qquad K_2 = \begin{pmatrix} 1 & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & -1 \end{pmatrix}.$$

The ordered pair $(P,K) \in S(10) \times O(3)$ is operating on position vectors $\boldsymbol{X}(n,\varphi)$, $n = 1, 2, \ldots, 10$, $\varphi \in P(\phi)$, such as

$$(P,K)\boldsymbol{X}(n,\varphi) = K\boldsymbol{X}(P^{-1}(n),\varphi)\,.$$

For the individual $\mathrm{F} \in F$ we can write

$$\text{if } h(\mathrm{F}) = (P,K) \text{ then } \boldsymbol{X}(n,\mathrm{F}(\varphi)) = K\boldsymbol{X}(P^{-1}(n),\varphi).$$

The Full Isometric Group

Due to the trivial point symmetry group of CLMF the full isometric group H is defined as a subgroup of $S(10) \times O(3)$:

$$H = h(F).$$

The Fixed Point Set

The fixed point set, FPS, of the $\mathrm{F} \in F$ is defined by the relation

$$\mathrm{FPS(F)} = \{\varphi \in D;\ \mathrm{F}(\varphi) = \varphi\}$$

For CLMF we receive

$$\mathrm{FPS(F_1)} = P(\phi),$$

$$\mathrm{FPS(F_2)} = \{(0°,0°), (0°,180°), (180°,0°), (180°,180°)\},$$

$$\mathrm{FPS(F_3)} = \{(\varphi_1,\varphi_2) \in P(\phi) \mid \varphi_1 = \varphi_2\},$$

$$\mathrm{FPS(F_4)} = \{(\varphi_1,\varphi_2) \in P(\phi) \mid \varphi_1 = -\varphi_2\}.$$

Point Symmetry Domains

Fixed points of non-trivial internal isometric transformations define nuclear configurations which may have higher point symmetry group then the point symmetry group of the CLMF. The following representations L^{NC} of point symmetry groups of nuclear configuration of CLMF are possible:

$$\varphi \notin \mathrm{FPS}(F_2) \cup \mathrm{FPS}(F_3) \cup \mathrm{FPS}(F_4) \quad \Rightarrow \quad L^{NC}(\varphi) = \{I\},$$

$$\varphi \in \mathrm{FPS}(F_2) - \{(0°,0°), (180°,180°)\} \quad \Rightarrow \quad L^{NC}(\varphi) = \{I,K_1\},$$

$$\varphi \in \mathrm{FPS}(F_3) - \{(0°,0°), (180°,180°)\} \quad \Rightarrow \quad L^{NC}(\varphi) = \{I,K_2\},$$

$$\varphi \in \mathrm{FPS}(F_4) - \{(0°,0°), (180°,180°)\} \quad \Rightarrow \quad L^{NC}(\varphi) = \{I,K_1K_2\},$$

$$\varphi \in \{(0°,0°), (180°,180°)\} \quad \Rightarrow \quad L^{NC}(\varphi) = \{I,K_1,K_2,K_1K_2\}.$$

Knowing the individual FPS(F), $F \in \mathcal{F}$, we can define point symmetry domains[3] of the nuclear configuration space as non-overlapping areas containing nuclear configurations of the same point symmetry group.

Potential Energy Surface

The potential energy surface, PES, may be defined by assigning an energy value to each formal nuclear configuration represented as a point in the $3N$-dimensional NCS or, similarly, in the INCS, or in the relaxed cross section of the INCS, respectively[3].

It was shown[3,10] that there exists the important relation between molecular point symmetry and the energetic stability of the molecules. There is a concept of catchment region[3,10] defined as a part of the NCS where any infinitely slow, vibrationless relaxation of each distorted nuclear arrangement leads to the same equilibrium nuclear configuration, i.e., to the same point where the gradient of the PES is zero. This is a tool for partitioning the NCS in distinct sets, as each catchment region represents a formal chemical species. It should be stressed that this definition applies to any stationary (critical) point, e.g., minima, saddle points and maxima. Mezey[3] has formulated the link between point symmetry domains and catchment regions as a catchment region minimum theorem: "If within a catchment region there is a point X with a symmetry element K not present anywhere else in the catchment region, then this point X must have the lowest energy value within the catchment region, and the point X is the critical point".

Partitioning of the NCS is distinct catchment regions enables us to find a molecular prototype (archetype) which belongs to a given equilibrium nuclear configuration and thus characterizes the statistic behaviour of the molecule under study.

There are several methods for reconstruction of PES in the Born–Oppenheimer approximation[11]. In this analysis two of them were used.

Empirical reconstruction is based on molecular mechanics[12]. Potential energy map $E(\phi_1,\phi_2)$ was calculated as a function of torsion angles ϕ_1, ϕ_2, by means of the AMBER molecular mechanics package[13,14] with the routine ORAL (ref.[15]) on an Alliant FX 80 computer. The benzene ring and both H–O–C rotating arms were assumed to be three rigid blocks where their mutual interaction controls the value of E. The intra-block interactions were "switched off" (ref.[15]). Atomic charges and force field parameters were taken from refs[16,17]. Particularly, the model values of atomic distances C(1)–O(7) and C(2)–O(8) were set to $1.37 \cdot 10^{-10}$ m, O(7)–H(9) and O(8)–H(10) to $1.00 \cdot 10^{-10}$ m and the angles C(1)–O(7)–H(9) and C(2)–O(8)–H(10) to 117° values. Similarly, C(2)–C(1)–O(7) and C(1)–C(2)–O(8) angles were set to 120°. This relatively simple approximation[1] was applied in order to test the approaches which are to be used in more ambitious problems concerning a family of similar compounds[18].

The structure correlation method was originally formulated by Bürgi and Dunitz[19]. The basic assumption behind this method is that a distribution of sample points corresponding to observed structures will tend to concentrate in low-energy regions of the NCS. This is equivalent to the assumption that the interaction energy between the molecule and its enviroment can be regarded as a small perturbation relative to the internal molecular potential energy. The usual source of "observed structures" are the crystallographic structural databases[4].

Clusters of representation points in the NCS indicate the energy minima or simple saddle points. They correspond to stable chemical species and to transitions states, respectively. The energy valleys correspond to the deformation of a fragment along chemical reaction paths.

Database Search

A fragment of general formula *I* (Fig. 1) was searched in the January 1989 (3.4) version of the Cambridge Structural Database[20] using the QUEST89 program[20]. In 77 retrieved compounds, the GSTAT89 program[20] identified 101 catechol-like molecular fragments (e.g. substituted di- and trihydroxybenzenes, their salts and adducts). This program was also used to calculate all interesting geometric parameters of the CLMF*.

The final input data were generated from the original set applying symmetry operations of the internal isometric group described above. In this way the total number of 404 (already dependent) data were analyzed.

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* Retrieved data and their evaluation are available upon request from the first author.

Cluster Analysis

The nearest neighbour method[21] was applied to 404 pairs $(\varphi_1,\varphi_2) \in (-180°,180°\rangle \times (-180°,180°\rangle$. The coefficient of nonsimilarity, δ, was defined for

$$(\varphi_1,\varphi_2),\ (\varphi_1',\varphi_2') \in (-180°,180°\rangle \times (-180°,180°\rangle$$

as

$$\delta((\varphi_1,\varphi_2),\ (\varphi_1',\varphi_2')) \ = \ \min\{\rho((\varphi_1 + k\,.\,360°,\ \varphi_2 + l\,.\,360°),\ (\varphi_1',\varphi_2'))|\ k, l \in \{-1,0,1\}\}\ ,$$

where

$$\rho((a,b),\ (c,d)) \ = \ ((a-c)^2 \ + \ (b-d)^2)^{1/2}\,.$$

Statistics

For m values of parameters φ_1, φ_2 the mean values M were calculated as

$$M(\phi_i) \ = \ \{\sum_{j=1}^{m} (\varphi_{ji})\}/m, \quad i = 1, 2\,,$$

the estimated standard deviations S were calculated as

$$S(\phi_i) \ = \ [\{\sum_{j=1}^{m} (M(\phi_i) \ - \ \varphi_{ji})^2\}/(m-1)]^{1/2}, \quad i = 1, 2\,,$$

and the correlation coefficient R was calculated as

$$R(\phi_1,\phi_2) \ = \ [\sum_{j=1}^{m} (\varphi_{j1}\ \varphi_{j2}) \ - \ m\,M(\phi_1)\,M(\phi_2)\,]/[\,(m-1)\,S(\phi_1)\,S(\phi_2)\,]\,,$$

where φ_{ji}, $j = 1, 2, \ldots, m$, are values of ϕ_i.

RESULTS AND DISCUSSION

Graphic Representation

Due to the equivalence $\phi_i = \phi_i + 360°$, $i = 1, 2$, for torsion angles a natural way of graphical representation of our relaxed cross section is a 2-dimensional surface of a toroid embedded in the 3-dimensional space[3,22]. However, a simpler way of description is a mapping of our periodic functions onto a 2-dimensional periodic lattice[23]. There are many ways to choose a unit cell in the periodic pattern of the catechol[24]. We have shown that the highest point symmetry group of nuclear configurations of CLMF is C_{2v}. An isomorphic mapping of this group onto the 2-dimensional space group cmm within a conventional unit cell is given in Fig. 2. The mutually corresponding symmetry elements are listed in Table I.

Another possibility is a subunit of the conventional cell which is in agreement with the standard conformational map introduced by Ramachandran and Sasisekhan[25] (Fig. 3). Only one quarter of this subunit defined by a triangle m_1, m_2, s_3 is the independent part of the subunit which is to be considered in detail. The rest of the space and thus all the functions defined above by ϕ_1 and ϕ_2 can be generated by application of the symmetry operations only.

TABLE I
Corresponding symmetry elements of the C_{2v} and cmm groups

Symmetry element of the group C_{2v}	Symmetry element of the group cmm
Identity	general position
Mirror plane x_1x_3	NW-SE mirror line
Mirror plane x_1x_2	twofold points
Twofold axis x_1	NE-SW mirror line

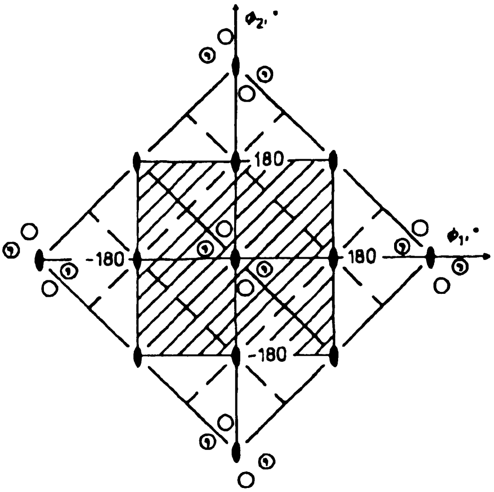

FIG. 2
Conventional unit cell of a 2-dimensional space group cmm. Heavy line: mirror line. Dashed line: glide line. Black lens: twofold rotation point. Circle: general position. Circle with an apostrophe: symmetry related position. Shadowed region: a subunit cell used in Fig. 3

Loci of the Fixed Points of Isometric Transformations and the Point Symmetry Domains

Let us assume the simplified cell of the standard conformational map (Fig. 3). General positions in the map constitute a family FPS(F_1) points. The four points of FPS(F_2) are identical with those marked in Fig. 3 as s_3, m_1, m_2 and m_3. Family of FPS(F_3) points is identical with the NE-SW (Northeast-Southwest) mirror line. Similarly, family of FPS(F_4) points coincides with the NW-SE mirror line. Loci of the fixed points of isometric transformations define the following point symmetry domains. Along the NW-SE mirror line all configurations belong to one of the two C_s point symmetry domains with the exception of the s_3 and m_3 points which form their own single-point C_{2v} point symmetry domains. Similarly, all configurations found along the NE-SW mirror line belong to one of the two C_2 point symmetry domains with the exception of the s_3 and m_3 points. Two isolated points m_1 and m_2 represent two single-point C_s point symmetry domains and are identified in the 2-dimensional space group cmm with the crossing of the glide lines. The rest of the configurations belong to the C_1 point symmetry domains with the previous point symmetry domains as their boundaries.

Potential Energy Map and Catchment Regions

The calculated potential energy surface as a function of ϕ_1 and ϕ_2 is represented in Fig. 3. The letters m_i, s_i, and M_i stand for minima, saddle points of transition structures and maxima, respectively. The faint solid contour lines represent isoenergetic levels with the increment of 10 KJ/mol. The areas enclosed by crosshatched lines are the catchment regions of the three minima m_i, i = 1, 2, 3, representing the stable conformers of the

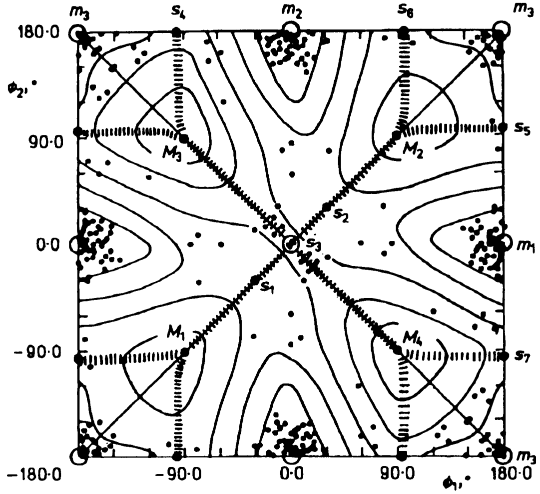

FIG. 3
Subunit cell of catechol conformational catchment regions. The cell is used for comparison of point symmetry domains and scattergram of all catechol-like fragments retrieved from the CSD. Letters *m*, *s*, and *M* stand for minimum, saddle point, and maximum, respectively. The faint solid lines are isoenergetic contours (spaced 10 KJ/mol), and the crosshatched lines are the boundaries of catchment regions of stable conformers. Crosshatched line segments of the *M-s-M* or *M-s-s* pattern are catchment regions representing transition structures

catechol molecule. Crosshatched line segments of the *M*-*s*-*M* pattern are catchment regions of transition structures. Within the relaxed cross section the maximum points are their own catchment regions. The two minima points m_1 and m_2 and the saddle point s_3 can be predicted from the catchment region minimum theorem mentioned previously[3]. On the other hand the saddle points s_1, s_2, s_4, s_5, s_6, and s_7 show no additional element of symmetry in respect to their vicinity and therefore should be calculated as stationary points of the potential energy function. The maxima M_i are the positions identical with the crossings of the mirror lines and the glide lines in the 2-dimensional space group cmm.

Two-Dimensional Scattergram

The superposition of the scattergram onto the energy map (Fig. 3) shows the coincidence of experimentally determined structures with the energy minima. The databank search resulted in 101 hits, where 61 hits with H atoms were in C(3) and C(6) positions, 20 hits with one of these hydrogenes substituted, and 20 hits, where both H atoms were substituted. Separate scattergrams of substituted and non-substituted H(3) and H(6) atoms lead to a similar results and thus all further analysis was carried out with the unified data set only.

A few points in low-energy valleys are in agreement with the concept of possible steepest descent reaction paths related to the saddle points. The structure–correlation principle is thus applicable and the intermolecular forces in the crystal structures retrieved can be supposed to be perturbations causing statistical distribution of the points. No nuclear configuration close to the four maxima was found.

Cluster Analysis and Statistics

Nearest neighbour method lead to three clusters *A1*, *A2*, and *A3*, under the constraint that only clusters containing more then five points are to be accepted.

The *A1* cluster:

$$(M(\phi_1),M(\phi_2)) = (0°,180°)$$

$$(S(\phi_1),S(\phi_2)) = (13.40°,14.10°)$$

$$R(\phi_1,\phi_2) = 0.020$$

$$m = 114$$

boundaries: $\langle -32°,32° \rangle \times ((-180°,-140° \rangle \cup \langle 140°,180° \rangle)$.

The *A2* cluster:

$$(M(\phi_1),M(\phi_2)) = (180°,0°)$$

$$(S(\phi_1),S(\phi_2)) = (14.10°,13.40°)$$

$$R(\phi_1,\phi_2) = 0.020$$

$$m = 114$$

boundaries: $((-180°,-140°\rangle \cup \langle 140°,180°)) \times \langle -32°,32°\rangle$.

The *A3* cluster:

$$(M(\phi_1),M(\phi_2)) = (180°,180°)$$

$$(S(\phi_1),S(\phi_2)) = (9.96°,9.96°)$$

$$R(\phi_1,\phi_2) = -0.066$$

$$m = 84$$

boundaries: $((-180\,°,-155°\rangle \cup \langle 155°,180°))^2$.

It should be stressed that the high density of points in the scattergram corresponds to the energy minima in *A1*, *A2*, and *A3*.

CONCLUSION

The described statistical results of catechol-like molecular fragments retrieved from the Cambridge Structural Database are in good agreement with theoretical studies published elsewhere[1,2].

Molecular mechanics was successfully used in the simple case of catechol. The results are in accord with more sophisticated calculations on small fragments[1 – 3]. The concept of the internal and full isometric group and the structure–correlation method were demonstrated here in detail.

All these procedures are to be implemented in a computer aided molecular modelling (CAMM) system which is under preparation.

REFERENCES

1. Arteca G. A, Heal G. A., Mezey P. G.: Theor. Chim. Acta *76*, 377 (1990).
2. Arteca G. A., Mezey P. G.: Int. J. Quantum Chem. QBS *15*, 33 (1988).
3. Mezey P. G.: J. Am. Chem. Soc. *112*, 3791 (1990).

4. *Crystallographic Databases*. Data Commission of the IUCr, Bonn – Cambridge – Chester 1987.
5. Hummel W., Huml K., Bürgi H. B.: Helv. Chim. Acta *71*, 1291 (1988).
6. Schneider B., Huml K., Rejholec V.: Collect. Czech. Chem. Commun. *56*, 2188 (1991).
7. Bauder A., Meyer R., Günthard Hs. H.: Mol. Phys. *28*, 1305 (1974).
8. Soldán P.: *M.Sc. Thesis*. Faculty of Nuclear Science and Physical Engineering, Technical University of Prague, Praha 1992.
9. Frei H., Bauder A., Günthard Hs. H.: Top. Curr. Chem. *81*, 1 (1979).
10. Mezey P. G.: *Potential Energy Hypersurfaces*. Elsevier, Amsterdam 1987.
11. Born M., Oppenheimer J.: Ann. Phys. *84*, 457 (1927).
12. Bürgi H. B. in: *Crystallographic Computing* (P. Paufler, V. Geist and D. Klimm, Eds). Karl-Marx-University Press, Leipzig 1986.
13. Weiner P. K., Kollman P. A.: J. Comput. Chem. *2*, 287 (1981).
14. Singh U. C., Weiner P. K., Caldwell J., Kollman P. A.: *AMBER*, version 3.0. University of California, San Francisco 1986.
15. Zimmermann K.: J. Comput. Chem. *12*, 310 (1991).
16. Weiner S. J., Kollman P. A., Case D. A., Singh U. C., Ghio C., Alagona G., Profeta S., Weiner P. K.: J. Am. Chem. Soc. *106*, 756 (1984).
17. Weiner S. J., Kollman P. A., Nguyen D. T., Case D. A.: J. Comput. Chem. *7*, 230 (1986).
18. Huml K., Hummel W., Zimmermann K.: Unpublished results.
19. Bürgi H. B., Dunitz J. D.: Acc. Chem. Res. *16*, 153 (1983).
20. *Cambridge Structural Database System*. Cambridge Crystalographic Data Center, Cambridge 1989.
21. Anderberg M. R.: *Cluster Analysis for Applications*. Academic Press, New York 1973.
22. Singer I. M., Thorpe J. A.: *Lecture Notes on Elementary Topology and Geometry*. Springer, 1976.
23. Dunitz J. D.: *X-Ray Analysis and the Structure of Organic Molecules*. Cornell University Press, Ithaca – London 1979.
24. *International Tables for Crystallography A* (T. Hann, Ed.). D. Reidel, Dordrecht 1983.
25. Ramachandran G. N., Sasisekharan V.: Adv. Protein Chem. *23*, 284 (1986).
26. Klyne W., Prelog V.: Experientia *16*, 521 (1960).

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