

tractable hydrogen in close proximity to the N lone pair, as in 2- or 8-methylquinolines, leads to a fast intramolecular hydrogen abstraction by the complexed chlorine atom through novel cyclic transition states. This intramolecular reaction results in unexpected regioselectivities in the reactions of  $\text{Cl}^\bullet$  with heteroaryl-methanes. Although bromine atoms also complex with heteroaromatic solvents, these complexes have a low reactivity toward benzylic hydrogens. Consequently,  $\text{Br}^\bullet$  shows normal regioselectivities in reactions with heteroarylmethanes, similar to the normal regioselectivities displayed by radicals such as  $(\text{CH}_3)_3\text{CO}^\bullet$  which are not known to complex with heteroaromatic solvents.

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**Supplementary Material Available:** Transient absorption spectra of quinoline/ $\text{Cl}^\bullet$  and pyridine/ $\text{Br}^\bullet$  complexes (2 pages). Ordering information is given on any current masthead page.

## A Hausdorff Chirality Measure

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**Abstract:** Chirality is a property that is independent of its physical and chemical manifestations. It is therefore possible to quantify chirality without any reference to pseudoscalar observables. In this paper we propose a new measure of chirality that is based on Hausdorff's concept of distances between sets and that is a natural choice as a measure for molecular models that represent structures as sets of atomic coordinates. This *Hausdorff chirality measure*, a continuous and similarity-invariant function of an object's shape, is zero if and only if the object is achiral. We have applied this measure to study the chirality of tetrahedral shapes—classical models of tetracoordinate carbon atoms—and have identified the extremal (most chiral) shapes for every chiral subsymmetry of  $T_d$  that can be realized by a tetrahedron. Our calculations show that the degree of chirality of the extremal objects increases with a decrease in symmetry, although the most symmetric chiral tetrahedron, with  $D_2$  symmetry, already possesses 87% of the maximal chirality value available for tetrahedra, and that the shape of the most chiral tetrahedron, with  $C_1$  symmetry, is very close to that of the most chiral  $C_2$  tetrahedron. The properties and the applicability of the Hausdorff chirality measure are compared with those of other measures of chirality that are based on common-volume or root-mean-square approaches.

Attempts to give a quantitative meaning to molecular chirality can be dated almost as far back as van't Hoff's and LeBel's proposition to extend the structural formulas of chemistry into three-dimensional space. In 1890 Guye introduced the first function designed to correlate a pseudoscalar property, i.e., optical rotation, with the molecular structure of chiroids—the first example of a chirality function in chemistry.<sup>1</sup> Chirality, however, is an inherent molecular property that depends only on symmetry and that is independent of its physical and chemical manifestations. It should therefore be possible to quantify chirality, i.e., to construct a chirality measure, without reference to any experimental data. Indeed, recent years have witnessed much interest in the development of such chirality measures.<sup>2</sup>

In his original definition, Kelvin formulated the concept of chirality as an *abstract* property of *geometric* objects: "I call any geometrical figure, or group of points, *chiral*... if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself".<sup>3,4</sup> Although enantiomorphs ( $Q$  and  $Q'$ ) cannot be superposed by any rotation-translation, they can be placed upon each

other (superimposed or overlapped) so that at least parts of them coincide. If one can establish a measure for the degree of overlap, then the means are available, in general, to optimize the overlap by rotation and translation of one enantiomorph with respect to the other. Once maximal overlap is achieved, the degree of overlap no longer depends on the relative orientation of the enantiomorphs and is only a function of the geometric shape; it might therefore serve to measure the chirality of an object (and its mirror image). Not every mathematical function, however, is suitable for such a measure.<sup>2</sup> In order to be called a *degree of chirality* a real-valued function  $f(Q)$  should have the following properties:<sup>5</sup> (1)  $f(Q)$  is a continuous function of  $Q$ , (2)  $0 \leq f(Q) \leq 1$ , (3)  $f(Q) = 0$  if and only if  $Q$  is achiral, and (4)  $f(Q)$  is similarity-invariant. The first requirement is a direct consequence of the fact that  $f(Q)$  is a function of the shape of  $Q$ : the shape of a geometric object can, in principle, change in a continuous way, and such changes should be reflected in the continuous changes of  $f(Q)$ . The function should yield the same value for objects that have the same shape but that differ in size: this is achieved by the invariance of  $f(Q)$  under similarity transformations.<sup>6</sup> In addition, as a *degree of chirality*,  $f(Q)$  should be dimensionless and normalized to the interval  $[0, 1]$ .

It should be noted that Kelvin's definition of chirality, when analyzed from an algebraic point of view, also implicitly contains a proposition for a measure of chirality,  $k(Q)$ , which can be paraphrased as follows: if any geometrical figure, or group of points, can be brought to coincide with its mirror image, then  $k(Q)$

(1) Guye, P.-A. *Compt. Rend. (Paris)* **1890**, *110*, 714. Guye, P.-A. *Ibid.* **1893**, *116*, 1378, 1451, 1454. See also: Crum Brown, A. *Proc. R. Soc. Edinburgh* **1890**, *17*, 181.

(2) For a critical discussion and review, see: Buda, A. B.; Auf der Heyde, T.; Mislow, K. *Angew. Chem., Int. Ed. Engl.*, in press. This review also describes highlights of the present work.

(3) Kelvin, W. T. *Baltimore Lectures on Molecular Dynamics and the Wave Theory of Light*; Clay, C. J.: London, 1904; p 619.

(4) From Kelvin's definition it follows that the chirality of an object (e.g., a geometric figure, a group of points, the geometric model of a molecule) is a function of the object's shape. Thus, to achieve chirality it is not sufficient to assign different labels to parts of an achiral object. For example, an irregular tetrahedron is chiral, but a regular tetrahedron in which the four different vertices are distinguished by different labels (indices) is not.

(5) See also: Grünbaum, B. *Proc. Symp. Pure Math., Am. Math. Soc.* **1963**, *7*, 233.

(6) A similarity transformation is a transformation that preserves angles in a transformed object,  $Q$ .

= 0 (i.e., the object is not chiral), otherwise  $k(Q) = 1$  (i.e., the object is chiral). It is easily seen that  $k(Q)$  possesses all the properties required for a degree of chirality but one:  $k(Q)$  is not continuous. This function therefore cannot serve as a measure for a degree of chirality.<sup>7</sup>

In this paper we report a new measure of chirality developed from Hausdorff's concept of the distance between sets.<sup>8</sup> Molecular structures are often represented by sets of atomic coordinates in 3-dimensional Euclidean space ( $E^3$ ). These arrays of atomic positions are sometimes supplemented by other atomic parameters, such as masses, charges, atomic numbers, and other data necessary for building an appropriate model of a molecule. In this way a rigid molecule is depicted by a mathematical model that is an algebraic set of points in  $n$ -dimensional space. If a molecule is chiral and therefore exists in two enantiomorphous forms, then each of these forms has a distinctive algebraic representation. The differences between these two sets can be used to measure the degree of molecular chirality. The Hausdorff distance between sets seems to be a natural choice for the construction of such a measure. Moreover, it is rather easy to create a numerical implementation of the metrics based on this concept.

## Method

**The Hausdorff Chirality Measure.** Let  $Q$  and  $Q'$  denote two enantiomorphous, nonempty, and bounded sets of points in  $E^3$ . Let  $d(q, q')$  denote the distance between two points:  $q \in Q$  and  $q' \in Q'$ . Then the Hausdorff distance between sets  $Q$  and  $Q'$  is defined as

$$h(Q, Q') = h(Q', Q) = \max\{\rho(Q, Q'), \rho(Q', Q)\}$$

where

$$\rho(Q, Q') = \sup_{q \in Q} \left\{ \inf_{q' \in Q'} \{d(q, q')\} \right\}, \quad \rho(Q', Q) = \sup_{q' \in Q'} \left\{ \inf_{q \in Q} \{d(q', q)\} \right\}$$

The Hausdorff distance  $h(Q, Q')$  between  $Q$  and  $Q'$  can also be expressed in a more pictorial way as the smallest number  $\delta = h(Q, Q')$  that has the following properties: (a) a spherical ball of radius  $\delta$  centered at any point of  $Q$  contains at least one point of  $Q'$ , and (b) a spherical ball of radius  $\delta$  centered at any point of  $Q'$  contains at least one point of  $Q$ .<sup>9</sup>

It is obvious that  $h(Q, Q') = 0$  only if  $Q = Q'$ . This means that if  $h(Q, Q') = 0$  then for every  $q \in Q$  there must be a  $q' \in Q'$  such that  $d(q, q') = 0$ , and for every  $q' \in Q'$  there must be a  $q \in Q$  such that  $d(q', q) = 0$ . In other words, the Hausdorff distance between two sets of points,  $Q$  and  $Q'$ , representing geometric objects can be zero only if these two objects are identical, i.e., achiral mirror images.

The value of the Hausdorff distance for a geometric object  $Q$  and its mirror image  $Q'$  depends not only on the shape of these objects but also on their sizes and their relative orientations in  $E^3$ . By rotating and translating one enantiomorph with respect to the other, one can find the minimal value  $h_{\min}(Q, Q')$  corresponding to the optimal overlap(s). We define the Hausdorff chirality measure as

$$H(Q) = h_{\min}(Q, Q')/d(Q)$$

where  $d(Q)$  denotes the diameter of  $Q$ , i.e., the largest distance between any two points of  $Q$ . In this form the Hausdorff chirality measure does not depend on the size of  $Q$  and  $Q'$  and on their relative position, and it can be easily shown that it has all the attributes demanded of a degree of chirality.

**Numerical Implementation.** Let  $Q$  be a set of  $n$  points in  $E^3$ ,  $Q = \{q_i\}$ ,  $i = 1, \dots, n$ , with the position of each point  $q_i$  defined by its Cartesian coordinates  $(x_i, y_i, z_i)$ . We shall treat  $Q$  as if it were a physical object with a unit mass assigned to each point.<sup>10,11</sup> The object  $Q$  is placed in

a standard position such that the center of mass coincides with the origin of the coordinate system and the principal axes of inertia are aligned along the axes of the coordinate system. This is done by diagonalizing the tensor of inertia,  $T_1$ , and then using its eigenvectors to construct the rotational matrix. For objects with three different eigenvalues of  $T_1$ ,  $I_1 > I_2 > I_3$ , the largest moment of inertia,  $I_1$ , is associated with the  $z$  axis and the smallest one with the  $x$  axis. For symmetric tops, with  $I_1 > I_2 = I_3$ , the corresponding eigenvalues for  $I_2$  and  $I_3$  are not uniquely defined and therefore only the  $z$  axis is aligned with the eigenvector corresponding to  $I_1$ . For spherical tops, with  $I_1 = I_2 = I_3$ , no rotation is performed because none of the eigenvectors are uniquely defined. The enantiomorphous object  $Q'$  is then generated by an inversion of  $Q$  through the center of the coordinate system. This position of  $Q$  in the coordinate system is kept fixed throughout the calculations, and the position of  $Q'$  is varied relative to it.

The calculation of  $H(Q)$  for an object of a given shape requires the analysis of many different superimpositions of  $Q$  and its mirror image  $Q'$ . For an object embedded in  $E^3$  the value of  $h(Q, Q')$  depends on six variables; three of them,  $u, v$ , and  $w$ , describe translations of  $Q'$  along  $x, y$ , and  $z$  axes, respectively, and three others,  $\phi, \theta$ , and  $\omega$ , define rotations around those axes. Determination of  $H(Q)$  thus becomes a typical problem of searching for a global minimum on a multidimensional hypersurface and can be addressed by standard computational means. We used the Broyden-Fletcher-Goldfarb-Shanno (BFGS) numerical procedure<sup>12</sup> to minimize  $h(Q, Q')$  as a function of  $u, v, w, \phi, \theta$ , and  $\omega$ :

$$H(Q) = \frac{\min_{u,v,w,\phi,\theta,\omega} \{h(Q, Q'; u, v, w, \phi, \theta, \omega)\}}{d(Q)}$$

There is, of course, no guarantee that the global minimum will be located by the BFGS procedure if a hypersurface contains many local minima and the minimization is launched from an arbitrary point. One method to overcome this problem is to locate as many local minima as possible by beginning minimization with different sets of starting parameters and then to identify the smallest minimized value as the global minimum. We generated the starting positions for minimization by rotating  $Q'$  from its initial position by an angle  $k \cdot 15^\circ$ , where  $k = 1, \dots, 24$ , around the  $x, y$ , and  $z$  axes. If an object  $Q$  was not symmetrically spanned in the coordinate system, e.g.,  $x_i (\min \{x_i\} - \max \{x_i\}) \neq 0$ , then, in addition to the rotations defined above,  $Q'$  was translated before an optimization by a vector  $(x_s, y_s, z_s)$ .

## The Shape Space of Tetrahedra

As noted above, the Hausdorff chirality measure is a function of the object's shape. We call  $S$ , an abstract  $n$ -dimensional space, a shape space of some class of objects  $T$  if there is a similarity-invariant function that maps  $T$  into  $S$ . The shape space may be partitioned into asymmetric units in each of which every shape in  $T$ , without any exclusions, is uniquely represented by exactly one point.<sup>13</sup>

In this section we discuss the construction of the shape space of tetrahedra and a procedure that establishes the relationship between  $T$  and  $S$ . The tetrahedron, in our treatment, is represented by its four vertices in  $E^3$ , and its shape is defined by the coordinates of those points. Our choice of the tetrahedron was motivated by its importance as a model for the tetracoordinate carbon atom—the chief building block in organic chemistry—and by its identity as the simplex in  $E^3$ .

It must now be emphasized that an asymmetric tetrahedron (or any four points asymmetrically distributed in  $E^3$ ) and its mirror image are chirally connected. That is, in Ruch's simile<sup>14</sup> they are potato-like.<sup>15</sup> This means that for every pair of enantiomorphous

(7) Another example of a non-continuous function designed to measure the chirality of geometric objects can be found in: Harary, F.; Mezey, P. G. *New Developments in Molecular Chirality*; Mezey, P. G., Ed.; Kluwer Acad. Publ.: Dordrecht, 1991; p 241. Mezey, P. G. *Ibid.*, p 257.

(8) Hausdorff, F. *Set Theory*; translated by Auman, J. R. et al.; Chelsey: New York, 1957; pp 166–168.

(9) This definition of the Hausdorff distance was suggested to us by Victor Klee.

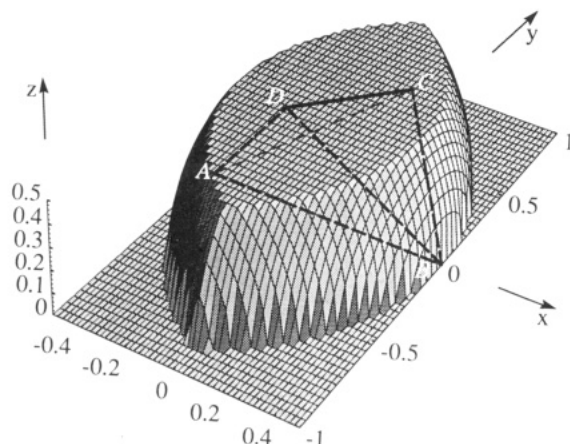
(10) This reformulation of a purely mathematical (geometric) problem into a physical (mechanical) analogue is in full compliance with mathematical tradition. As noted by Giering (Giering, O. *Elem. Math.* 1967, 22, 5), mechanical interpretations have a distinguished history as tools in solving problems in geometry. The classic example is the use of levers by Archimedes to determine the volume of a sphere (see also van der Waerden, B. L. *Elem. Math.* 1953, 8, 121; 1954, 9, 1).

(11) The concept of a chirality measure based on Hausdorff set theory is applicable to geometric objects regardless of whether they are represented as discrete sets of points or as solids in  $E^3$ , e.g., convex sets. In this paper we analyze the chirality of objects depicted as discrete sets of points that represent vertices of geometric figures.

(12) Press, W. H.; Flannery, B. P.; Teukolsky, S. A.; Vetterling, W. T. *Numerical Recipes*; Cambridge University Press: Cambridge, 1986. See also: Broyden, C. G. *J. Inst. Maths. Applies.* 1970, 6, 222. Fletcher, R. *Comp. J.* 1970, 13, 317. Goldfarb, D. *Math. Comput.* 1970, 24, 23. Shanno, D. F. *Math. Comput.* 1970, 24, 647.

(13) We consider the shape of an object to be different from that of its enantiomorph, even though the two objects are isometric. The complete asymmetric unit therefore contains the representations of both enantiomorphs.

(14) Ruch, E. *Angew. Chem., Int. Ed. Engl.* 1977, 16, 65.

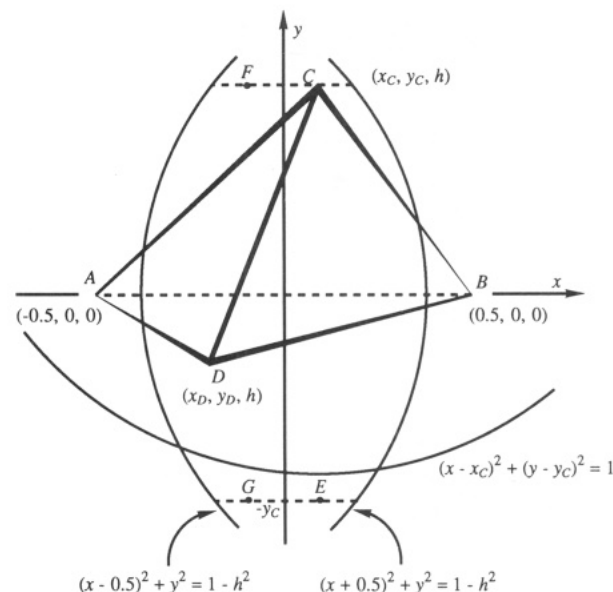


**Figure 1.** Schematic representation of the shape space for tetrahedra with unit diameter and height  $h = 0.5$ . The longest edge of the object is aligned with the  $x$  axis and its vertices are located at  $A (-0.5, 0, 0)$  and  $B (0.5, 0, 0)$ . Two other vertices,  $C (x_C, y_C, 0.5)$  and  $D (x_D, y_D, 0.5)$ , are located on a plateau  $\Delta$  that is created by the intersection of two unit spherical domains centered at  $A$  and  $B$  and by a plane parallel to the  $xy$  plane at  $z = 0.5$ . In general, the shape of a tetrahedron is represented by a point in  $E^5$  with  $(h, x_C, y_C, x_D, y_D)$  coordinates.

asymmetric tetrahedra there exist an infinite number of paths by which the enantiomorphs can be interconverted by continuous deformation without ever passing through an achiral shape.<sup>16</sup> It follows that the set of points representing achiral tetrahedra in an asymmetric unit does not bisect that unit into two heterochiral regions.<sup>17</sup> That is, even though an asymmetric unit in the shape space of tetrahedra can be partitioned into two subsets, each of them containing the representation of one enantiomorph, one cannot assign a common sense of handedness to members of these subsets. An important corollary is that concepts like "left-handed" and "right-handed" with reference to asymmetric tetrahedra are meaningless. Indeed, because the tetrahedron is the simplex in  $E^3$ , every such classification is meaningless (or, at best, arbitrary) for any geometric object in  $E^3$  in the absence of well-defined constraints (such as, for example, the maintenance of helicity).<sup>18</sup>

The size and shape of a tetrahedron is fully defined by a minimum of six geometric parameters; at least five of them are required for a complete definition of its shape and at least one more for fixing the size. In order to achieve similarity invariance of the shape space representation, the size aspect must be removed from the description of tetrahedra. We chose, arbitrarily, to constrain the size of tetrahedra by setting the length of one edge equal to unity and constraining all other edges to be no longer than the first. In other words, a given tetrahedron must be shrunk, or expanded, by a similarity transformation until its longest side(s) equal(s) unity. The diameter of such a tetrahedron is  $d(Q) = 1$ .

It can be shown that every tetrahedron can be oriented in the Cartesian coordinate system in such a way that if two vertices are placed on the  $xy$  plane, the other two vertices are located in a second plane, parallel to the  $xy$  plane and at some height  $h$  on the positive part of the  $z$  axis.<sup>19</sup> Let us denote by  $A$  and  $B$  the



**Figure 2.** Projection along the  $z$  axis of the schematic representation shown in Figure 1. Vertex  $C$  is mapped at height  $z = h$  into the positive quadrant of  $\Delta$  (see text). The position of vertex  $D$  is restricted to the interior part of  $\Delta$  that is delimited by the two dashed lines at  $y = y_C$  and  $y = -y_C$ ; this position cannot be further away from  $C$  than the unit distance depicted by the arc of circle  $(x - x_C)^2 + (y - y_C)^2 = 1$ . For the significance of points  $E$ ,  $F$ , and  $G$ , see the text.

two vertices that form the unit edge and place them in the Cartesian coordinate system at  $(-0.5, 0, 0)$  and  $(0.5, 0, 0)$ , respectively. Let  $\Xi$  denote the intersection of two unit hemispherical domains, with  $z \geq 0$ , centered at  $A$ ,  $(x + 0.5)^2 + y^2 + z^2 \leq 1$ , and  $B$ ,  $(x - 0.5)^2 + y^2 + z^2 \leq 1$ . Two other vertices,  $C$  and  $D$ , whose Cartesian coordinates are denoted by  $(x_C, y_C, h)$  and  $(x_D, y_D, h)$ , respectively, are located on a plane parallel to the  $xy$  plane, with  $z = h$ ; both belong to  $\Xi$  since otherwise at least one of the edges  $AC$ ,  $AD$ ,  $BC$ , or  $BD$  would be longer than the edge  $AB$  (Figure 1). For similar reasons, edge  $CD$  cannot be longer than unity. Figure 2 shows a projection along the  $z$  axis of the intersection,  $\Delta$ , of the second plane with  $\Xi$ . At any particular height  $h$ ,  $0 < h \leq \sqrt{3}/2$ ,  $\Delta$  consists of two partially overlapping domains delimited by circles:  $(x + 0.5)^2 + y^2 = 1 - h^2$  and  $(x - 0.5)^2 + y^2 = 1 - h^2$ . However,  $\Delta$  does not represent a unique mapping region for vertices  $C$  and  $D$ ; in fact, for every tetrahedral face  $ABC$  with the point  $C$  at  $(x_C, y_C, h)$  there is another point  $E$  at  $(x_C, -y_C, h)$  which, together with  $A$  and  $B$ , defines a face equivalent to  $ABC$  (Figure 2). In addition, there are two other points,  $F$  and  $G$ , at  $(-x_C, y_C, h)$  and  $(-x_C, -y_C, h)$ , respectively, which represent isometric faces that can be obtained by a mirror reflection of  $ABC$ . Since  $H(Q) = H(Q')$ , it is only necessary to search the part of the shape space that contains one representation for each isometric shape. It is therefore desirable to restrict the position of vertex  $C$  to one quadrant of  $\Delta$ , e.g., to the part of  $\Delta$  that is bounded by the positive segments of the  $x$  and  $y$  axes. The position of the fourth vertex,  $D$ , must also be mapped into  $\Delta$ ; because the distance  $|CD|$  cannot be greater than unity,  $D$  must belong to the intersection of  $\Delta$  and a domain bounded by a circle  $(x - x_C)^2 + (y - y_C)^2 = 1$  (Figure 2). In addition, the  $y$  coordinate of vertex  $D$  must be limited to the interval  $y_C > y_D \geq -y_C$ . The shape of the tetrahedron is therefore in general represented by a point in five-dimensional space; this point is defined by a set of five shape coordinates  $(h, x_C, y_C, x_D, y_D)$ , with each of these coordinates restricted to the limits specified above.

Desymmetrization of the regular tetrahedron can only yield three chiral subsymmetries of  $T_d$ :  $D_2$ ,  $C_2$ , and  $C_1$ .<sup>20</sup> The re-

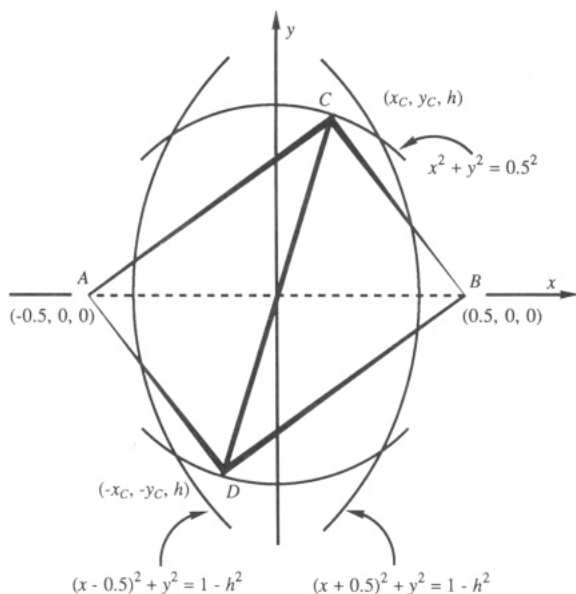
(15) On the subject of chiral connectedness, see also: Guenzi, A.; Johnson, C. A.; Cozzi, F.; Mislow, K. J. *Am. Chem. Soc.* **1983**, *105*, 1438, esp. p 1442.

(16) Although achiral shapes can be circumvented, this does not mean that interconversion of enantiomorphs by way of such shapes (e.g.,  $C_{2v}$  or  $C_{3v}$ ) is excluded.

(17) In contrast, triangles, simplexes in  $E^2$ , are partitioned into heterochiral sets. For a discussion of the shape space for triangles, see: Buda, A. B.; Auf der Heyde, T. P. E.; Mislow, K. J. *Math. Chem.* **1991**, *6*, 243.

(18) Under the constraint of  $D_2$  symmetry, chiral tetrahedra can be partitioned into heterochiral classes. That is, interconversion of enantiomorphs makes passage through an achiral shape unavoidable. The set of achiral shapes then constitutes the boundary that separates the two classes and it becomes possible to describe such tetrahedra as "left-handed" or "right-handed" with reference to an arbitrarily chosen coordinate system. The same obtains for tetrahedra under the constraint of  $C_2$  symmetry. However, relaxation of those constraints allows circumvention of achiral states by way of  $C_1$  tetrahedra.

(19) This statement is a direct consequence of the geometric rule that a plane is uniquely determined by a point and two directions given by two linearly independent vectors. See: Bronshtein, I. N.; Semendyayev, K. A. *Handbook of Mathematics*; translated by Hirsch, K. A.; Verlag Harri Deutsch: Thurn and Frankfurt/Main, 1985; p 208.



**Figure 3.** Projection along the  $z$  axis of the schematic representation of the shape space for  $D_2$  tetrahedra. By symmetry, the position of vertex  $C$  at height  $z = h$  is constrained to the arc of circle  $x^2 + y^2 = 0.5^2$  and delimited by the  $y$  axis on the left-hand side and by the border of  $\Delta$  on the right-hand side. Vertex  $D$  occupies a position that is related to that of  $C$  by the 2-fold axis perpendicular to  $xy$  and passing through the origin of the coordinate system.

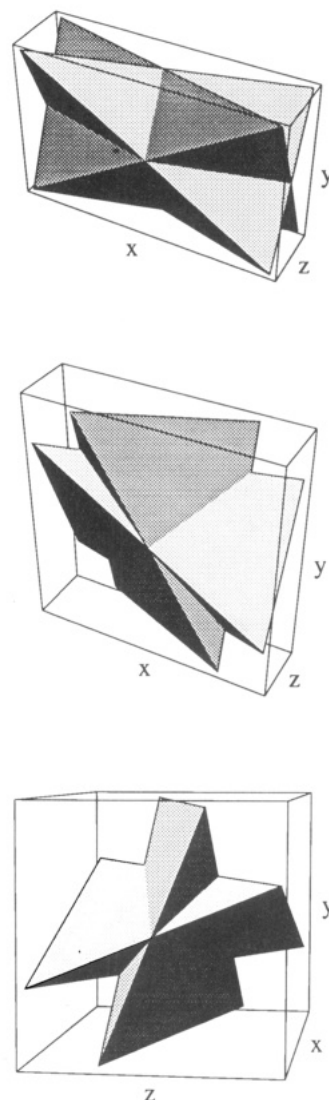
restrictions on the tetrahedral shape that are specific for a given subsymmetry must be reflected in additional constraints on the shape coordinates and are discussed separately below. The shape space of tetrahedra, as defined in this section, contains a unique representation for every pair of enantiomorphous tetrahedra with  $D_2$  and  $C_2$  symmetries and for every pair of enantiomorphous  $C_1$  tetrahedra with only one edge of unit length. For these objects, therefore, the shape space at the same time constitutes an asymmetric unit. However,  $C_1$  tetrahedra with two or more unit edges are, in general, represented in this shape space by more than one point.

## Results

In order to gauge the properties of a class of objects  $T$ , it is convenient to find a subclass of objects that is extremal with respect to the property concerned and to compare other objects with members of this extremal class. In this paper we report on the results of our search for the class of tetrahedra that are extremal with respect to the Hausdorff chirality measure, i.e., for those tetrahedra that are characterized by the highest value of this measure.<sup>21</sup> These studies have provided an answer to the following question: What is the shape of the most chiral tetrahedron, according to the Hausdorff measure?

**Tetrahedra with  $D_2$  Symmetry.** Figure 3 shows the perpendicular projection of the intersection of the shape space with a plane parallel to the  $xy$  plane containing two vertices,  $C$  and  $D$ .  $D_2$  symmetry requires the  $CD$  edge to be equal in length to the  $AB$  edge ( $|AB| = |CD| = 1$ ). This means that  $C$  and  $D$ , in addition to all other restrictions specific to the shape space, must lie on a circle,  $x^2 + y^2 = 0.5^2$ , and must be related to each other by a 2-fold axis that is perpendicular to the  $xy$  plane and that passes through the origin of the coordinate system. The shape of a  $D_2$  tetrahedron is therefore fully determined by a set of two variables,  $h$  and  $x_C$ .

In order to find the most chiral tetrahedron with  $D_2$  symmetry,  $Q$ , one has to locate the point in the shape space that corresponds to the highest value of the degree of chirality, i.e.,  $H(Q) =$



**Figure 4.** Three superimpositions of the most chiral  $D_2$  tetrahedron and its enantiomorph, identified by an optimization procedure as the most effective overlaps. The shape of each union is visualized by two interpenetrating solid tetrahedra, although their Hausdorff chirality measures are determined by the distances between vertices. Within the error limit of the computational method, the three unions ( $\Gamma$ ) are characterized by the same value of the Hausdorff distance. The symmetries of these unions are  $D_{2h}$  ( $\Gamma_1$ , top) and  $D_{2d}$  ( $\Gamma_2$  and  $\Gamma_3$ , middle and bottom, respectively).

$\max\{H(Q) \equiv H(h, x_C)\}$ . This two-dimensional space can be easily explored by the grid method. The results of the calculations show that there is only one maximum located inside the shape space. Maximization by the BFGS method localizes the point in the shape space that corresponds to the most chiral  $D_2$  tetrahedron:  $H(h, x_C) = 0.221$ ,  $h = 0.221$ ,  $x_C = 0.216$ .<sup>22</sup>

Figure 4 shows the optimal overlap of  $Q$  with its mirror image,  $Q'$ . There are three different overlaps that are characterized by the same value of  $H(Q)$  but that differ in the geometry of the union  $\Gamma = Q \cup Q'$ . The first union,  $\Gamma_1$ , has  $D_{2h}$  symmetry. It can be viewed as an object in which  $Q'$  is generated from  $Q$  by an inversion through its centroid. Therefore, each of the three 2-fold axes of  $Q$  coincides with the corresponding axes of  $Q'$ .<sup>23</sup> Two other unions,  $\Gamma_2$  and  $\Gamma_3$ , can be obtained from  $\Gamma_1$  by a 90° rotation of  $Q'$  around the  $z$  and  $x$  axes, respectively. Both have  $D_{2d}$  symmetry; like  $\Gamma_1$  they are achiral and concentric, but unlike

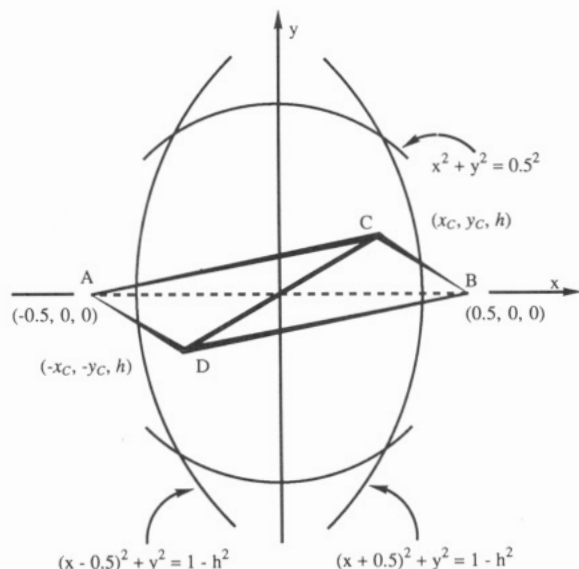
(20) The other two chiral subsymmetries,  $T$  and  $C_3$ , cannot be realized by a tetrahedron. See: Prelog, V.; Helmchen, G. *Helv. Chim. Acta* **1972**, *55*, 2581.

(21) There is, of course, another and trivial class of extremal tetrahedra: the achiral tetrahedra, which are characterized by a zero Hausdorff chirality measure.

(22) The internal angles of the faces of the most chiral  $D_2$  tetrahedron are 35.1°, 60.5°, and 84.4°.

(23) By corresponding axes we mean the pair of principal axes of inertia for  $Q$  and  $Q'$ , respectively, that are characterized by the same eigenvalue of the tensor of inertia.





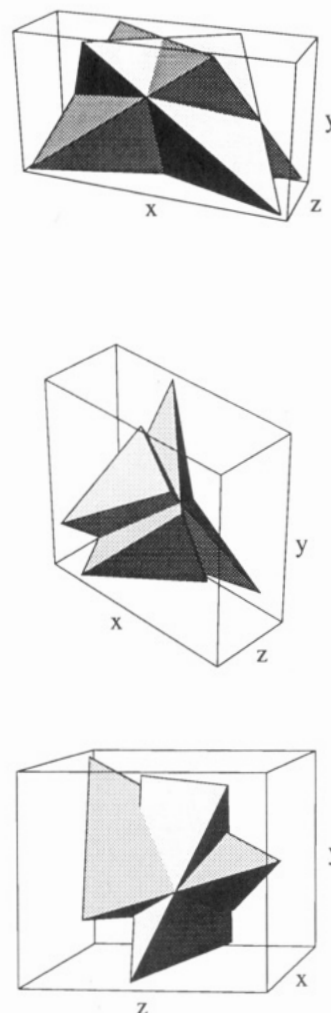
**Figure 5.** Projection along the  $z$  axis of the schematic representation of the shape space for  $C_2$  tetrahedra. The position of vertex  $C$  at  $z = h$  is mapped into the positive quadrant of the intersection of  $\Delta$  with the circular domain  $x^2 + y^2 \leq 0.5^2$ . Vertex  $D$  is related to  $C$  by the 2-fold axis perpendicular to  $xy$  and passing through the origin of the coordinate system.

$\Gamma_1$  they are not centrosymmetric. There is, of course, a third possibility to construct a  $D_{2d}$  union ( $\Gamma_4$ ) by a  $90^\circ$  rotation of  $Q'$  around the  $y$  axis. However,  $\Gamma_4$  corresponds to a local minimum that is characterized by a much larger value of  $h(Q, Q') = 0.44$  and is therefore unable to compete with  $\Gamma_1$ ,  $\Gamma_2$ , and  $\Gamma_3$  for  $H(Q)$ .

One might ask why do three different overlaps yield the same value of  $h_{\min}(Q, Q')$ ? It is reasonable to expect, and borne out by our calculations, that for an ordinary tetrahedron there is, in general, only one way to superimpose  $Q$  and  $Q'$  that corresponds to the smallest value of  $h(Q, Q')$  and hence to  $H(Q)$ . However, it is easy to realize that the extremal case cannot be determined by only one overlap scheme. For example, the Hausdorff distance in  $\Gamma_1$  is defined by the distance between the pairs of vertices that lie along the shortest sides (along the  $z$  axis) of the box embedding  $\Gamma_1$  (see Figure 4). If the box were slightly expanded by elongation of its shortest sides, then the Hausdorff distance for a new, expanded, tetrahedron would be larger, suggesting that the new object is more chiral. However, at the same time  $\Gamma_2$ , or  $\Gamma_3$ , or both undoubtedly would have smaller values of  $h_{\min}(Q, Q')$ , thus excluding  $\Gamma_1$  from the determination of  $H(Q)$  for the new tetrahedron. We note that the same principle has previously also been found for the Hausdorff chirality measure of triangles<sup>2</sup> and, independently, for a measure of chirality that is based on common volumes.<sup>24</sup>

**Tetrahedra with  $C_2$  Symmetry.** Figure 5, like Figure 3, shows the perpendicular projection of the intersection of the space shape with a plane parallel to the  $xy$  plane and containing two vertices,  $C$  and  $D$ . While  $C_2$  symmetry does not require the  $CD$  edge to be equal in length to  $AB$ , vertices  $C$  and  $D$ , in addition to all other restrictions specific to the space shape, must be related to each other by a 2-fold axis that is perpendicular to the  $xy$  plane and that passes through the origin of the coordinate system. The shape of a  $C_2$  tetrahedron is therefore fully determined by a set of three coordinates,  $h$ ,  $x_C$ , and  $y_C$ .

The exploration of the shape space by the grid method shows that this space contains two regions characterized by a high degree of chirality. One of these is located near the position of the most chiral  $D_2$  tetrahedron. However, the BFGS maximization launched from this  $D_2$  structure fails to localize any tetrahedron in this region with  $C_2$  symmetry and with a higher degree of chirality. The second region is separated from the first by a region



**Figure 6.** Three superimpositions of the most chiral  $C_2$  tetrahedron and its enantiomorph that were identified by an optimization procedure as the most effective overlaps. The symmetries of these unions are  $C_{2v}$  ( $\Gamma_1$ , top) and  $C_2$  ( $\Gamma_2$  and  $\Gamma_3$ , middle and bottom, respectively). The orientations of the unions in the Cartesian coordinate system were unified with those in Figure 4.

of lower chirality. The maximization of  $H(Q)$  by the BFGS method initiated from a point within this region localizes the point that represents the region's most chiral  $C_2$  tetrahedron:  $H(h, x_C, y_C) = 0.252$ ,  $h = 0.500$ ,  $x_C = 0.175$ ,  $y_C = 0.176$ .<sup>25</sup> However, it should be noted that these two regions are only artificially separated from each other by the construction of the shape space. In fact, relaxation of the constraint that no edge be longer than  $AB$  permits localization of the most chiral  $C_2$  tetrahedron by starting maximization from the most chiral  $D_2$  tetrahedron. This  $C_2$  tetrahedron is located outside the part of the shape space shown in the Figure 5, but it can be mapped into it by a similarity transformation.

Figure 6 shows the optimal overlaps of the most chiral  $C_2$  tetrahedron and its enantiomorph. As noted above, the most chiral structure, regardless of its symmetry, can only be established as a kind of consensus between at least two different schemes of superimposition. Indeed, the calculations show three different unions of  $Q$  and  $Q'$  that are characterized by the same value of the Hausdorff distance. The first union,  $\Gamma_1$ , has  $C_{2v}$  symmetry; the enantiomorphs are overlapped in such a way that their 2-fold axes coincide and their centroids are superposed. Although the union is concentric, it is not centrosymmetric. It is possible, of course, to construct a centrosymmetric ( $C_{2h}$ ) union from these tetrahedra, but the corresponding Hausdorff distance is much

(24) Buda, A. B.; Mislow, K. *Elem. Math.* **1991**, *46*, 65. Buda, A. B.; Mislow, K. *J. Mol. Struct. (Theochem)* **1991**, *232*, 1.

(25) The shape of the most chiral  $C_2$  tetrahedron can also be characterized by four independent internal angles:  $\theta_{ACD} = 45.6^\circ$ ,  $\theta_{CAD} = 34.7^\circ$ ,  $\theta_{CAB} = 38.0^\circ$ , and  $\theta_{CBA} = 58.5^\circ$ , with the  $C_2$  axis bisecting edges  $AB$  and  $CD$ .

higher than that calculated for  $\Gamma_1$ . The other two unions,  $\Gamma_2$  and  $\Gamma_3$ , have  $C_s$  symmetry. Because the most chiral  $C_2$  tetrahedron was obtained from a  $D_2$  structure by relaxation of the symmetry constraints and subsequent continuous maximization of the degree of chirality, the three overlap unions of the most chiral  $C_2$  tetrahedron are directly related to the three unions found for the most chiral  $D_2$  tetrahedron. Indeed, if certain elements of symmetry are removed from the  $D_{2h}$  union ( $\Gamma_1$ ) due to the changes in the symmetry of the component tetrahedra (from  $D_2$  to  $C_2$ ), the symmetry of the union becomes  $C_{2v}$ . Similarly, the loss of all elements of symmetry but  $\sigma$  from the two  $D_{2d}$  unions ( $\Gamma_2$  and  $\Gamma_3$ ) yields the corresponding unions with  $C_s$  symmetry.

**Tetrahedra with  $C_1$  Symmetry.** Under conditions of  $C_1$  symmetry, the only constraint on the positions of  $C$  and  $D$ , apart from those resulting from the construction of the shape space, is that  $y_C > y_D > -y_C$ . The shapes of such tetrahedra are therefore described by a set of five coordinates,  $h$ ,  $x_C$ ,  $y_C$ ,  $x_D$ , and  $y_D$  (see Figure 2).

Owing to the high dimensionality of the shape space for  $C_1$  tetrahedra, use of the grid technique is rendered practically prohibitive as a method for the exploration of this space. The Monte Carlo procedure was therefore used in a search for regions characterized by a high degree of chirality. After sampling the shape space by 150 000 random tests, only two such regions were identified: one near the most chiral  $D_2$  tetrahedron and the other near the most chiral  $C_2$  tetrahedron. The final search by use of the BFGS method localized the point in the vicinity of the second region that represents the most chiral  $C_1$  tetrahedron:  $H(h, x_C, y_C, x_D, y_D) = 0.255$ ,  $h = 0.500$ ,  $x_C = 0.189$ ,  $y_C = 0.181$ ,  $x_D = -0.185$ ,  $y_D = -0.180$ .<sup>26</sup> Once again, the same value of  $H(Q)$  is represented by more than one overlap scheme, with the geometry of the unions very similar to those calculated for the most chiral  $C_2$  tetrahedron. In all cases these unions have  $C_s$  symmetry.

## Discussion

Our calculations show that as the symmetry of a chiral tetrahedron is lowered, the maximal value of the Hausdorff chirality measure that can be achieved by that object under each particular symmetry constraint increases:  $H(Q) = 0.221$ ,  $0.252$ ,  $0.255$  for  $D_2$ ,  $C_2$ , and  $C_1$  tetrahedra, respectively.<sup>27</sup> We note that these numbers are small in magnitude on the 0-to-1 scale for the degree of chirality, suggesting that even the most chiral tetrahedron is not *very* chiral. It should also be pointed out that the value of  $H(Q)$  for the most symmetric ( $D_2$ ) tetrahedron is very close to that of the most chiral tetrahedron. Even more remarkable, and not intuitively obvious, is the finding that the value of the Hausdorff chirality measure for the most chiral  $C_1$  tetrahedron is virtually the same as that for the most chiral  $C_2$  tetrahedron, and that the geometries of these two tetrahedra are so similar that they are almost indistinguishable by visual inspection (see Figure 7).

It is also noteworthy that  $H(Q)$  values for all tetrahedra, whether extremal or not, correspond to achiral unions of  $Q$  and  $Q'$ . This numerical result parallels analytical and numerical trends observed<sup>2</sup> for a variety of chirality measures in  $E^2$  and provides further support for the conjecture<sup>2</sup> that the union of an object and its mirror image under conditions of maximal overlap is achiral. This does not, however, mean that the centroids (or centers of mass) of  $Q$  and  $Q'$  are necessarily superposed under these conditions. In fact, superposition of centroids under these conditions is, as a rule, observed only for chiral tetrahedra with  $D_2$  symmetry.

The Hausdorff distance between sets is not, of course, the only metric that can be used to measure the distance between enantiomorphs. For example, the common volume of two enantiomorphs under conditions of maximal overlap, properly normalized,

(26) Five independent internal angles for the most chiral tetrahedron with  $C_1$  symmetry completely define its shape:  $\theta_{CAB} = 37.7^\circ$ ,  $\theta_{CAD} = 36.0^\circ$ ,  $\theta_{BAD} = 59.4^\circ$ ,  $\theta_{ADB} = 82.8^\circ$ , and  $\theta_{ADC} = 99.4^\circ$ . The seven other internal angles are derived from these five.

(27) The reported values of  $H(Q)$  are specific to the tetrahedral model defined in this paper, i.e., a set of four vertices in  $E^3$ . Different models of the same tetrahedral shape, e.g., solid tetrahedral domains or tetrahedral graphs, could yield different values of  $H(Q)$ .

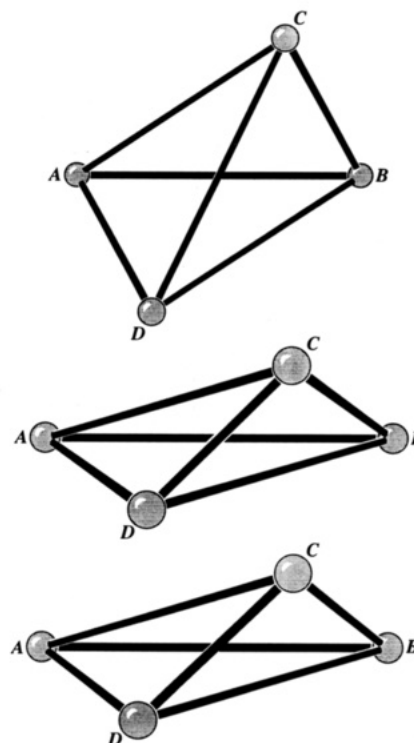


Figure 7. Perspective projections of the most chiral  $D_2$  (top),  $C_2$  (middle), and  $C_1$  (bottom) tetrahedra. The independent internal angles between vertices for these structures are listed in refs 22, 25, and 26, respectively. It is clearly seen that the shape of the most chiral  $C_1$  tetrahedron is very similar to that of the most chiral  $C_2$  tetrahedron.

can be used as well. We had previously applied this method to triangles and found that the extremal object—the most chiral triangle—is infinitely flat and approachable only in the limit.<sup>24</sup> By extrapolation from these results, we conjecture that, according to this measure, the most chiral tetrahedron might not exist and might be approachable only in the limit, as an infinitely flat or even infinitely linear structure. Although this kind of functional behavior is fully acceptable in the mathematical sense, it is obviously unsatisfactory from the chemical point of view. For reasons discussed elsewhere,<sup>2</sup> the Hausdorff chirality measure does not suffer from this feature, and the most chiral tetrahedron, as measured by  $H(Q)$ , is therefore a truly three-dimensional object. As to the potential for applications in chemistry, we note at this point that the procedure described in this paper can in principle be extended to include appropriate atomic parameters.

In connection with our results, a recent proposal by Rassat<sup>28</sup> to apply Hausdorff set theory to the classification of chiral point systems requires some comment. According to Rassat, the handedness of a geometric object,  $Q$ , can be established using the Hausdorff distances between  $Q$  and two arbitrarily chosen enantiomorphous reference structures,  $R$  and  $R'$ :

$$\delta h_{\min}(Q) = h_{\min}(Q, R) - h_{\min}(Q, R')$$

Evidently  $\delta h_{\min}(Q) = -\delta h_{\min}(Q')$ , and since, as discussed above, geometric objects in  $E^3$  are, in general, chirally connected, there exists in general a *chiral*  $Q^\circ$  such that  $h_{\min}(Q^\circ, R) = h_{\min}(Q^\circ, R')$ , and hence  $\delta h_{\min}(Q^\circ) = 0$ . The cryptochirality<sup>29</sup> of  $Q^\circ$  can be lifted, of course, by a different choice of reference structures  $R$  and  $R'$ , but this inevitably induces cryptochirality in another  $Q^\circ$ . It is obvious that this seriously violates one of the key requirements for any degree of chirality, and  $\delta h_{\min}(Q)$  is therefore in general unsuitable as a measure of chirality.

Finally, we need to comment on the applicability of the root-mean-square (rms) fit of points, a popular measure of molecular similarity,<sup>30</sup> as a method for measuring the degree of chirality.

(28) Rassat, A. *Compt. R. Acad. Sci. (Paris)* **1984**, *II* 299, 53.

(29) Mislow, K.; Bickart, P. *Isr. J. Chem.* **1976/1977**, *15*, 1.

In the formalism developed for molecular similarity analysis, "corresponding" atoms (points) from two similar structures are matched in pairs. In contrast, chirality measures, by their very essence, compare *different*, rather than similar, structures: in fact, one can view the most chiral object as the one that differs from its mirror image as much as possible. It is therefore not feasible, in general, to find an unambiguous match of "corresponding" points in enantiomorphs. Take, for example, an asymmetric tetrahedron,  $Q = abcd$ , and its mirror image,  $Q'$ . Identifying points  $a/a'$  and  $b/b'$  as matched pairs in  $Q$  and  $Q'$  mismatches  $c/d'$  and  $d/c'$ , and this is true of all six possible pairwise matches, since each produces a different mismatch of the remaining pairs. By

the same token, pairwise matching of *all* points that are related by mirror reflection symmetry, i.e.,  $a/a'$ , ...,  $d/d'$ , results in a similarity measure that does not vanish for achiral tetrahedra. It is therefore not surprising that this approach may yield contradictory results, and it follows that the methodology of rms similarity analysis is unsuitable as a measure of chirality. In contrast, the Hausdorff chirality measure does not require identification and matching of "corresponding" points and is therefore free from any ambiguity arising from the need to define such points. Moreover, the method described in this paper not only can be used to calculate the degree of chirality but also may prove to be valuable as a tool in molecular similarity analysis.

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## Inclusion of Azulene and Alcohol by $\beta$ -Cyclodextrin in Aqueous Solution

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**Abstract:**  $\beta$ -Cyclodextrin ( $\beta$ -CD) has been found to form a ternary inclusion complex with alcohol and azulene, with a stoichiometry of 2:2:1. By means of a fluorescence method, equilibrium constants for the formation of the ternary inclusion complex have been evaluated for alcohols from ethanol to 1-pentanol. Induced circular dichroism studies suggest that in the ternary inclusion complex azulene slightly extrudes from the  $\beta$ -CD cavity compared with a 1:1 inclusion complex between  $\beta$ -CD and azulene. From an analysis of a  $^1\text{H-NMR}$  spectrum for azulene in  $\text{D}_2\text{O}$  containing both  $\beta$ -CD and 1-propanol, 1-propanol incorporated into the  $\beta$ -CD cavity is deduced to be in close proximity to H-2 and H-6 of azulene in the ternary inclusion complex.

$\beta$ -Cyclodextrin ( $\beta$ -CD) is a cyclic oligosaccharide consisting of seven glucose units. Because of the characteristic doughnut-like shape of  $\beta$ -CD, various kinds of organic compounds are incorporated into the  $\beta$ -CD, forming inclusion complexes. The ability of  $\beta$ -CD to form inclusion complexes is highly affected by the size, shape, and hydrophobicity of guest molecules. Usually, a single guest molecule is accommodated into the  $\beta$ -CD cavity, with a host/guest stoichiometry of 1:1. However, inclusion complexes of 1:2, 2:1, or 2:2 stoichiometry are also known.<sup>1-9</sup> In addition to these binary inclusion complexes, there are ternary inclusion complexes that contain  $\beta$ -CD(s) and two different kinds of guests.<sup>10-18</sup> Recently, Munoz de la Pena et al. have revealed that in a  $\beta$ -CD-alcohol-pyrene system a ternary inclusion complex has a stoichiometry of not 1:1:1 but 2:2:1  $\beta$ -CD/alcohol/pyrene.<sup>19</sup> Owing to the complicated nature of ternary complexes, however, molecular structures (relative dispositions of component molecules) of ternary complexes are not fully understood. Spectroscopic studies involving absorption and fluorescence spectra and fluorescence lifetime measurements have preferentially been performed for the characterization of the ternary inclusion complexes.

We found that azulene forms a ternary inclusion complex with  $\beta$ -CD and alcohol. Fortunately, azulene is relatively soluble in water. Thus, we could investigate the nature and structure of the

ternary inclusion complex of azulene by means of induced circular dichroism (ICD) and  $^1\text{H-NMR}$  measurements in addition to absorption and fluorescence spectral techniques. Our results demonstrated that the ternary inclusion complex is composed of two  $\beta$ -CD, two alcohol, and one azulene molecule(s), and that,

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