Vol. 98, No. 2, 1981 BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS
January 30, 1981 Pages 482-487

STRONG INTERACTION BETWEEN DISULFIDE DERIVATIVES AND AROMATIC GROUPS IN PEPTIDES AND PROTEINS

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Received December 15,1980

SUMMARY: The intermolecular interaction energy of complexes of dimethyldisulfide with benzene and cyclohexane, respectively, was computed as function of the relative distance and orientation within each pair of molecules. The energy of the most stable orientation of the dimethyldisulfide-cyclohexane complex is -2.57 kcal/mol, while that of the most stable orientation of the dimethyldisulfide-benzene complex is -3.33 kcal/mol. The energy difference of ∿0.8 kcal/mol is due to favorable specific nonbonded interactions between the sulfur atoms and the atoms of the aromatic ring. Proper parameterization of empirical interatomic energies, used in computations in this laboratory, accounts for these interactions without the need for a special sulfur-aromatic potential energy function.

It was pointed out recently by Morgan et al (1) that, in the three-dimensional structures of many proteins, there are groupings of alternating aromatic and sulfur-containing side chains. It was suggested that the presence of such structures is likely to be caused by unusually strong noncovalent interactions between sulfur atoms and the π-electron system of aromatic rings. In a related nmr study, the presence of a 1:1 complex between aromatic compounds and various alkyl sulfides, disulfides, and related sulfur compounds in CCl_4 solution was demonstrated (2). The enthalpy of complex formation was estimated, from the temperature dependence of the chemical shift of the complex, to be in the range of -0.79 to -0.96 kcal/mol, and it was proposed that the sulfur-aromatic interaction, which is stronger than the usual van der Waals interactions, should be included in conformational energy calculations on proteins and peptides (2).

0006-291X/81/020482-06$01.00/0

We wish to point out that the computational procedure ECEPP (Empirical Conformational Energy Program for Peptides) used in this laboratory (3) contains energy parameters which correspond to a strong sulfur-aromatic nonbonded interaction. In order to demonstrate the effect of these parameters, we have computed the interaction energy of dimethyldisulfide with benzene and cyclohexane, respectively. As reported below, the interaction of the disulfide compound with benzene is about 0.8 kcal/mol stronger than with cyclohexane.

METHODS

Molecular geometry. Bond lengths and bond angles were those defined for ECEPP (3,4). The cyclohexane molecule was fixed in the "chair" form. The dihedral angle for rotation around the S-S bond in dimethyldisulfide was fixed at 90° (3,5), and the dihedral angles around the C-S bonds were fixed at 60°.

Interaction energy. The interaction energy between two molecules was computed as the sum of electrostatic and nonbonded energies, as defined in ECEPP (3). The electrostatic energy is computed as the sum of Coulomb interactions between partial charges on each atom. The partial charges were obtained from a CNDO/2 (ON) calculation (6) and are shown in Table I. The nonbonded energy is of the form of a "6-12" potential function (3):

$$U_{NB}(r_{ij}) = \sum\sum\left(\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}}\right) \qquad (1)$$

where the summations extend over all atoms of the two interacting molecules, r_{ij} is the distance between atoms i (in the first molecule) and j (in the second molecule), and the parameters A and B depend on the nature of atoms i and j. The parameters for sulfur and for C and H atoms of aromatic groups, published originally for use with ECEPP (3,7), have been updated recently (8) on the basis of lattice energy calculations on crystals of sulfur-containing aromatic compounds. The values of A and B are shown in Table II.

Computation of the intermolecular energy of interaction. The energy of interaction between dimethyldisulfide and either benzene or cyclohexane was computed as a function of the relative position and orientation of the two molecules. The zero of the intermolecular energy scale pertains to infinitely-separated molecules. In each computation, the hydrocarbon molecule was fixed in space, and the dimethyldisulfide molecule was allowed to translate and rotate. In a set of preliminary calculations, the

Table I

Partial Charges of Atoms[a]

Compound	Atom	Partial Charge (e.c.u.)[b]
Dimethyldisulfide	S	0.0170
	C	-0.1940
	H	0.0590
Benzene	C	-0.0110
	H	0.0110
Cyclohexane	C	-0.0206
	H (axial)	0.0149
	H (equatorial)	0.0057

a. Computed with a CNDO/2 (ON) method (6).
b. Electronic charge units.

energy was computed at 1 Å intervals of translation and 30° intervals of rotation (around three perpendicular axes) in order to map the regions of low intermolecular energy. Subsequently, the energy was minimized as a function of the translational and rotational variables of the molecule, starting from 14 different positions. These starting positions included all different relative orientations of the two molecules, omitting redundancies due to symmetry-related positions. Minimization was carried out with the Powell algorithm (9) with a convergence criterion of 0.001 kcal/mol.

RESULTS

Cyclohexane-dimethyldisulfide. Twelve different minimum-energy complexes were found (not counting symmetry-related

Table II

Nonbonded Energy Parameters[a]

Pair of atoms	A ($Å^{12}$kcal/mol)	B ($Å^{6}$kcal/mol)	ε[b] (kcal/mol)	ρ[c] (Å)
S...C(aromatic)	26.18×10^{12}	3.916×10^{6}	-0.1464	3.925
S...C(aliphatic)	52.27	4.583	-0.0917	4.135
S...H(aromatic)	1.173	0.6053	-0.0782	3.540
S...H(aliphatic)	1.143	0.6002	-0.0788	3.535

a. Computed from data shown in Table II of ref. 8. All other nonbonded energy parameters are those in the ECEPP program (3,7).
b. Depth of the pairwise potential energy minimum.
c. Interatomic distance at the energy minimum.

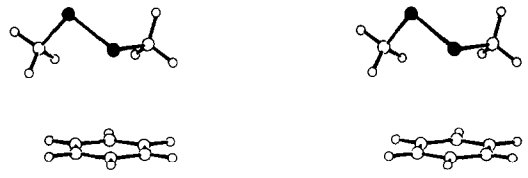

Figure 1. Stereoscopic drawing of the lowest-energy complex formed by dimethyldisulfide and benzene. The two methyl C atoms and the lower S atom are located 3.3 to 3.6 Å above the plane of the benzene ring; they are at about van der Waals contact distance from several of the benzene C atoms. The upper S atom is 4.6 Å from this plane. The benzene molecule is placed in the xy-plane, with its center at the origin, and two C atoms located on the x-axis. The coordinates of the midpoint of the S-S bond of dimethyldisulfide (i.e. the center of symmetry of the molecule) are (x,y,z) = (-0.72 Å, 0.15 Å, 4.12 Å). The orientation of this molecule is obtained by three successive rotations of +122°, +29°, and +128° (in this order) around axes parallel to the z, y, and x axes, respectively. In the orientation used as reference state for this rotation, the S-S bond is parallel to the x-axis (and closer than the two methyl groups to the benzene ring), and the two-fold axis of symmetry coincides with the z-axis.

minima), with energies ranging from -1.46 to -2.57 kcal/mol. These values are representative of the interaction energy between the disulfide compound and an aliphatic hydrocarbon.

Benzene-dimethyldisulfide. Four different minimum-energy conformations were found, with the following energies: -1.54, -2.57, -2.88, and -3.33 kcal/mol. The lowest-energy conformation is shown in Fig. 1. The dimethyldisulfide molecule is located above the plane of the benzene ring, i.e. it interacts with the π-electron shell. The two methyl groups and one of the S atoms are located within van der Waals contact distance of several atoms of the benzene molecule. Even though the intrinsically strongest pairwise interactions between atoms of the two molecules are those between the S and aromatic C atoms (see the column labeled ε in Table II), the dimethyldisulfide molecule does not have an orientation in which both S atoms would be symmetrically placed close to the aromatic ring. In the orientation shown in

Fig. 1, one of the S atoms is at a larger than optimal distance from the atoms of the benzene ring. This is more than compensated, however, by the approach of the two methyl groups to van der Waals distance from the aromatic ring, causing a net lowering of the energy as compared with a symmetrical orientation. Thus, the orientation of the molecule in the lowest-energy complex is determined by the optimization of the sum of all pairwise interactions.

The energy of this complex is 0.76 kcal/mol lower than that of the lowest-energy complex with cyclohexane. This energy difference is due almost entirely to the nonbonded interactions of Eq. 1. The electrostatic energy, due to bond dipoles, is very small and it varies very little for different complexes and for different relative positions.

The energy difference between the two complexes, computed here, is that for isolated pairs of molecules. It can be compared to the observed energy of the dimethyldisulfide-benzene complex in solution in an inert solvent (2) if it is assumed that the interaction energy of dimethyldisulfide with the solvent is similar to that with the cyclohexane molecule. The experimental energies (2) were obtained for complexes of sulfur compounds with 1-methylnaphthalene, rather than with benzene. The former is a larger molecule. The favorable aromatic carbon-sulfur interaction dominates at short interatomic separations, however. Therefore, the size of the aromatic molecule should not have a strong affect on the sulfur-aromatic interaction, and hence the computed and observed energies of interaction are in reasonable agreement.

CONCLUSIONS

The empirical energy parameters, used in this laboratory

for conformational energy calculations on peptides (3), have been derived from crystal packing calculations on rigid model compounds (3,6,8). We have shown that these energy parameters predict that the interaction energy between a disulfide derivative and an aromatic compound is about 0.8 kcal/mol lower than the corresponding interaction energy between the disulfide derivative and a comparable aliphatic group. This result confirms empirical observations (1) and experimental studies (2) concerning complex formation between sulfur compounds and aromatic groups. Proper parameterization, as used in ECEPP (3,8), can account for the enhanced interaction between sulfur and the atoms of the aromatic ring, without the need for introducing special functions into the energy computations.

ACKNOWLEDGMENTS

We thank Dr. R.S. Morgan for calling this problem to our attention and S. Rumsey for help in the preparation of the ORTEP drawing. This work was supported by research grants from the National Institute on Aging (AG-00322) and from the National Institute of General Medical Sciences (GM-14312) of the National Institutes of Health, and from the National Science Foundation (PCM79-20279).

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