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Conformational Analysis of Some Antibacterial Agent 4-Aminodiphenyl Sulfones

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Abstract□Conformational free energy calculations using an empirical potential function (ECEPP/2) and hydration shell model were carried out on the four 4-aminodiphenyl sulfone analogues of 4, 4'-diamino-2'-methyldiphenyl sulfone, 4, 2', 4'-triaminodiphenyl sulfone, 4, 4'-diaminodiphenyl sulfone, and 4-aminodiphenyl sulfone as antibacterial agents on *Mycobacterium lufu*. The conformational energy was minimized from starting conformations which included possible combinations of torsion angles in the molecule. The conformational entropy change of each conformation was computed using a harmonic approximation. To understand the hydration effect on the conformation of the molecule in aqueous solution, the contributions of water-accessible volume and the hydration free energy of each group or atom in the lowest-free-energy conformation was calculated and compared each other. From comparison of the computed lowest-free-energy conformations of four analogues with their antibacterial activities, it is known that the conformation and the hydrophobicity of sulfonyl group and its adjacent carbon atom in each compound are the essential factors to show the strong antibacterial activity.

Keywords□Conformation, antibacterial agents, 4-aminodiphenyl sulfone analogues, hydration free energy.

Regardless of limited utility in the management of many bacterial infections, 4, 4'-diaminodiphenyl sulfone (dapsone, DDS) is a uniquely effective bacteriostatic agent against *Mycobacterium leprae*. While dapsone has remained the agent of choice, used singly or in combination, in the chemotheraphy of leprosy for a number of years, few definitive investigations of its mechanism of action, of its structure-activity relationships, or of the reasons underlying the development of dapsone resistance have been reported. This is principally due to the lack of *in vitro* models since the *M. leprae* organism remains virtually impossible to grow in cultures.[1]

Recently a series of 4-aminodiphenyl sulfone derivatives, dapsone analogues were examined on *M. lufu* found to be similar to *M. leprae* in many respects by Seydel *et al.*, [2] and they concluded that the electronic influence of the substituents is responsible for inhibition potency from the analysis of the structure-activity data on these compounds. Lopez *et al.* were to identify the active conformation for 4-aminodiphenyl sulfones (DDS analogues) with antibacterial activity on *M. lufu*, [1] using both linear free energy and molecular modeling methods.[3]

Recently, the correlation between conformation and physiological properties for bioactive molecules has been studied using the theoretical methods, which are called the QSAR (Quantitative Structure-Activity Relationship). Although the water as solvent in biological system is important in stabilizing the conformation of biomolecules, the previous QSAR methods do not include the hydration effect because of no efficient theory for the interaction of the molecule with water. To overcome this kinds of weak points, the "hydration shell model" [4-7] can be used in the OSAR methods. Using this model, the most stable conformation of bioactive molecules in aqueous solution can be obtained by the calculation of the intramolecular interaction energies for the conformational changes and of the hydration free energy.

In this work, the correlation between the conformations in aqueous solution and the activities on *M. lufu* of 4-aminodiphenyl sulfone analogues is studied using the empirical potential function (ECEPP/2)[8] and hydration shell model.[4-7]

METHODS

The nomenclature and convensions used for torsion angles follow the recommendations of the IUPAC commision on Nomenclature of Organic Chemistry.[9] The bond angles and bond lengths adopted for the molecules were taken as similar values in a general literature.[10] In conformational energy calculations, bond lengths and bond angles were fixed and only the torsion angles for internal rotation were taken as the variables. The definition of torsion angles in the molecules is shown in Fig. 1.

All the present work was done in the context of the "CONBIO" program package of Kang.[11] The conformational energy computations were carried out with ECEPP/2,[8] whose potential parameters were originally optimized to give a good fit of calculated physical and thermodynamic quantities of organic molecules with various functional groups to experimental values. The total conformational energy is the sum of the electrostatic, the nonbonded, and the torsional energies. The hydrogen-bond energy is included in the nonbonded energy component. The partial charge for each atom of the molecule was determineded using the CNDO/2 (ON) method[12] for the fully extended conformation. The hydration shell model improved recently [4-7] was used to compute the hydration free energy of each conformation of the molecules in the hydrated state, where the hydration free energy was obtained as the sum of two contributions from water-accessible volume and polarization (see ref 4-7 for details). To minimize the conformational energy, a variable metric algolithm SUMSL[13] was used. All the torsion angles of the molecules were allowed to vary during minimization. In order to calculate conformational energy for 4, 4'-diamino-2'-methyldiphenyl sulfone (DMDS), the 256 conformations were selected as starting points for energy minimization from the four combinations of 0°, ±90° and 180° for ϕ_1, ϕ_2, ϕ_3, and ϕ_4, where ϕ_4 denotes the torsion angle for NH_2 group substituted in R_3 position. The 1024 conformations for 4, 2', 4'-triaminodiphenyl sulfone (TDS) were selected as starting points for energy minimization from the five combinations of 0°, ±90° and 180° for ϕ_1, ϕ_2, ϕ_3, ϕ_4, and ϕ_5, where ϕ_4 and ϕ_5 denote the torsion angles for NH_2 groups substituted in R_1 and R_3 positions, the 256 combinations for 4, 4'-diaminodi phenyl sulfone (DDS) were selected as starting points for energy minimization from the four combinations of 0°, ±90°, 180° for ϕ_1, ϕ_2, ϕ_3 and ϕ_4, where ϕ_4 denotes the torsion angle for NH_2 group substituted in R_3 position, and the 64 conformations for 4-aminodiphenyl sulfone (ADS) were selected as starting points for energy minimization from the three combinations of 0°, ±90°, 180° for ϕ_1, ϕ_2, and ϕ_3. The selection of these torsion angles of was based on the similar structures in literature.[10] These torsion angles of 4-amino diphenyl sulfone analogues were allowed to vary during energy minimization. For each conformation obtained by minimization of the unhydrated molecules, the hydration free energy was computed without further minimization.[14] At each energy minimum in the hydrated state, the conformational entropy was computed using a harmonic method of Gō and Scheraga.[15] The elements of a hessian matrix of second derivatives at each minimum were numerically calculated.[16] The seven- and five-point formulas were employed for calculation of off-diagonal and diagonal elements, respectively, with the step size of each variable equal to 1°.

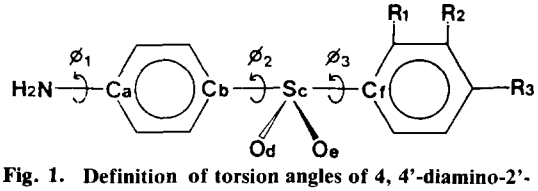

Fig. 1. Definition of torsion angles of 4, 4'-diamino-2'-methyldiphenyl sulfone (DMDS; $R_1 = CH_3$, $R_2 = H$, $R_3 = NH_2$), 4, 2', 4'-triaminodiphenyl sulfone (TDS; $R_1 = NH_2$, $R_2 = H$, $R_3 = NH_2$), 4, 4'-diaminodiphenyl sulfone (DDS; $R_1 = H$, $R_2 = H$, $R_3 = NH_2$), and 4-aminodiphenyl sulfone(ADS; $R_1 = H$, $R_2 = H$, $R_3 = H$). Torsion angle ϕ_4 corresponds to the NH_2 group substituted in R_3 position for DMDS and DDS, and in R_1 position for TDS, and torsion angle ϕ_5 corresponds to the NH_2 group substituted in R_3 position for TDS.

The relative total free energy is given by $\Delta G_{tot} = \Delta G + \Delta \Delta G_{hyd}$, where ΔG is therelative conformational free energy (i.e., $\Delta G = G - G°$, where $G°$ is the lowest free energy), and $\Delta \Delta G_{hyd}$ is the relative hydration free energy (i.e., $\Delta \Delta G_{hyd} = \Delta G_{hyd} - \Delta G_{hyd}°$, where $\Delta G_{hyd}°$ is the hydration free energy of the conformation with the lowest free energy). The relative conformational energy is given by $\Delta E = E - E°$, where $E°$ is the conformational energy of the conformation of lowest free energy. The relative entropic contribution to the relative free energy is given by $-T\Delta S$. Also the normalized statistical weight of each conformations was computed using an equation of Zimmerman *et al.* [17] All the thermodynamic quantities have been calculated for T = 25°C.

RESULTS AND DISCUSSION

Energetics of low-free-energy conformations (i.e., $\Delta G_{tot} < 3$ kcal/mol) in the hydrated state, their torsion angles, and hydration free energy of each group for four molecules are listed in Tables I-IV, respectively.

For each conformation, Tables I-IV contain (1) the conformational letter codes, (2) the relative total free energy ΔG_{tot}, (3) the normalized statistical weights ω, (4) the relative conformational energy ΔE, (5) the relative conformational free energy ΔG, (6) the relative entropic contribution to conformational free energy $-T\Delta S$, (7) the relative hydration free energy $\Delta\Delta G_{hyd}$, and (8) the relative energy components ΔE_{es}, ΔE_{nb}, and ΔE_{tor} of ΔE.

Conformational analysis

(1) 4, 4'-Diamino-2'-methyldiphenyl sulfone (DMDS). From the 256 starting conformations of DMDS, the six conformations have the relative free energy (ΔG_{tot}) less than 3.0 kcal/mol and are shown to be the most probable conformation ($\Delta G_{tot} < 1.0$ kcal/mol) in aqueous solution. The stereoview of lowest-free-energy conformation (eg te) of DMDS is drawn in Fig. 2a. During the energy minimization, it is known that torsion angles ϕ_2 and ϕ_3 of DMDS moved somewhat largely, whereas ϕ_1 and ϕ_4 do not change from initial values. The calculated thermodynamic quantities for the low-free-energy conformations of DMDS are listed in Table I.

From the analysis of total free energies of six conformations, the conformational entropy and electrostatic energy are the major contributions to the total free energy, and the nonbonded and torsional energies contributed somewhat a little to the conformational change, and the hydrogen bonding is not involved in the total interaction. Comparing only the torsion angles of low-free-energy conformations, it is shown that the low-free-conformations of DMDS have torsion angles ϕ_2 and ϕ_3 kept in *gauche* and *trans*/or *gauche* form, respectively. Therefore, it is known that torsion angle ϕ_2 and ϕ_3 are a decisive factor for the low-free-energy conformation of DMDS from the fact that the conformational energy is strongly dependent on the torsions of ϕ_2 and ϕ_3.

(2) 4, 2', 4'-Triaminodiphenyl sulfone (TDS). From the 1024 starting conformations of TDS, the six conformations have the relative free energy (ΔG_{tot}) less than 3.0 kcal/mol, and the most probable conformation ($\Delta G_{tot} < 1.0$ kcal/mol) in aqueous solution is found to be the only three. The stereoview of lowest-free-energy conformation (eg+g+ee) of TDS is drawn in Fig. 2b. During the energy minimization, it is shown that torsion angles ϕ_2 and ϕ_3 of TDS moved somewhat largely, whereas ϕ_1, ϕ_4, and ϕ_5 do not change from initial values. The calculated thermodynamic quantities for the low-free-energy conformations of TDS are shown in Table II.

The torsional energy, nonbonded energy, conformational entropy, hydration free energy, and hydrogen bonding (r $(O_{15}\cdots H_{31}) = 2.047$-$2.293$ Å, r $(O_{16}\cdots H_{31}) = 2.211$-$2.916$ Å; O_{15} and O_{16} are ox-

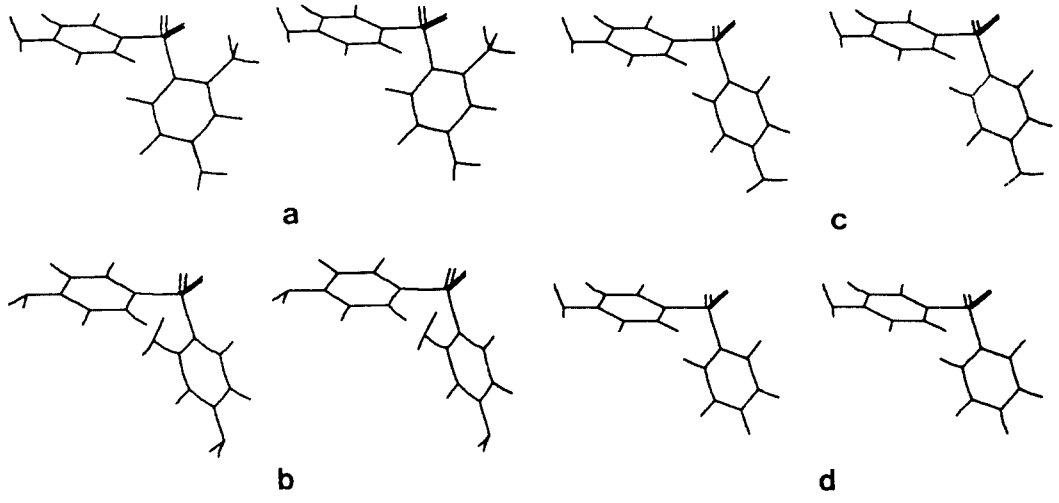

Fig. 2. Stereoview of the lowest-free-energy conformation of (a) DMDS, eg⁻te, (b) TDS, eg⁺g⁺ee, (c) DDS, eg⁻g⁻e, and (d) ADS,eg⁻g⁻

Table I. Energetics and torsion angles of low-free-energy conformations of 4, 4'-diamino-2'-methyldiphenyl sulfone (DMDS)[a, b]

Conf. Letter code[c]	Torsional Angle[d] ϕ_1	ϕ_2	ϕ_3	ϕ_4	ΔG_{tot}[e]	ω[f]	ΔE[g]	ΔG[h]	$-T\Delta S$[i]	$\Delta\Delta G_{hyd}$[j]	ΔE_{es}[k]	ΔE_{nb}[l]	ΔE_{tor}[m]
e g⁻ t e	0	−72	174	0	.000	.234	.000	.000	.000	.000	.000	.000	.000
e g⁺ t e	0	72	−174	0	.031	.222	.063	.066	.003	.001	.053	.012	−.002
e g⁻ g⁻ e	0	−51	−66	0	.063	.210	.068	.318	.250	−.036	.446	−.311	−.067
e g⁺ g⁺ e	0	51	66	0	.176	.174	.212	.461	.249	−.035	.588	−.310	−.066
e t g⁻ e	0	164	−69	0	.617	.083	.656	.937	.281	−.039	.569	−.114	.202
e t g⁺ e	0	−164	69	0	.660	.007	.699	.980	.281	−.039	.603	−.114	.211

[a]Energies are in kcal/mol, and free energies and entropic contributions are calculated at 298 K.
[b]Only the conformations with the relative total free energy to that of conformation eg⁻te ($\Delta G_{tot} < 3.0$ kcal/mol) are listed.
[c]Each conformation is defined by four torsion angles of ϕ_1, ϕ_2, ϕ_3, and ϕ_4 defined in Fig. 1; $-30° \leq e \leq 30°$, $-120° \leq g^- < -30°$, $30° < g^+ \leq 120°$, $120° < t \leq 180°$° or $-180° \leq t < -120°$.
[d]Units are in degree.
[e]The total free energy of each conformation in the hydrated state; $\Delta G_{tot} = G_{tot} - G_{tot}°$, $G_{tot}° = -31.658$ kcal/mol.
[f]Normalized statistical weight.
[g]Intramolecular interaction energy change; $\Delta E = E - E°$; $E° = E_{es}° + E_{nb}° + E_{tor}° = -10.942$ kcal/mol.
[h]Free energy change; $\Delta G = \Delta E - T\Delta S$, $G° = 0.714$ kcal/mol.
[i]Conformational entropic contribution.
[j]Hydration free energy of each conformation; $\Delta\Delta G_{hyd} = \Delta G_{hyd} - \Delta G_{hyd}°$, $\Delta G_{hyd}° = -20.717$ kcal/mol.
[k]Electrostatic energy change; $\Delta E_{es} = E_{es} - E_{es}°$, $E_{es}° = -4.737$ kcal/mol.
[l]Nonbonded energy change; $\Delta E_{nb} = E_{nb} - E_{nb}°$, $E_{nb}° = -6.442$ kcal/mol.
[m]Torsional energy change; $\Delta E_{tor} = E_{tor} - E_{tor}°$, $E_{tor}° = 0.237$ kcal/mol.

Table II. Energetics and torsion angles of low-free-energy conformations of 4, 2', 4'-triaminodiphenyl sulfone (TDS)[a, b]

Conf. Letter code[c]	Torsional Angle[d] ϕ_1	ϕ_2	ϕ_3	ϕ_4	ϕ_5	ΔG_{tot}[e]	ω[f]	HB[g]	ΔE[h]	ΔG[i]	$-T\Delta S$[j]	$\Delta\Delta G_{hyd}$[k]	ΔE_{es}[l]	ΔE_{nb}[m]	ΔE_{tor}[n]
e g⁺ g⁺ e e	0	61	66	−1	0	.000	.428	15-31	.000	.000	.000	.000	.000	.000	.000
e t g⁺ e e	0	−172	72	−2	0	.235	.288	15-31	.400	.609	.209	−.165	−.046	−.194	.252
e g⁺ t e e	0	66	−163	−2	0	.592	.158	16-31	.898	1.060	.162	−.306	−.020	.527	.391
e g⁻ t e e	0	−73	176	0	0	1.121	.065	16-31	1.316	1.387	.071	−.195	.106	1.026	.192
e g⁻ g⁺ e e	0	−76	88	−3	0	1.200	.057	15-31	1.456	1.496	.040	−.256	−.286	.544	1.197
e g⁻ g⁻ e e	0	−57	−71	3	0	2.673	.005	16-31	1.739	2.067	.328	.934	1.022	.525	2.460

[a, b, c, d, f, j]See the footnotes of Table I.
[e]$G_{tot}° = -34.744$ kcal/mol.
[g]Hydrogen bond pair (atom numbers 15 and 16 denote oxygens of sulfonyl group; atom number 30 denotes hydrogen of amine group substituted in R_1 position in Fig. 1).
[h]$E° = -5.640$ kcal/mol.
[i]$G° = 0.325$ kcal/mol.
[k]$\Delta G_{hyd}° = -29.104$ kcal/mol.
[l]$E_{es}° = 2.328$ kcal/mol.
[m]$E_{nb}° = -8.027$ kcal/mol.
[n]$E_{tor}° = 0.059$ kcal/mol.

ygens of sulfonyl group and H_{31} is hydrogen of amine group substituted in R_1 position, in Fig. 1) are known to be the major contributions to the total energy from the analysis of energetics of low-free-energy conformations.

Comparing the torsion angles of DMDS with those of TDS of lowest-free-energy conformations, torsion angles ϕ_1 and ϕ_2 show the same trend,

whereas ϕ_3 has a different trend for DMDS and TDS, i.e., ϕ_1, ϕ_2, and ϕ_3 have *eclipse*, *gauche*, and *gauche* form, respectively. From the results described above, if the reaction site were ϕ_1, ϕ_2, and ϕ_3 position of 4-aminodiphenyl sulfones and the hydrogen bonding is essential for the activities, these two molecules show different activities each other.

(3) 4, 4'-Diaminodiphenyl sulfone (DDS). From the 256 starting conformations of DDS, 8 conformations have the relative free energy (ΔG_{tot}) less than 3.0 kcal/mol, and the seven conformations ($\Delta G_{tot} < 1.0$ kcal/mol) seem to be the most probable conformations in aqueous solution. The stereoview of lowest-free-energy conformation (eg$^-$g$^-$e) of DDS is drawn in Fig. 2c. During the energy minimization , torsion angles ϕ_2 and ϕ_3 moved somewhat largely, whereas ϕ_1 and ϕ_4 do not change from initial values. The calculated thermodynamic quantities for the low-free-energy conformations of DDS are shown in Table III.

From the analysis of total free energies of low-free-energy conformations of DDS, it is known that the torsional energy, nonbonded energy, electrostatic energy, and conformational entropy are the major contributions to the total free energies of the low-free-energy conformations, and there is no any hydrogen bonding. Comparing only the torsion angles of probable conformations with low-free-energies, torsion angles ϕ_1, ϕ_2, and ϕ_3 are shown to be *eclipse*, *gauche*, and *gauche* form, respectively. The trend on torsion angles of DDS is shown to be different from that of DMDS. If the hydrogen bonding effect on the activities, the activity of DDS may be thought to differ from those of DMDS and TDS.

(4) 4-Aminodiphenyl sulfone (ADS). From the 64 starting conformations of ADS, 8 conformations have the relative free energy (ΔG_{tot}) less than 3.0 kcal/mol, and the six conformations ($\Delta G_{tot} < 1.0$ kcal/mol) seem to be the most probable conformations in aqueous solution. The stereoview of lowest-free-energy conformation (eg$^-$g$^-$) of ADS is drawn in Fig. 2d. During the energy minimization, torsion angles ϕ_2 and ϕ_3 moved somewhat largely, whereas ϕ_1 does not change from initial value. The calculated thermodynamic quantities for the low-free-energy conformations of ADS are shown in Table IV.

From the analysis of total free energies and torsion angles of low-free-energy conformations of ADS, ADS has the same trend on torsion angles as those of DDS. Therefore the activity of ADS may be thought to be similar with of that DDS.

On the bases of the results for the conformation analysis described above, it may be thought that the antibacterial activity of DMDS is different from those of TDS, DDS, and ADS. If the hydrogen bonding affects the activities, the antibacterial activity of TDS is different from those of DDS and ADS. As a fact, the activities of 4-aminodiphenyl sulfones

Table III. Energetics and torsion angles of low-free-energy conformations of 4, 4'-diaminodiphenyl sulfone (DDS)[a, b]

Conf. Letter code[c]	Torsional Angle[d] ϕ_1	ϕ_2	ϕ_3	ϕ_4	ΔG_{tot}[e]	ω[f]	ΔE[g]	ΔG[h]	$-T\Delta S$[i]	$\Delta\Delta G_{hyd}$[j]	ΔE_{es}[k]	ΔE_{nb}[l]	ΔE_{tor}[m]
e g$^-$ g$^-$ e	0	−59	−60	0	.000	.083	.000	.000	.000	.000	.000	.000	.000
e g$^+$ g$^+$ e	0	59	60	0	.117	.068	.116	.111	−.005	.001	.115	.001	.001
e t g$^-$ e	0	170	−69	0	.787	.022	.798	1.015	.217	−.010	.335	.232	.232
e g$^-$ t e	0	−68	168	0	.808	.021	.820	1.031	.211	−.011	.220	.320	.280
e t g$^+$ e	0	−170	69	0	.844	.020	.854	1.070	.216	−.010	.391	.227	.236
e g$^+$ t e	0	68	−167	0	.880	.019	.891	1.099	.208	−.011	.288	.315	.288
e g g$^+$ e	0	−73	77	0	.991	.016	1.009	1.098	.089	−.018	.078	.339	.592
e g$^+$ g$^-$ e	0	73	−77	0	1.004	.015	1.022	1.109	.087	−.018	.089	.340	.593

a, b, c, d, f, i See the footnotes of Table I.
[e] $G_{tot}^\circ = -29.475$ kcal/mol.
[g] $E^\circ = -8.517$ kcal/mol.
[h] $G^\circ = 1.412$ kcal/mol.
[j] $\Delta G_{hyd}^\circ = -20.958$ kcal/mol.
[k] $E_{es}^\circ = -2.357$ kcal/mol.
[l] $E_{nb}^\circ = -6.162$ kcal/mol.
[m] $E_{tor}^\circ = 0.002$ kcal/mol.

Table IV. Energetics and torsion angles of low-free-energy conformations of 4-aminodiphenyl sulfone (ADS)[a, b]

Conf. Letter code[c]			Torsional Angle[d] ϕ_1	ϕ_2	ϕ_3	ΔG_{tot}[e]	ω[f]	ΔE[g]	ΔG[h]	$-T\Delta S$[i]	$\Delta\Delta G_{hyd}$[j]	ΔE_{es}[k]	ΔE_{nb}[l]	ΔE_{tor}[m]
e	g⁻	g⁻	0	−59	−60	.000	.181	.000	.000	.000	.000	.000	.000	.000
e	g⁺	g⁺	0	59	60	.075	.159	.074	−.883	−.006	.001	.065	.008	.001
e	t	g⁺	0	−170	69	.789	.048	.806	.067	.212	−.017	.333	.231	.243
e	t	g	0	171	−70	.797	.047	.814	.075	.212	−.017	.347	.232	.236
e	g	g⁺	0	−72	79	.918	.038	.933	.106	.124	−.015	.019	.299	.614
e	g⁺	g⁻	0	72	−78	.990	.034	1.004	.169	.116	−.014	.092	.298	.614
e	g	t	0	−66	158	1.267	.021	1.275	.561	.237	−.008	.257	.397	.621
e	g⁺	t	0	66	−158	1.351	.018	1.359	.642	.234	−.007	.338	.398	.622

[a], [b], [c], [d], [f], [i] See the footnotes of Table I.
[e] $G_{tot}^{\circ} = -24.932$ kcal/mol.
[g] $E^{\circ} = -10.269$ kcal/mol.
[h] $G^{\circ} = 0.951$ kcal/mol.
[j] $\Delta G_{hyd}^{\circ} = -14.663$ kcal/mol.
[k] $E_{es}^{\circ} = -4.806$ kcal/mol.
[l] $E_{nb}^{\circ} = -5.465$ kcal/mol.
[m] $E_{tor}^{\circ} = 0.002$ kcal/mol.

Table V. The hydration free energies for groups or atoms in the lowest-free-energy conformations and antibacterial activities of four 4-aminodiphenyl sulfone alalogues

Compound	N[a]	C_a[a]	C_b[a]	S_c[a]	O_d[a]	O_e[a]	C_f[a]	Activity[b]
DMDS	−.725	−.972	−.820	−1.520	−1.735	−1.727	−.809	6.19
TDS	−.716	−.970	−.808	−1.534	−1.783	−1.788	−.820	5.99
DDS	−.726	−.978	−.827	−1.572	−1.862	−1.862	−.840	5.92
ADS	−.725	−.978	−.825	−1.605	−1.862	−1.864	−.868	4.92

[a] Refer to the Fig. 1 and units in kcal/mol.
[b] Log $(1/I_{50})$; I_{50}, 50% inhibitory concentrations, units in μmole/l, taken from ref 1.

show the order DMDS>TDS>DDS> ADS (see Table VI). If only the results of conformational analysis are considered, it is known that the activities are increased when torsion angles ϕ_1, ϕ_2, and ϕ_3 keep in *eclipse, gauche,* and *trans* form, respectively.

Charge distribution and dipole moments

The net atomic charges and dipole moments of the lowest-free-energy conformations of four 4-aminodiphenyl sulfones were computed by CNDO/2 (ON) method,[12] and correlated with their antibacterial activities. However the correlation is not so good. Therefore, it may be thought that the electrostatic interaction is not an important contribution to the interaction energy between 4-aminodiphenyl sulfones and receptor.

Hydration effect

Although the hydration free energy is important in stabilizing the low-free-energy conformation of TDS only, the hydration free energy were calculated for some groups and atoms of the molecules to see the correlation between solvent accessibilities and their activities. The antibacterial activity, hydration free energy (ΔG_{hyd}), and water-accessible volume (V_{wa}) of N, C_a, C_b, S_c, O_d, O_e and C_f (see Fig. 1) of the lowest-energy conformations of four 4-aminodiphenyl sulfone analogues are listed in Table V and VI, respectively.

Comparing the activity with ΔG_{hyd} of DMDS, TDS, DDS, and ADS, the activities are increased when the ΔG_{hyd} of sulfonyl group (i.e., S_c, O_d, and O_e) and C_f atom have large positive values.

Table VI. The water-accessible volumes for groups or atoms in the lowest-free-energy conformations and antibacterial activities of four 4-aminodiphenyl sulfone analogues

Compound	N[a]	C_a[a]	C_b[a]	S_c[a]	O_d[a]	O_e[a]	C_f[a]	Activity[b]
DMDA	426.715	487.950	411.607	425.102	337.120	338.125	406.535	6.19
TDS	427.787	487.366	405.696	430.107	342.635	343.826	411.669	5.99
DDS	427.967	491.051	415.599	440.109	350.025	351.110	421.689	5.92
ADS	427.970	490.968	414.350	438.248	352.715	352.062	435.989	4.92

[a]Refer to the Fig. 1 and units in Å^3.
[b]See the footnotes of Table V.

To study more detailed hydration structure of the hydrated conformations, the water-accessible volumes of groups and atoms (i.e., N, C_a, C_b, S_c, O_d, O_e, and C_f) of four molecules are calculated. From Table VI, the activities are decreased when the water-accessible volumes of sulfonyl group and C_f atom are increased. The increase of ΔG_{hyd} and decrease of water-accessible volumes of groups and atoms in the molecules mean the increase of the hydrophobicity.

In general, the hydrophobic interaction is known to be very important in the interactions between drug and side-chains of receptor protein.[18-20] From the correlation between hydration free energy, water-accessible volumes of sulfony group and atoms, and antibacterial activities of four 4-aminodiphenyl sulfones, it is known that the hydrophobic interaction may be one of the most essential factors in the interaction between 4-aminodiphenyl sulfone analogues and receptor protein.

CONCLUSION

If the lowest-energy conformations of 4-aminodiphenyl sulfone analogues are conserved while interacting with receptor site in aqueous solution, the following conclusions can be obtained.

From the conformational analysis, 4-aminodiphenyl sulfone analogues show strong antibacterial activities when the torsion angles ϕ_1, ϕ_2, and ϕ_3 of low-free-energy conformations are kept in *eclipse, gauche,* and *trans* form, respectively. From comparision of the dipole moments and partial atomic charges with antibacterial activities of 4-aminodiphenyl sulfone analogues, it is known that the electrostatic interaction is not an important contribution to the interaction energy of the 4-aminodiphenyl sulfone analogues and the receptor. Comparing the hydration free energies (ΔG_{hyd}), water-accessible volumes (V_{wa}) of sulfonyl group and its adjacent carbon atom (C_f) in the 4-aminodiphenyl sulfone analogues, and the antibacterial activities, the antibacterial activity is well correlated the increased of the hydrophobicity of the sulfonyl group and its adjacent carbon atom (C_f) in 4-aminodiphenyl sulfone analogues. Therefore, the hydrophobic interaction may be one of the most essential factors in the interaction between 4-aminodiphenyl sulfone analogues and the side chain of receptor protein.

On the basis of these results, the chemical structure and conformation exhibiting the optimal antibacterial activities of 4-aminodiphenyl sulfone analogues could be predicted.

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