Molecular Similarity from Atomic Electrostatic Multipole Comparisons. Application to Anti-HIV Drugs

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A procedure is presented for the rapid calculation of the similarity between a pair of molecules based on atomic electrostatic multipole comparison. The multipoles are derived from semiempirical SCF wave functions, and the results obtained compare favorably with *ab initio* results. The method is illustrated by correlating the similarity and anti-HIV-1 activity of a series of azo compounds. Some generalizations are presented on the structure–activity relationships which are based on the atomic multipole distribution in the azo compounds.

Introduction

Medicinal chemists assume that two drugs with similar structures will show similar biological activity. A classical approach to similarity involves topological comparison of molecular drawings, volumes, shapes, or graphs.[1] A more general definition of molecular similarity advanced by Carbo, Leyda, and Arnau[2] states that two molecules are similar if they have similar electron density distributions. At this level, a molecule is characterized as a three-dimensional array of atomic nuclear point (+) charges imbedded in a continuous anisotropic (−) charged electron density field. Intrinsic in this approach is a comparison of molecular size and shape, since nuclear positions determine the electron distribution.

Established methods[3] of comparing the electron distribution of two molecules require the evaluation of the integral of the product of the two respective molecular electron density functions as developed by Richards[4] or calculation of the sum of wave function overlap between the two (number of overlapping electrons, NOEL[5]). In the former procedure the molecules to be compared are embedded in a rectilinear grid, and an approximation[2,6] to the electron density at each grid intersection is calculated. The latter method calculates the square of the overlap integral between all atomic centers of the molecule pair. Rotations and translations of one molecule relative to the other are carried out to maximize the result of the calculation. Since multicenter integrals are calculated, these procedures scale with the fourth power of the atomic size or the third power of the number of electrons and are computationally intensive.[7] For large molecules as often encountered in drug discovery, these methods would be almost prohibitive. Richards modified his procedure to calculate the correspondence between Gaussian-fitted Slater-type orbitals at the atomic centers of the molecules which were candidates for comparison.[3c] This modification was computationally expedient, but some variation of similarity with grid spacing (but not extent) was noted. We have developed a new procedure for calculation of molecular similarity which preserves the concept of electron density correspondence, does not involve repetitive integral evaluation and questions of grid construction, and is applicable to large molecules with minimal computational effort. This atomic multipole similarity method is illustrated by correlating the similarity and anti-HIV activity of a series of azo dyes related to Chicago Sky Blue.[8]

Approach

This approach involves the discretization of the electron density via an atomic multipole expansion of the wavefunctions derived from a semiempirical modified neglect of different overlap (MNDO)[9] self-consistent field (SCF) calculation. If the SCF basis set is composed of Slater s and p atomic functions, this expansion gives each atomic center a monopole, three dipoles (x, y, z), and six quadrupoles (xx, yy, zz, xy, xz, yz).

For two molecules, **A** and **B**, the correspondence or similarity of their respective atomic multipoles are determined. Both molecules are placed in their lowest energy conformation in the MM2 force field,[10] and the MNDO wave functions are determined for the molecules in these conformations. The wave functions obtained are then subjected to atomic multipole expansions. The atomic dipolies and quadrupoles associated with each molecule are not rotationally invariant, and a method to determine the direct correspondence between the two molecules would require rotation of the molecules and their wave functions, recalculation of the multipoles, and superposition of the two molecules to determine their similarity. This time-consuming computation could be avoided if the potential of each molecule were calculated over a three-dimensional surrounding grid of points. This grid could be rotated and translated in space to determine the point of maximum potential correspondence. However, the results of this procedure are dependent upon the number and spacing of the grid points. To avoid this problem, a grid of the atomic positions of one of the molecular partners was used in the similarity calculation. Calculation of the electrostatic interaction energy of the multipoles was used rather than the potential. In molecule **A**, the sign of all atomic monopoles were reversed (to create a convex minimization problem), and these reversed sign mono-

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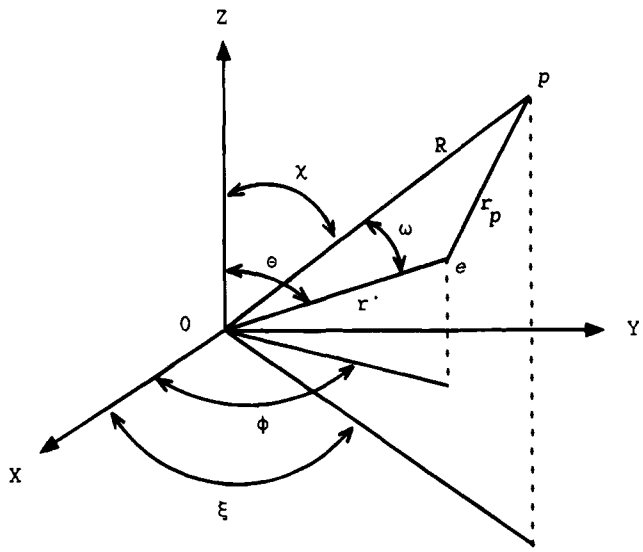


Figure 1. Coordinate frame definition used in integral evaluation.

poles were assigned to the nuclear positions of **A** (the molecular monopolar array, MMA). The product of these reversed monopoles with the calculated electrostatic potential from the multipole expansion of molecule **B**, at any orientation during the calculation, is the electrostatic MMA energy, E_A. The MMA was rotated and translated in real space until the largest negative E_A was obtained. Then, molecule **B** was used to generate the MMB and the energetic minimum, E_B, found. The total energy, $E_{A,B}$ for the **A**–**B** system is given by

$$E_{A,B} = E_A + E_B \tag{1}$$

For a series of drugs with known activities, one was selected as the reference (usually the most active), and the energy minima for the reference and each of the drugs, x, found. By definition, the normoalized (in the interval 0 to 1 by using absolute values for E) similarity index (SI) is given by

$$\mathrm{SI}_{\mathrm{reference},x} = \frac{|(E_{\mathrm{reference,reference}} - E_{\mathrm{reference},x})|}{|E_{\mathrm{reference,reference}}|} \tag{2}$$

Theory

The electrostatic potential, $V(r)$, arising from an atomic electronic charge distribution, $\varrho(r)$, at any point r_i is rigorously given by eq 3 in which Z_A is the effective nuclear charge on atom A located at R_A.

$$V(r) = \sum_A \frac{Z_A}{|R_A - r|} - \int \frac{\varrho(r)\,\mathrm{d}r}{|r_i - r|} \tag{3}$$

The potential, V, at a point, q, located at a distance, R, from an origin R_A, due to a charge, e_i, located at a distance, r_i, from R_A and r from q as shown in Figure 1 is

$$V = \frac{e}{r_p} = e[R^2 + r^2 - 2Rr\cos\omega]^{-1/2} \tag{4}$$

which may be expanded in power of r/R

$$V = \frac{e}{R} + \frac{er\cos\omega}{R^2} + \frac{er^2[3\cos^2\omega - 1]}{2R^3} + \ldots \tag{5}$$

where the terms in R^{-1} defined a monopole, R^{-2} the dipole, and R^{-3} the quadrupole moments of the charge distribution relative to the origin. The relationship between the coordinates of e_i, R_A, and q in the polar frame of Figure 1 is given by

$$\cos\omega = \mathrm{cis}\,\chi\cos\Theta + \sin\chi\cos\xi\sin\Theta\cos\Phi + \sin\chi\sin\xi\sin\Theta\sin\Phi \tag{6}$$

The r is determined for the various charge distributions at each atomic center for the molecule as defined by the availiable ground state wave functions. This process is simplified if the wave functions are overlap-free, removing the necessity of the division of the overlap population (Mulliken[11] or similar proceedure) and the attendant error so introduced. A further simplification is provided by introduction of the collapsed-core approximation and consideration of only the charge distributions associated with the valence shell electrons. If the MO-LCAO approximation is used, each occupied molecular orbital coefficient (c) weighted atomic orbital (ϕ) contributes a charge barycenter to the total atomic charge distribution given by the integral

$$c_i c_j \left\langle \phi_i \left| \frac{1}{r} \right| \psi_j \right\rangle \tag{7}$$

where ϕ is an s or p atomic orbital. If the atomic orbital basis is of the Slater type, these one-center integrals may be evaluated exactly in terms of the effective nuclear charge, Z, in the indicated coordinate system. For second row atoms with a 2s,2p basis set the result is

$$\left\langle S \left| \frac{1}{r} \right| S \right\rangle = \frac{1}{R} \tag{8}$$

$$\left\langle P_z \left| \frac{1}{r} \right| P_z \right\rangle = \frac{1}{R} + \frac{3}{Z^2R^3}[9\cos^2\chi + 3\sin^2\chi\cos^2\xi + 3\sin^2\chi\sin^2\xi - 5] \tag{9}$$

$$\left\langle S \left| \frac{1}{r} \right| P_z \right\rangle = \left[\frac{Z_s^5 + Z_p^5}{3}\right]^{1/2} \frac{320\cos\chi}{R^2(Z_s + Z_p)^6} \tag{10}$$

$$\left\langle P_x \left| \frac{1}{r} \right| P_x \right\rangle = \frac{1}{R} + \frac{3}{Z^2R^3}[3\cos^2\chi + 9\sin^2\chi - 6\sin^2\chi\sin^2\xi - 5] \tag{11}$$

$$\left\langle S \left| \frac{1}{r} \right| P_x \right\rangle = \left[\frac{Z_s^5 Z_p^5}{3}\right]^{1/2} \frac{320\sin\chi\cos\xi}{R^2(Z_s + Z_p)^6} \tag{12}$$

$$\left\langle P_y \left| \frac{1}{r} \right| P_y \right\rangle = \frac{1}{R} + \frac{3}{Z^2R^3}[3\cos^2\chi + 3\sin^2\chi + 6\sin^2\chi\sin^2\xi - 5] \tag{13}$$

$$\left\langle S \left| \frac{1}{r} \right| P_y \right\rangle = \left[\frac{Z_s^5 Z_p^5}{3}\right]^{1/2} \frac{320\sin\chi\sin\xi}{R^2(Z_s + Z_p)^6} \tag{14}$$

$$\left\langle P_z \left| \frac{1}{r} \right| P_x \right\rangle = \frac{18}{Z^2R^3}\cos\chi\sin\chi\cos\xi \tag{15}$$

$$\left\langle P_z \left| \frac{1}{r} \right| P_y \right\rangle = \frac{18}{Z^2 R^3} \cos\chi \sin\chi \sin\xi \qquad (16)$$

$$\left\langle P_x \left| \frac{1}{r} \right| P_y \right\rangle = \frac{18}{Z^2 R^3} \sin^2\chi \cos\xi \sin\xi \qquad (17)$$

Thus, the asymmetric electron density within a molecule may be approximated by an atomic multipole expansion. If the molecular wave functions are derived from a s,p atomic base, then each non-hydrogen atomic center has associated with it a monopole (eq 8), x,y,z-dipole (eqs 10, 12, and 14) and x,x, y,y, z,z, x,y, y,z, x,z-quadrupoles (eqs 9, 11, 13, 15, 16, and 17) contribution to the total potential at any external point. If the wave functions are derived from a Slater atomic basis and are overlap-free, the one-center integrals are easily obtained for the multipoles. Wave functions which meet the above criteria and give calculated dipole moments which correspond closely with the experimental value are those from the Dewar MNDO semiempirical SCF procedure.

The total potential at point q due to a molecule of n atoms, where $e_i = -1$, is

$$V_{\text{total}} = \sum_{1}^{n} \frac{Z_A}{R_A} - \sum_{1}^{n} \sum_{\text{occ}} \sum_{i} \sum_{j} c_i c_j \left\langle \phi \left| \frac{1}{r} \right| \phi \right\rangle \qquad (18)$$

For a charge, q_c, located at q the electrostatic energy is $q_c V_{\text{total}}$.

Sample Calculation and Comparison to *ab Initio* Results

Acrolein is an example of a simple test molecule used to validate the correctness of this electrostatic calculation. Nucleophilic (−1 charge) attack may occur at the carbonyl carbon (1,2-addition) or the β-carbon (1,4-addition) with the former site being preferred from chemical experience. Francl[12] has used *ab initio* wave functions (STO-3G, 3-21G, and 6-31G*) from the GAUSSIAN 82 program to calculate the first-order electrostatic interaction energy and a test −1 charge at regularly spaced points on a plane 2 Å above the molecular plane at acrolein. Contours in this plane of equal energy at the 3-31G and STO-3G level indicated only 1,2-addition was preferred. Hartree-Fock perturbation theory was then used to compute a second order polarization correction to the first-order energy. This corrected energy at 3-21G revealed two channels for nucleophilic attack; 1,2 approach at 17.0 kcal/mol and 1,4 at 15 kcal/mol. At the minimal basis STO-3G both channels were visible at 12 and 10 kcal/.mol, repesctively. This author states that the perturbation method yields results in close agreement with those obtained from exact calculation. Although the correct answer was obtained with the polarization correction at the minimal basis level, it was computationally expensive (48 min on a VAX 11/780 for a 25 × 25 point grid).[13]

In the present work the multipole expansion up to the quadrupole level using Slater s,p orbitals and MNDO wave functions[6] was applied to acrolein and the results contoured as above. The 1,2-addition channel was at 12.3 kcal/mol and the 1,4-addition channel at 11.8 kcal/mopl which agrees with the *ab initio* result in order and partially in magnitude. The computation time for acrolein was fast (30 s on a VAXstation II for a 100 × 100 grid), which suggests that mapping large molecules would be possible with modest computer facilities. Truncation of the expansion at the dipole level gave an electrostatic map which did not differentiate between the 1,2- and 1,4-channels, indicating that the quadrupolar term is important in properly describing (−) charge interactions with electrophilic π−systems.

Details of Calculations

Subroutines were added to program MODEL (Clark Still, Columbia University) to carry out evaluation of E_A and E_B in eq 1, to input the wave functions, and to assist in the graphics manipulation of the molecules for a starting point in the electrostatic minimization. Molecular geometries were first optimized with the MM2/MMP1[14] force field, and then orbital calculations were carried out with program AMPAC[15] using the MNDO Hamiltonian.[16] Computation of E_A proceeded as follows. The wave functions for **B** and the SCF charges (monopoles) were read from the AMPAC output. The sign of the **B** monopoles were reversed and **A** manually embedded in the MMB and rotated (three polar angles) and translated (x,y,z) until a minimum electrostatic interaction energy was obtained for a starting point for final minimization. R in eqs 8−17 was replaced by $R + 10^{-4}$ to prevent division by zero. Minimization was performed using a quasi-Newton method[17] employing numerical first and second derivatives and the Hessian matrix updated after every movement of **B**. This procedure repeated to obtain E_B.

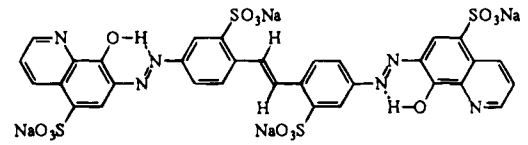
The atomic multipole method may be used to visualize the distribution of the potential in space surrounding a molecule. The van der Waal surface of the molecule in question was constructed, and a test charge of +1 was placed at regular intervals on this surface. At each test charge position, the electrostatic interaction energy of the charge with all of the atomic multipoles was calculated and saved. A final electrostatic energy map was created by generating contours of equal energy on this van der Waal (VDW) surface. The maps shown here were constructed using 6400 equispaced surface points and contoured at 3 kcal/mol increments. The color code for transition from low to high electron density contours is red−orange−yellow−magenta−turquoise−blue−violet. The molecule is shown as a dark solid line, and the van der Waal surface is not outlined.

Results and Discussion

This method of obtaining molecular similarity has been applied to a class of polyanionic compounds which show promise as anti-HIV drugs. Many polyanionic sustances have shown antiviral activity, and in fact, the first drug to be used for patients with AIDS was suramin, a compound of this class which inhibits viral adsorption to the target cell. Clanton *et al.*[18] analyzed over 50 commercially available sulfonic acid containing dyes for the ability to prevent HIV-1-induced T4 cell killing and inhibition of HIV-1 replication. Chicago Sky Blue (**4**, CSB) proved highly effective and appeared to disrupt the interaction between viral proteins and cell membranes, both in the fusion step and the development of syncytia. The mechanism of action of the sulfonated dye Evans Blue (EB) has been reported to be due to inhibition of binding of gp120 to CD4 receptors.[19]

We, therefore, decided to synthesize azo dyes modeled after CSB and EB in order to determine the structural

requirements for optimum binding inhibition. However, since azobenzidine compuonds such as CSB and EB may be expected to metabolize to carcinogenic amines *in vivo*, we decided to replace the center biphenyl moiety by the vinylogous stilbene group.



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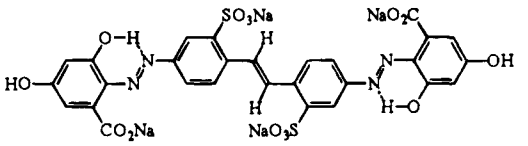

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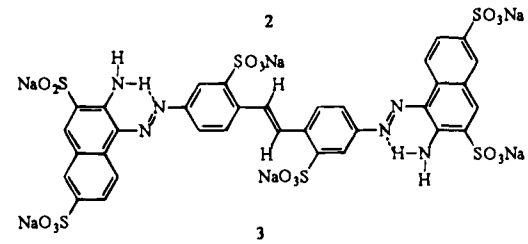

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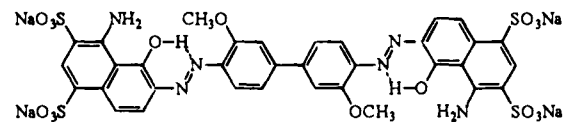

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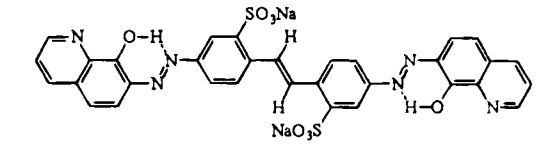

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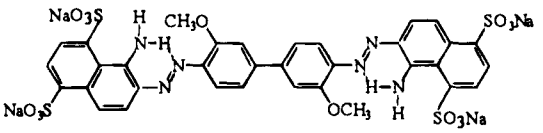

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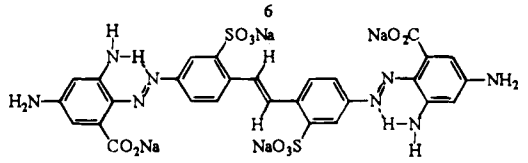

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Over 60 stilbene-linked azo compounds were synthesized and screened by the NCI. Only five congeners had an $EC_{50} < 10\ \mu M$ and two, quinobene (**1**)[20] and resobene (**2**), had activities in the therapeutically useful range. These two active compounds had a common central stilbene unit but what would appear to be quite different terminal groups, a 3,5-dihydroxybenzoic acid vs a 8-hydroxyquinoline-5-sulfonic acid moiety. We have determined the similarity index (SI) for the five most active $EC_{50} < 10\ \mu M$) drugs (**1**–**5**) and some with moderate activity. Using quinobene as the reference compound, the results are displayed in Table 1, and, as can be seen, an excellent correlation of activity of the most potent

Table 1. Similarity Index (SI) for Some HIV-Active Azo Compounds

structure	EC_{50} (μM)	SI
1 (quinobene)	1.3	0.00
2 (resobene)	1.4	0.16
3	2.9	0.31
4 (Chicago Sky Blue)	4.8	0.40
5	6.4	0.45
6	13.8	0.50
7	31.0	0.69

drugs and SI exists. Determination of the SI for compounds (not shown) with $EC_{50} > 30\ \mu M$ were scattered in the range 0.7–0.8, and thus this SI procedure is most accurate with drugs that have activity close to the reference compound.

The exact mechanism of by which these azo compounds inhibit HIV replication or protection of CD4-expressing cells is unknown. However, some generalizations are possible. Domain 1 (D1) and 2 (D2) of a recombinant fragment of the CD4 glycoprotein have been crystallographically resolved to 2.3 Å.[21] The binding site for HIV-1 virus has been detaied using the viral gp120 affinity for many mutant CD4 recombinants.[22] These mutant proteins have also been used to map the binding site of a number of monoclonal antibodies. The surface of D1–D2 has many positive charged amino acids, the calculated[16b] surface potential is mostly positive at neutral pH, and polyanionic drugs should have a high affinity for CD4 D1–D2. D1 is most important for gp120 binding, and of the 98 residues within this domain only 19 have an effect on gp120 interaction without changing the global conformation of this domain. Of the 19 residues, 14 are in the span of 38–60. Some stilbenedisulfonate salts have been shown to be CD4 antagonists by binding to the same site as a anti-CD4 monoclonal antibody, OKT4a.[23] This antibody binding involves residues: Arg 58, Arg 59, Ser 60, and Gly 66. The adjacent arginines have a high fractional solvent accessibility (0.73 and 0.82, respectively), and it is tempting to suggest that these residues are the locus of the sulfonated stilbene salt binding. Arginine can form a specific network of hydrogen bonds to the related phosphate function which is a basis for recognizing specific RNA structures by the so called "arginine fork".[24] This fork can bind two bidentate anionic groups and, thus, two adjacent arginines may hydrogen bond to a total of four sulfonate anions provided the three-dimsional spacing of the high electron density regions are complementary to the arginine pair. Modeling studies indicate that two phosphate centers separated by ca. 7 Å may effectively hydrogen bond to the guanidinium function of the arginine side chain.[20] Many published studies indicate anti-HIV activity is a function of the spacial relationship of anionic centers. De Clercq first noted that the biphenylene bisazo dye, Evans Blue, containing two sodium 1-amino-8-hydroxy-2,4-naphthalenedisulfonate functions was active while the isomeric dye, Trypan Blue, with a 3,5-naphthalenedisulfonate unit was inactive.[25] Mohan has shown that bisamides constructed from 1-amino-8-hydroxy-3,6-naphthalenedisfulfonate units with various linear dicarboxylic acid had HIV activity that was a function of the number of chain atoms which spanned the two carboxamides.[26] The activity of a series of sulfated sterols isolated from marine invertebrates was dependent on the substitution pattern and the A/B ring junture stereochemistry.[27]

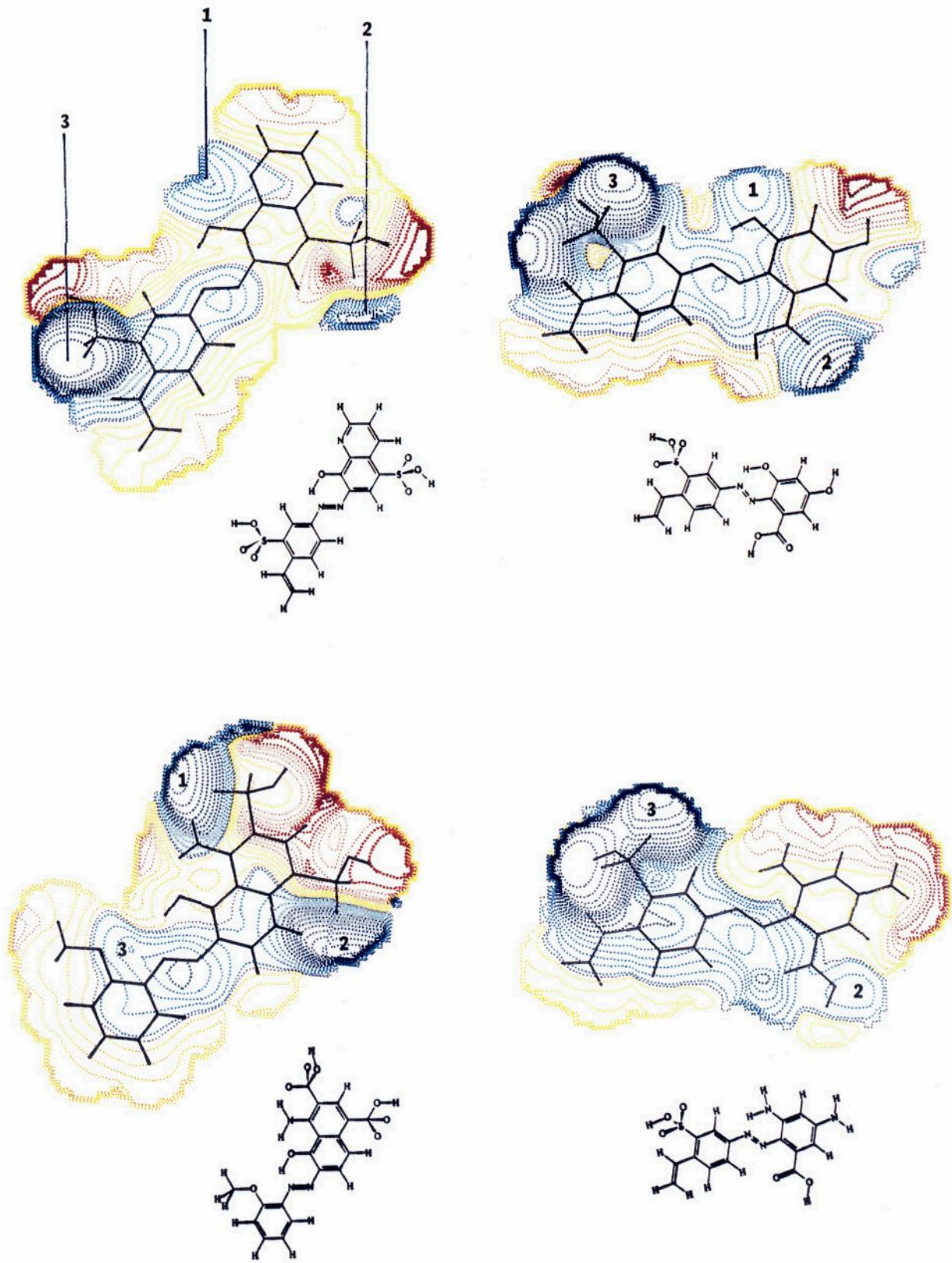

Figure 2. Van der Waal surface electrostatic maps for the half molecules representing compounds **1** (upper left), **2** (upper right), **4** (lower left), and **7** (lower right). The high electron density regions corresponding to the pharmacophore are labeled 1, 2, and 3. Compound **7** has no region 1. The structure shown below each map are keyed to the stick structure embedded in the map.

The present work illustrates the similarity procedure with azo compounds which in the case of 1, 2, 3, 5, and 7 have a common central bisazostilbene-*o,o'*-disulfonate linkage, yet the HIV activity varies over 1 order of magnitude. No sulfonate moiety exists in the terminal units of 2, 5, and 7, yet 2 ranks as one of the most active congeners in the series. The replacement of the two hydroxyl function of 2 to amino in 7 results in loss of activity. It may be concluded that in addition to sulfonate the location of anionic groups in other regions

are of importance in activity. The atomic multipole expansion may be used to locate the sites of high electron density in these polyanionic drugs in order to identify the pharmacophore responsible for the activity. Visual superposition of these van der Waal surface electrostatic maps for two drugs provides a qualitative estimate of their similarity. The low-energy conformation of these molecules was dominated by hydrogen bonding of the ortho hydroxyl or amino function to the distal nitrogen atom of the azo linkage. The maps for compounds **1**, **2**, **4**, and **7** are shown in Figure 2 (since the compounds have C_2 symmetry only the half molecule is shown). Inspection of these maps for the few active and a large number of inactive congeners revealed that the pharmacophore resides in six regions of space (numbered 1, 2, and 3 for the half molecule).

It is apparent that Chicago Sky Blue has a diminished region 3 in comparison to quinobene and resobene which may be responsible for the increased activity of the latter two congeners. Pharmacophore region 1 appears to be of great importance in comparing the almost equally active drugs, resobene and quinobene. In the case of resobene the high electron density region associated with the hydroxyl group ortho to the azo linkage is enhanced by the latter's nonbonding electron pairs, while in quinobene this argumentation of hydroxyl electron density is due to the quinoline nitrogen nonbonding electron pair. Replacement of the hydroxyl groups in resobene with an amino function completely removes pharmacophore 1 as is evident from the map of the inactive compound **7**. Hydroxyl and amino groups are totally different in the atomic multipole electrostatics. The spacing of regions 1, 2, and 3 are in the order of 7−9 Å and compatible with the dimensions required of multiple hydrogen bonding to the arginines of the recombinant CD4 discussed above.

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