

## Appendix J

This particular modeling application (Macromodel<sup>®</sup> 5.0) is based upon a molecular mechanics approach in which a molecule is considered to be a collection of masses interacting with each other via harmonic forces (model of weights connected with springs). Electronic and nuclear motions are considered to be uncoupled from each other (Born-Oppenheimer approximation) and electrons are not explicitly included in the calculations. Thus, each type of bond and atom are characterized by a set of parameters-length, charge, stretching, volume, bending- determined experimentally or calculated using *ab initio* methods. The particular set of parameters (force field) utilized in this study is known as the AMBER\* force field<sup>i</sup>.

This force field describes the free energy of solvation ( $G_{sol}$ ) as the sum of a solvent-solvent cavity term ( $G_{cav}$ ), a solute-solvent van der Waals term ( $G_{vdW}$ ), and a solute-solvent electrostatic polarization term ( $G_{pol}$ ):

$$(1) \quad G_{sol} = G_{cav} + G_{vdW} + G_{pol}$$

Values for  $G_{cav}$  and  $G_{vdW}$  are related to the solvent-accessible surface area (SA) by<sup>ii</sup>:

$$(2) \quad G_{cav} + G_{vdW} = \sum \sigma_k SA_k$$

where  $SA_k$  is the total solvent-accessible surface area of atoms of type k and  $\sigma_k$  is an empirical atomic solvation parameter.

For  $G_{pol}$ , the total electrostatic free energy ( $G_{es}$ , kcal/mol) of a system is given below as the sum of Coulomb's law in a dielectric (term 1) and the Born equation (term 2).

$$(3) \quad G_{es} = 332 \sum_{i=1}^{n-1} \sum_{j=i+1}^n \frac{q_i q_j}{r_{ij} \epsilon} - 166 \left( 1 - \frac{1}{\epsilon} \right) \sum_i^n \frac{q_i^2}{\alpha_i}$$

where  $r$  = particle separation distance (Å)

$q$  = electron charge

$\alpha$  = Born radius (Å)

$\epsilon$  = dielectric constant of medium

Terms 1 and 2 can be expanded algebraically to account for the effect of the dielectric medium on the pairwise interactions of charged particles.

$$(4) \quad G_{es} = 332 \sum_{i=1}^{n-1} \sum_{j=i+1}^n \frac{q_i q_j}{r_{ij}} - 332 \left( 1 - \frac{1}{\epsilon} \right) \sum_{i=1}^{n-1} \sum_{j=i+1}^n \frac{q_i q_j}{r_{ij}} - 166 \left( 1 - \frac{1}{\epsilon} \right) \sum_i^n \frac{q_i^2}{\alpha_i}$$

The sum of terms 2 and 3 in equation (4) is equal to  $G_{pol}$  and has been termed the generalized Born (GB) equation<sup>iii</sup>. These two terms can be combined in view of classical electrostatics as:

$$(5) \quad G_{pol} = -166 \left( 1 - \frac{1}{\epsilon} \right) \sum_{i=1}^n \sum_{j=1}^n \frac{q_i q_j}{f_{GB}}$$

$$\begin{aligned} \text{where } f_{GB} &= (r_{ij}^2 + \alpha_{ij}^2 e^{-D})^{0.5} \\ \alpha_{ij} &= (\alpha_i \alpha_j)^{0.5} \\ D &= r_{ij}^2 / (2\alpha_{ij})^2 \end{aligned}$$

$G_{pol(i)}$  is evaluated numerically for each solute atom  $i$  within a continuum dielectric medium assuming that all other atoms are neutral and displace the dielectric. The total free energy of solvation ( $S_{ol}$ ) is evaluated for each arbitrary conformation to allow for minimization of the free energy of the entire solvent-solute system. Further details regarding this procedure have been eloquently described by Still *et al.*<sup>iv</sup>

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<sup>i</sup> S.J. Wiener, P.A. Coleman, D.T. Nguyen, and D.A. Case, *Journal of Computational Chemistry*, 7, 230 (1986).

<sup>ii</sup> R.B. Hermann, *Journal of Physical Chemistry*, 76, 2754 (1972).

<sup>iii</sup> R. Constanciel and R. Contreras, *Theoretical Chimica Acta*, 65, 1 (1984).

<sup>iv</sup> W.C. Still, A. Tempczyk, R.C. Hawley, and T. Henrickson, *Journal of the American Chemical Society*, 112, 6127 (1990).