The hydrogen-bonding cohesive energy contributions, $-U_{H,i}$, are also considered additive, and its component of the solubility parameter is estimated using:

$$\delta_H = \sqrt{\frac{\sum\left(-U_{H,i}\right)}{\bar{V}}} \tag{2.53}$$

Experimental results suggest that the hydrogen-bonding component is the most difficult to estimate by group contribution data (Barton, 1983). Nevertheless, the hydrogen-bonding component could be the most critical of the three components in determining solubility in water. Indeed, hydrogen-bonding potential has proved to be critical in recent computational chemistry approaches to prediction of drug solubility in water (Jorgensen and Duffy, 2002; Schaper et al., 2003; Raevsky et al., 2004) and of drug-excipient miscibility (Alhalaweh et al., 2014). By adding hydrogen bond donor strength to the computational model, the prediction of solubility in water improved substantially (Schaper et al., 2003; Raevsky et al., 2004).

The three-dimensional solubility parameters are substituted for the solubility parameters in Equation 2.42 to arrive at an expression describing the activity coefficient in these solutions:

$$\ln\gamma_2 = \frac{\bar{V}_2\phi_1^2}{RT}\left[\left(\delta_{D1}-\delta_{D2}\right)^2+\left(\delta_{P1}-\delta_{P2}\right)^2+\left(\delta_{H1}-\delta_{H2}\right)^2\right] \tag{2.54}$$

If this activity coefficient term is applied to Equation 2.43, the mole fraction solubility can be shown to reach a maximum when $\delta_{D1}$ equals $\delta_{D2}$, $\delta_{P1}$ equals $\delta_{P2}$, and $\delta_{H1}$ equals $\delta_{H2}$. Teas (1968) presented a triangular plot where the sides represent the three contributions to the solvent solubility parameter, $f_D$, $f_P$, and $f_H$, expressed as the percentage of the one-dimensional solubility parameter. For example, the dispersion force contribution would be:

$$f_D = 100\%\frac{\delta_D^2}{\delta_T^2} \tag{2.55}$$

and its value would be found on one side of the triangle. The other two sides would be the polar and the hydrogen-bonding contributions, and similar equations would define $f_P$ and $f_H$ as single values on those two triangle sides A solvent, then, would be represented by a single point in such a plot. From the solubility of testosterone propionate in various solvents, it was found that, in such a triangular plot, the maximum solubilities were in the vicinity of $f_D = 65$, $f_P = 20$, and $f_H = 15$ (James et al., 1976). Approximate component solubility parameters for testosterone propionate, suitable for solvent selection, were estimated using $\delta_T = 9.5\ \sqrt{\text{cal/cm}^3}$ and equations similar to rearranged Equation 2.55, such as:

$$\delta_D = \sqrt{f_D\frac{\delta_T^2}{100}} = \sqrt{65\frac{9.5^2}{100}} = 7.7\sqrt{\text{cal/cm}^3} \tag{2.56}$$

Similar calculations yield $\delta_P = 4.2$ and $\delta_H = 3.7\ \sqrt{\text{cal/cm}^3}$.

If the $\delta_D$, $\delta_P$, and $\delta_H$ values of two chemicals are each comparable in magnitude, those two chemicals will have high affinity for each other (Hansen, 2007). Similar $\delta_T$ values might not indicate this high affinity since $\delta_T$ is a mathematical combination of the three partial solubility parameters. The similarity of $\delta_T$ for ethanol and nitromethane has been noted, yet the two demonstrate markedly different physicochemical properties (Hansen, 1967). For example, ethanol is miscible with water; nitromethane is insoluble.