

ABSTRACT

Molecular modeling was employed to investigate correlations between calculated properties and thin layered chromatography (TLC) retention factors (Rf). The Rf's were measured experimentally; molecular dipole moments and Log P values were calculated using semi-empirical quantum mechanical calculations. It was found that neither property could predict the Rf value with high certainty; however, excluding hydroxy containing acids and esters did lead to good correlation coefficients with the dipole moments, $R^2 = 0.689$ and 0.692 , respectively. Log P values correlated poorly with or without hydroxy containing compounds. The use of AM1-SM2 solvation calculations did provide good correlations to Rf's with all carboxylic acid and esters compounds, $R^2 = 0.756$ and 0.655 , respectively. The AM1-SM2 calculations modeled both hydrogen bonding and non-hydrogen bonding compounds in relation to their TLC retention properties.

INTRODUCTION

Thin layer chromatography (TLC) is an important experimental technique for both qualitative monitoring of reactions, as well as purification of chemicals. Chromatography separation involves partitioning a molecule between a stationary, solid phase, and a mobile, liquid phase. With normal phase TLC, the stationary phase is composed of finely divided silicon oxide, SiO_2 , a polar substance. The polarity of the mobile phase is adjusted by using different combinations of solvents. The solvent's ability to move the compound off of the stationary phase, causing the compound to move up the plate via capillary action, is referred to as its eluting power. The eluting power of a solvent generally increases as the solvent becomes more polar. How far a compound will move up the TLC plate is a function of how well it will interact with the stationary phase versus how it will interact with the solvent phase. The competition between the two phases is measure by the R_f value, the distance a spot travels divided by the total distance the solvent travels via capillary action. If the compound (C, see Figure 1) has a greater affinity for the solid phase, it will travel less, and its R_f value will be small. If the compound has a strong affinity for the mobile liquid phase it will travel more and have a larger R_f . The more polar compounds tend to have smaller R_f values in normal phase TLC.

Molecular modeling can predict the geometry of a molecule in addition to numerous other physical properties. Some properties related to polarity that can be modeled are the dipole moment, and the interaction a molecule has with various solvents. The dipole moment is a function of both unequal electron distribution and molecular shape. The interaction with solvents can be modeled by calculation of the Log P values. The Log P value is a measure of a compound's preference to partition between water and octanol. A value larger than one indicates a preference for octanol, less than one indicates water if preferred. Thus the more polar a compound, the smaller Log P value for that compound.

The aim of this study is to determine which measure of polarity, a compound's dipole moment or its Log P value correlates better with experimental R_f values. Two classes of compounds were investigated, carboxylic acids and esters. Both groups varied by the presence of electron donating groups (EDG) and electron withdrawing groups (EWG) of various strength (see Figure 2).



METHODS

Compounds in Figure 2 were built using Spartan (Wavefunction, Inc.) and collated using the software's spreadsheet function. The geometry optimization was performed using the semi-empirical PM3 Hamiltonian. Using the PM3 geometries, a single point energy calculation at a higher level of theory, B3LYP/6-31+G*, was employed to obtain the dipole moment. The Log P values were calculated using the method of Villar¹ as implemented by the Spartan software. Solvation energies were calculated using the AM1-SM2 method developed by Cramer and Truhlar².

All compounds in Table 2 were commercially available from either Sigma Aldrich Co. or Acros Co. with exception of ethyl p-toluate. Ethyl p-toluate was made from toluic acid via Fischer esterification using absolute ethanol and H_2SO_4 as a catalyst (Figure 3). Briefly, 0.15 mol of toluic acid and 100 mL of absolute ethanol were refluxed for one hour in a 100 mL round bottom flask. Ethanol was removed via rotovap, and the resulting mixture taken into 200 mL of chloroform, washed 1X100 mL Na_2CO_3 , 1X100mL brine, and dried over $MgSO_4$. After evaporation of chloroform, the ester (colorless liquid) was used without further purification and identified via 1H and ^{13}C NMR (Figure 3).

TLC for compounds in Figure 2 were performed on aluminum backed Whatman 20 x 20 cm, 250 μ m normal phase TLC sheets. All 12 compounds could be administered to a single sheet. Carboxylic acids were developed in 70:30 hexane:ethyl acetate solvent mixture containing 0.5% acetic acid. Esters were developed in 80:20 hexane:ethyl acetate solvent mixture containing 0.5% acetic acid.

1) Kantola, Angelina; Villar, Hugo O.; Loew, Gilda H. Atom based parametrization for a conformationally dependent hydrophobic index. *Journal of Computational Chemistry* 1991, 12(6), 681-9.

2) Cramer C J; Truhlar D G AM1-SM2 and PM3-SM3 parameterized SCF solvation models for free energies in aqueous solution. *Journal of computer-aided molecular design* 1992, 6(6), 629-66.

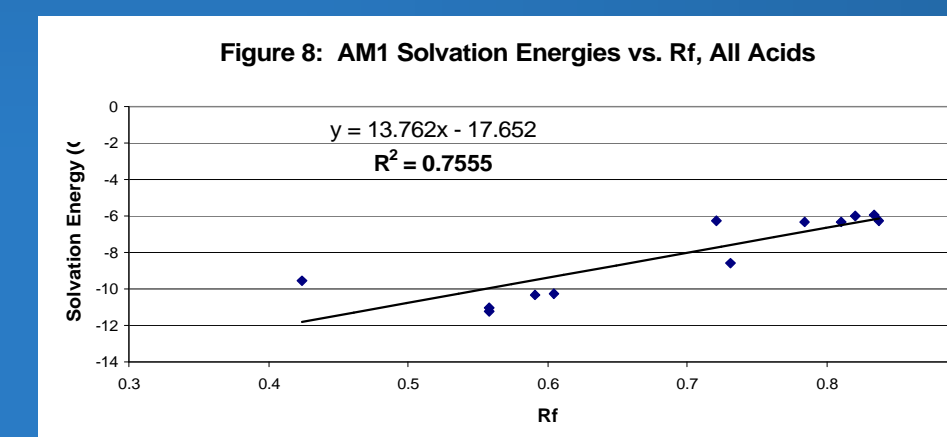
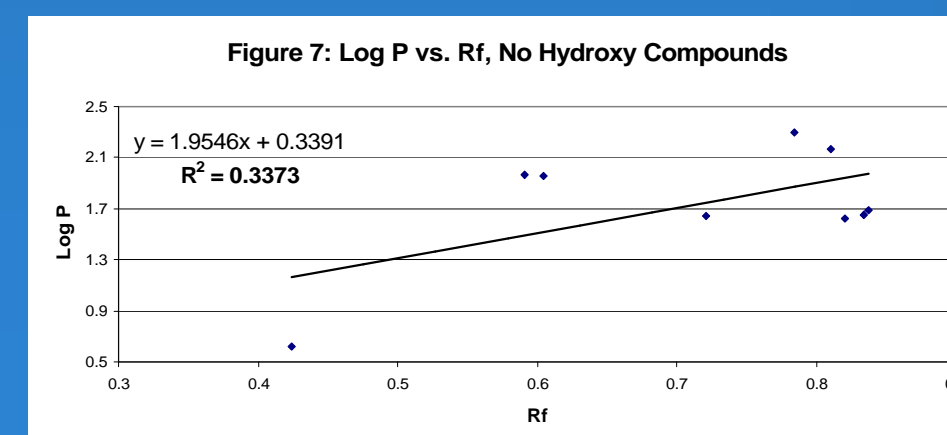
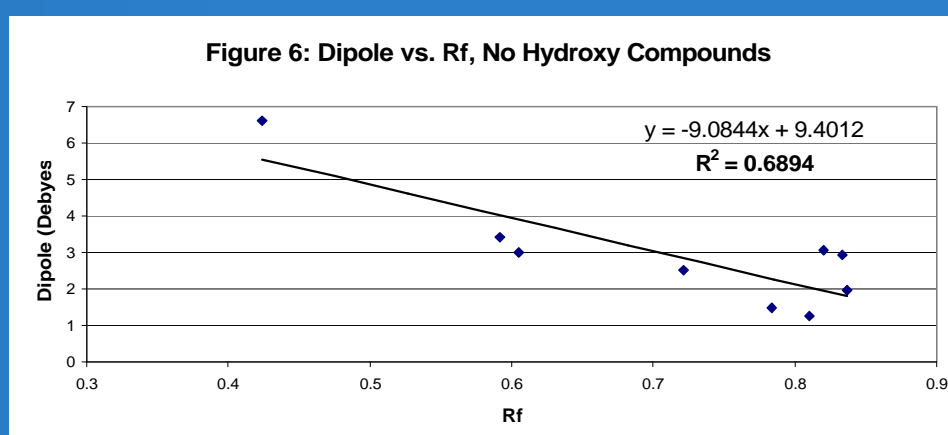
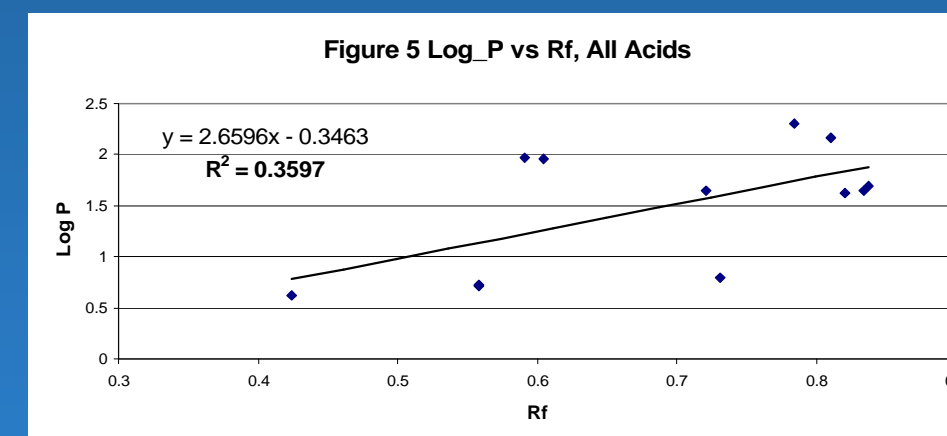
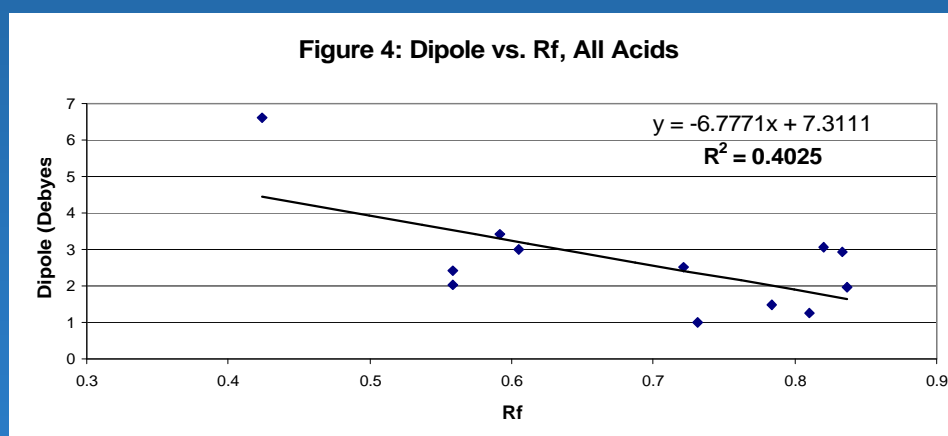
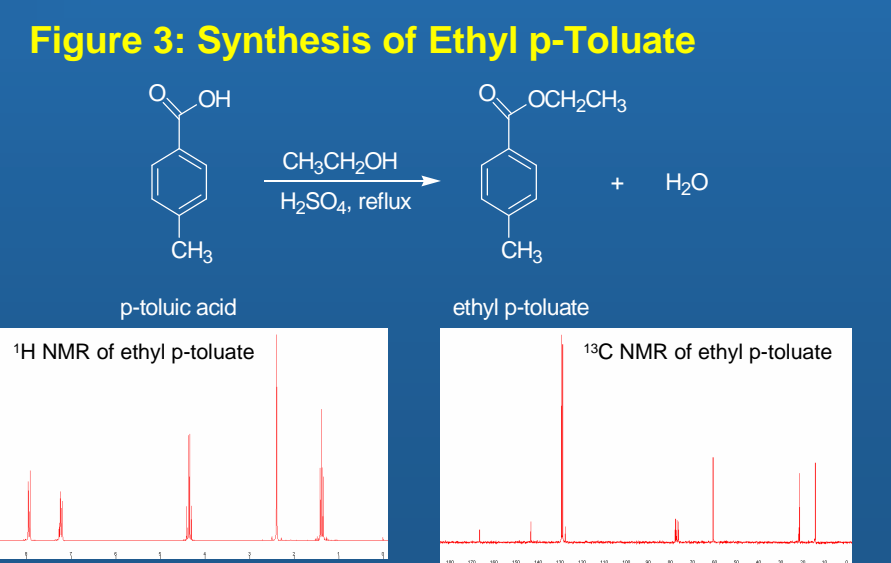
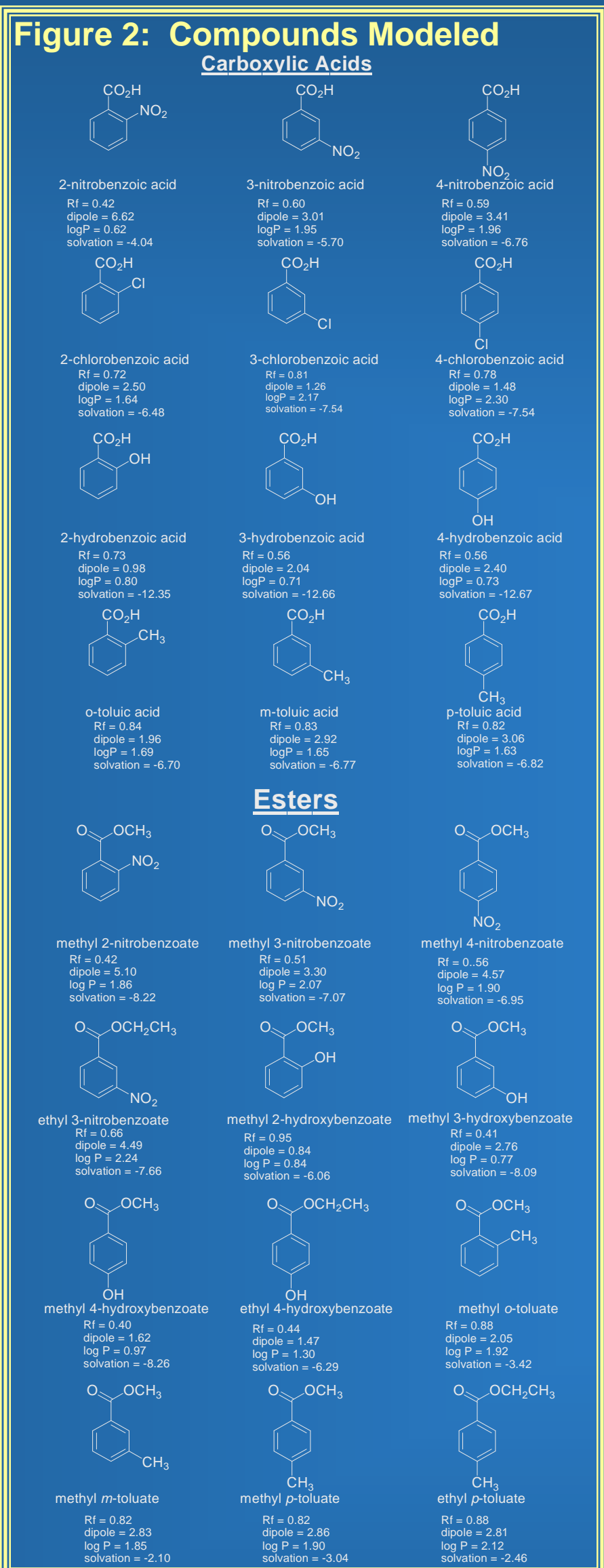


MOLECULAR MODELING AS A TOOL FOR PREDICTING THIN LAYER CHROMATOGRAPHY RETENTION FACTORS

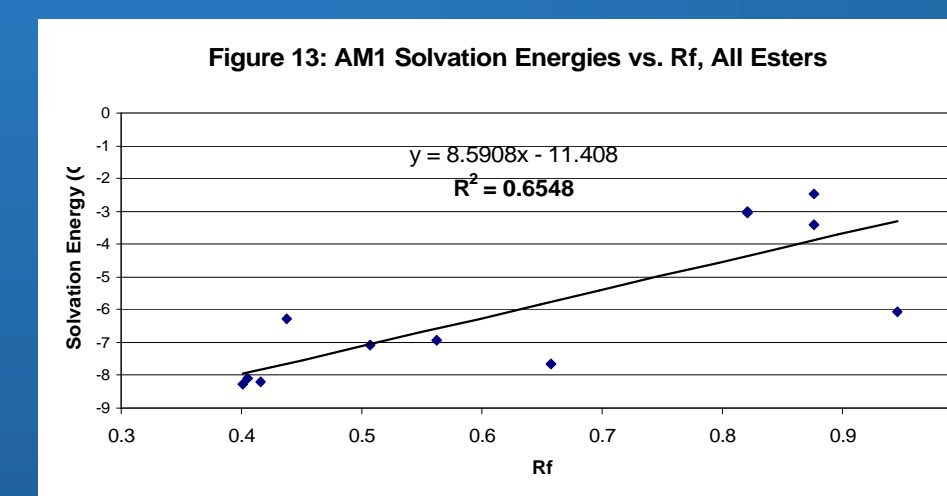
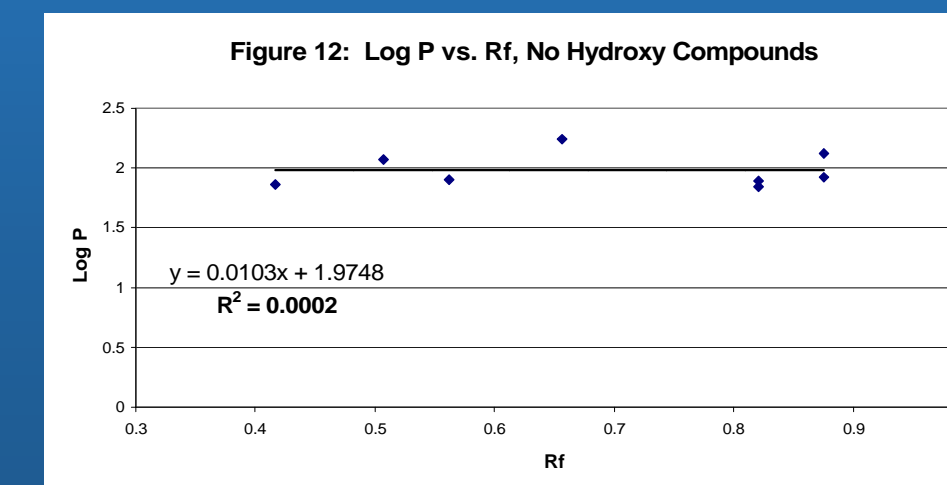
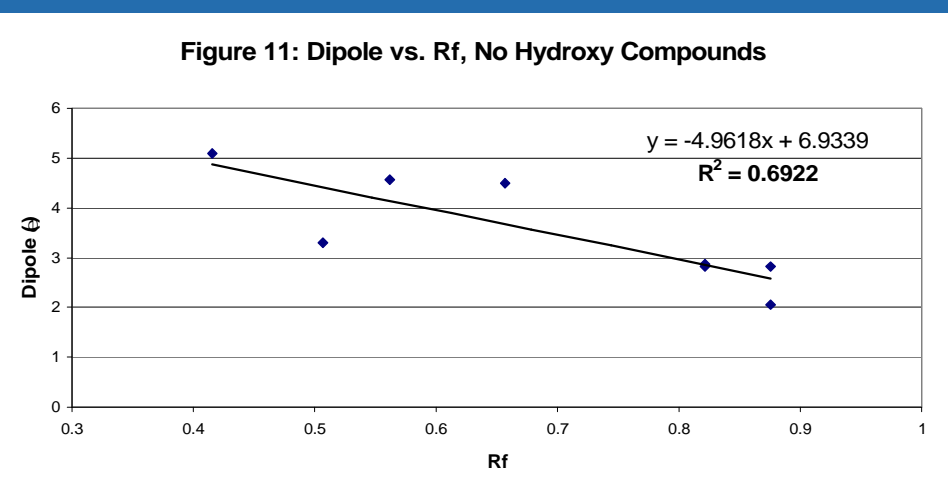
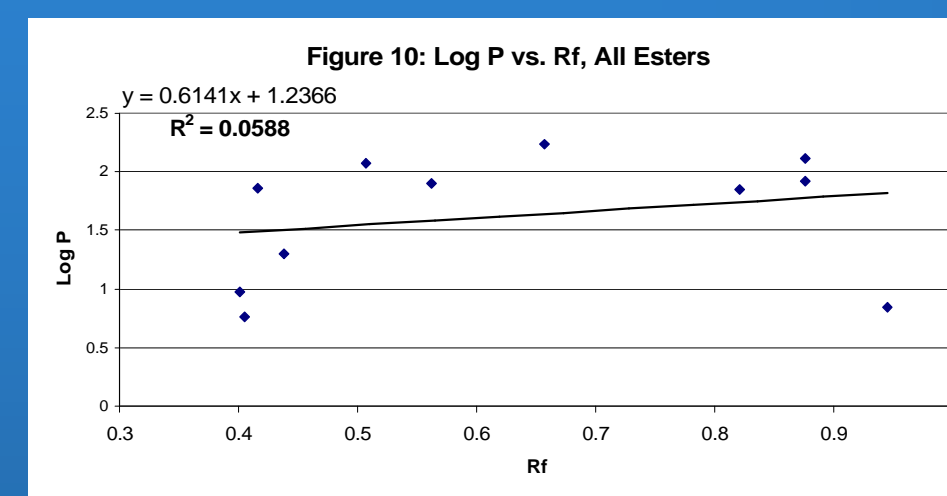
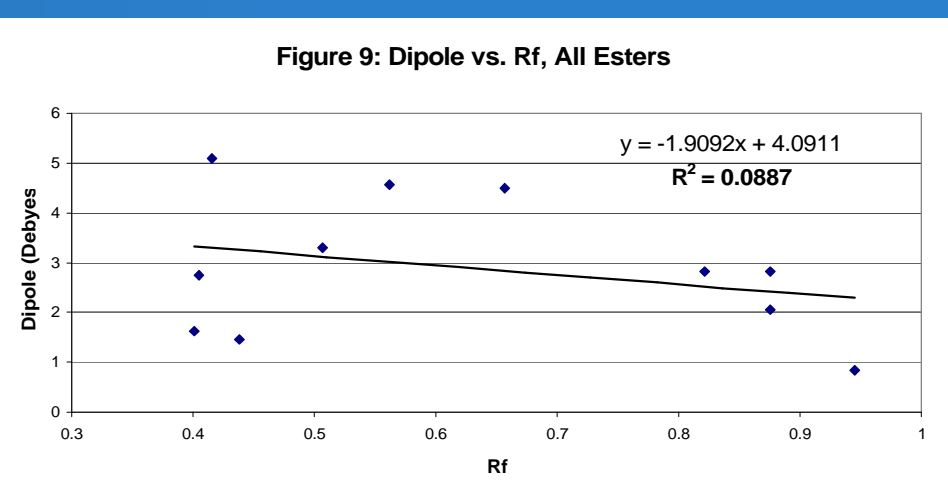


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Results: Carboxylic Acids



Results: Esters



RESULTS AND DISCUSSION

Figures 4 and 5 show the plot of dipole moment and Log P, respectively, as a function of Rf values for the modeled carboxylic acids. Neither graph shows a strong correlation between the dipole moment and TLC elution. When surveying the data, it appeared that the hydroxy containing carboxylic acids had low Rf values compared to the other acids. When excluding the hydroxy containing compounds the correlation coefficient increased from 0.402 to 0.684, Figure 6. However, excluding the same group from the Log P calculations did not improve the correlation coefficient, Figure 7.

Since TLC involves the interaction between two molecules, steric interactions as well as electronic interactions will contribute to the observed Rf value for a given compound. The hydroxy compounds, while having dipoles smaller than the nitro and toluic compounds, are capable of hydrogen bonding to the TLC stationary phase. Hydrogen bonding interactions are stronger than a dipole alone would predict since it involves the close approach of two dipoles due to hydrogen's small Van der Waals radius. Hence, a steric component in necessary when modeling the effects of hydrogen bonding. When the "abnormally" high affinity for hydroxy compounds to normal phase TLC plates was removed, the correlation to the Rf values improved substantially, Figures 4 and 6. The Log P calculation does include parameters that account for a compound's ability to hydrogen bond to both water and octanol (the two liquids used to establish a Log P). Thus, little change in the correlation coefficient is observed when removing the hydroxy compounds, Figures 5 and 7. The low correlation in both Figures 5 and 7 shows that the parameters used to emulate interaction with octanol and water are not appropriate in modeling TLC behavior (at least the those parameters used in Villar's method).

After the discovery that some account of steric interactions are important, we decided to model the AM1-SM2 solvation energies as a function of Rf. The AM1-SM2 method involves calculating the energy of displacing water molecules to form a solvation cavity, then adding to that energy the electrostatic interaction between the molecule and the solvent. The creation of the cavity is endergonic, but the following electrostatic interactions are exergonic for polar compounds. Since these calculations account for the Van der Waals radius of the compound, they can model both hydrogen bonding and non-hydrogen bonding compounds alike in their interaction with a polar medium. Thus, Figure 8 shows good correlation between the AM1-SM2 solvation energies and Rf values.

The esters showed the same behavior as the acids except initial correlation involving all compounds was poorer compared to the acids, Figures 9 and 10. Like the acids, removal of the hydroxy containing compounds improved the correlation coefficient for the dipole calculations (figure 11), but not the Log P

CONCLUSIONS

Log P values, as calculated by the Villar method, do not correlate well with TLC Rf values. Dipole moments do correlate well with Rf values if hydrogen bonding compounds are excluded. Solvation energies, as calculated by Cramer and Truhlar using the AM1-SM2 methods, correlate well with Rf values from carboxylic acids and esters containing both hydrogen bonding and non-hydrogen bonding groups.

ACKNOWLEDGEMENTS

Portions of this project were funded from an NSF STEP grant, NSF-0336462.