

## Equilibrium Reactions in Supercritical Difluoromethane

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A dielectrometry technique is used to follow the extent of two equilibrium reactions in supercritical difluoromethane (sc HFC32), and the validity of the technique is demonstrated in the liquid state and compared to results obtained using gas chromatography–mass spectroscopy (GC–MS). The apparent equilibrium constant for the acid-catalyzed esterification of benzoic acid with 1-butanol decreased as the pressure increased, and this was proposed to be due to clustering at lower solvent density. In supercritical carbon dioxide (sc CO<sub>2</sub>), the equilibrium constant was similar to that in sc HFC32, despite the large difference in the dielectric constant of the fluids. The solute had a significant effect on the solution dielectric constant, such that the two solutions were similar. An acid-catalyzed aldol condensation reaction was also studied, and the apparent equilibrium constant was observed to change in a manner similar to that observed for the esterification reaction. The overall change in equilibrium constant was less than that observed for the esterification reaction and this was rationalized, in terms of the different dipole moments of the reagents in the two reactions.

### Introduction

The recent growth in the use of supercritical (sc) fluid solvents as media for chemical synthesis<sup>1</sup> has inspired several research groups to examine chemical equilibria to probe intermolecular interactions in supercritical fluids. Solvents influence reaction thermodynamics through the environment produced around the solute. Among the most important solvent properties that characterize this reaction environment are the polarity and the polarizability. The solvent polarity corresponds to the permanent dipole–dipole interactions, whereas polarizability is indicative of inductive forces, where the solute molecule induces a dipole in the solvent. Thus, measuring pressure effects on equilibria in supercritical fluids can give insight into molecular interactions.

Kimura and co-workers<sup>2–4</sup> addressed the issue of how fluid structure influences chemical reactions by examining the effect of solvent density on the equilibrium constant for the dimerization of 2-methyl-2-nitrosopropane in CO<sub>2</sub>, CClF<sub>3</sub>, CHF<sub>3</sub>, argon, and xenon. The results showed that the equilibrium constant in CO<sub>2</sub>, CClF<sub>3</sub>, and CHF<sub>3</sub> increased as the density in the gas phase decreased in the low-density supercritical region and then increased again as the density was increased. It was suggested that these observations were due to the different dominant molecular interactions of the fluid within each of these density regions.

Chemical equilibria have also been related to hydrogen bonding in supercritical fluids. Gupta and co-workers<sup>5</sup> studied the hydrogen bonding between methanol and triethylamine in sc SF<sub>6</sub>, where a pronounced solvent effect was observed. The equilibrium for methanol–triethylamine association increased as the pressure decreased toward the critical point, with the pressure effect being most dominant around the critical point.

O'Shea et al.<sup>6</sup> probed the hydrogen bonding and polar interactions in sc ethane, fluoroform, and CO<sub>2</sub> by measuring the tautomeric equilibrium of 4-(phenylazo)-1-naphthol in these solvents. The less-polar tautomer was dominant in ethane, almost-equal amounts of the tautomers were observed in CO<sub>2</sub>, and in fluoroform, the more-polar tautomer was observed to be dominant. These shifts in equilibrium composition favoring the more-polar tautomer were attributed to the large quadrupole moment of CO<sub>2</sub> and hydrogen-bond donor ability of fluoroform. From these results, it is suggested that pressure can be used to control processes that involve polar molecules in some supercritical fluids.

Studies in the literature on aldol and esterification reactions in supercritical fluids are very limited. Ikariya and co-workers reported the catalytic asymmetric Mukaiyama aldol reaction of a ketene silyl acetal of thioester in sc CHF<sub>3</sub> and CO<sub>2</sub>.<sup>7</sup> The reaction proceeded to give the silylated aldol product in moderate yields. The yield and enantioselectivity of the reaction were influenced by the solvent used. A maximum in enantioselectivity and yield of 88% and 46%, respectively, was observed for the reaction in sc CHF<sub>3</sub>. On comparison with CO<sub>2</sub>, the reaction proceeded only slightly to give 8% of the aldol product and also a reduced enantioselectivity of 72%. The low yield in sc CO<sub>2</sub> was reported to be due to its low polarity, which results in low solubility of the acid catalyst in this medium.

Ellington and co-workers<sup>8,9</sup> used UV–Vis spectroscopy to find the apparent bimolecular rate constant for the esterification of phthalic anhydride with methanol in sc CO<sub>2</sub> at temperatures of 313 and 323 K and pressures of 97.5–166.5 bar. This reaction was chosen as a representative reaction between a dilute solute (phthalic anhydride) and a typical co-solvent (methanol) in sc CO<sub>2</sub>. At 313 K, the calculated bimolecular rate constants exhibited a 4-fold increase with a decrease in pressure, from 145.8 bar to 97.5 bar. At 323 K, a 25-fold increase in the rate constant was observed when the pressure was decreased from 166.5 bar to 97.5 bar. The enhanced reaction rate constants at lower pressures were attributed to the local concentration of

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methanol around the phthalic anhydride molecules exceeding the average bulk methanol concentration. Using estimated local densities and local compositions, it was shown that the observed increase in rate constant could be accounted for.

The esterification of acetic acid and ethanol in compressed CO<sub>2</sub> was studied at 333 K over a range of pressures<sup>10</sup> and found to reach equilibrium in 3 h under supercritical conditions and in 6 h under subcritical conditions. Results showed that the apparent equilibrium constant ( $K_X$ ) increased as the pressure increased in the gas phase and reached a maximum in the critical region where the system becomes one phase. After the critical point was passed,  $K_X$  decreased as the pressure increased. The observed increase in  $K_X$  at low pressures was explained, with respect to the degree of clustering/local density enhancement at these pressures. At high pressures, where clustering is insignificant,  $K_X$  for the reaction was similar to that of the reaction in the absence of CO<sub>2</sub>.

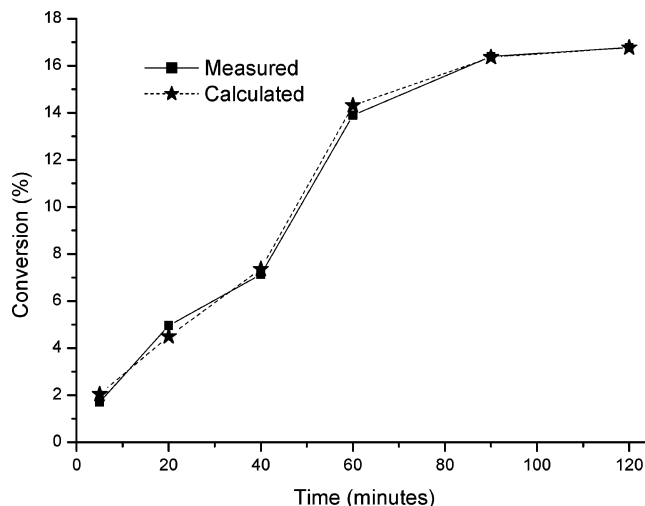
In the present study, we report the first equilibrium reactions in supercritical difluoromethane (sc HFC32) (critical temperature of  $T_c = 78.1$  °C; critical pressure of  $p_c = 57.8$  bar). This solvent has previously been shown to be useful, because of its high dielectric constant<sup>11</sup> and large polarizability change with pressure.<sup>12,13</sup> A recent study has also shown that HFC 32 is a strong hydrogen-bond donor close to the critical pressure<sup>14</sup> and has demonstrated high solubility for polar aromatic solutes.<sup>15</sup>

## Experimental Procedure

The high-pressure apparatus used in this study was the same as that described previously.<sup>15</sup> HFC 32 (Ineos Fluor, 99.99%) and CO<sub>2</sub> (BOC, 99.9%) were used as received. The esterification of benzoic acid (Scientific and Chemical Supplies, Ltd., 98%) with 1-butanol (Fisher, 98%), using *p*-toluenesulfonic (*p*-Tos) acid as the catalyst, was performed using reagent concentrations of 0.04 mol dm<sup>-3</sup>. The acid-catalyzed aldol condensation of cyclohexanone (Aldrich, 98%) was performed using *p*-Tos acid as the catalyst. All experiments were conducted at 363 K and in the pressure range of 60–220 bar. The reactants were placed into the doser and the acid catalyst was placed in the reaction vessel. This was then heated to the desired temperature and subsequently pressurized, forcing the reactants from the doser into the reaction vessel. The total time taken for the vessel to reach the reaction pressure was <1 min. The system was left to react for the desired time and where applicable capacitance measurements were taken. The products were trapped by depressurization into a larger volume autoclave, which also stopped the reaction and the products were analyzed by gas chromatography–mass spectroscopy (GC–MS) (Perkin–Elmer).

## Results and Discussion

**Esterification Reaction.** It has previously been shown that a dielectrometry technique can be used to determine the solubility of solutes in supercritical fluids.<sup>15</sup> Therefore, it is logical that the same technique can be used to follow the changes in solution concentration during a reaction, because it is a rapid, in situ method for measuring capacitance changes of reaction systems. Dielectrometry is not affected by solution concentration, high pressure, and turbidity restraints that are present with spectroscopic techniques. However, note that there are some limitations: (i) it can only be used with reagents that are readily soluble, because accurate capacitance measurements can only be obtained in homogeneous solutions, and (ii) a large difference in dielectric constant between the reactants and products is necessary, so that product formation produces a change in the



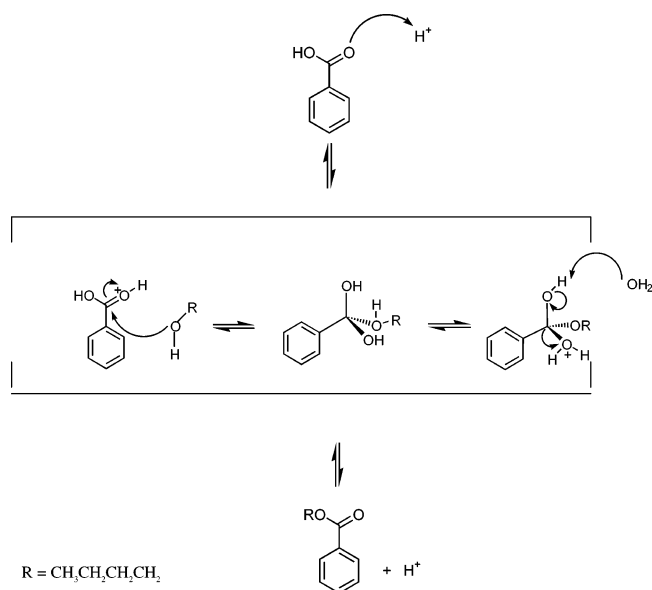
**Figure 1.** Comparison of measured and calculated conversion for the esterification reaction.

capacitance of the solution. For this to occur, the products also must remain in solution as the reaction proceeds.

With these limitations in mind, the esterification reagents used were benzoic acid, 1-butanol, and *p*-Tos acid as the catalyst. Benzoic acid was observed to have a high solubility in sc HFC 32 (at 363 K and 100 bar, the solubility was 0.542 mol dm<sup>-3</sup>), which is considerably in excess of the concentrations used in these experiments (0.04 mol dm<sup>-3</sup>). The 1-butanol and *p*-Tos acid were readily soluble in the solvents under the reaction conditions.

The dielectrometry technique was used to monitor the solution concentration of reagents in liquid dichloroethane (DCE), because of its similar dielectric properties to HFC 32 (for DCE,  $\epsilon = 10.37$  at 278 K; for HFC 32,  $\epsilon = 8.99$  at 363 K and 200 bar). The results were compared to those obtained using GC–MS. The reaction was followed over a 2-h period, using dielectrometry and GC–MS. Dielectrometry measurements were measured in situ, and for the GC–MS measurements, 2-mL aliquots of the reaction solution were taken. The actual reaction conversion was obtained from the GC–MS results at specific time intervals. The conversion value from the dielectrometry measurements was calculated from knowledge of the final conversion of the reaction, from GC–MS, and the capacitance value at each time interval. The measured (GC–MS) and calculated (dielectrometry) conversions for this esterification reaction are shown in Figure 1. This figure shows that the dielectrometry readings correlate well with those from GC–MS, signifying that the dielectrometry technique is suitable for following the progress of this reaction.

The esterification reaction was then performed in sc HFC 32 as the reaction solvent. It is assumed that this esterification reaction follows the mechanism shown in Scheme 1. Using an optical cell, it was visually observed that the reaction was homogeneous under all conditions studied in this work. The dielectrometry technique was used to follow the progress of the benzoic acid esterification reaction as a function of time, and the results are shown in Figure 2 at selected pressures. The uncertainty of the conversion is no greater than  $\pm 2\%$ . Figure 2 shows that this dielectrometry technique is useful for following equilibrium reactions, because the point at which the reaction reaches equilibrium can be easily observed. This figure shows that the reaction has reached equilibrium in 2 h or less, under the conditions studied. The reaction was performed for up to 6 h without any appreciable change in yield. Therefore, in the

**SCHEME 1. The Mechanism for Esterification between Benzoic Acid and 1-Butanol**


rest of this work, a reaction time of 2 h was used to ensure that the system had reached equilibrium.

In a supercritical fluid, the pressure of the system affects the activity of reactants and products; therefore, the equilibrium constant should be expressed in terms of mole fraction instead of concentration, giving

$$K = \frac{\gamma_C X_C \gamma_D X_D}{\gamma_A X_A \gamma_B X_B} \quad (1)$$

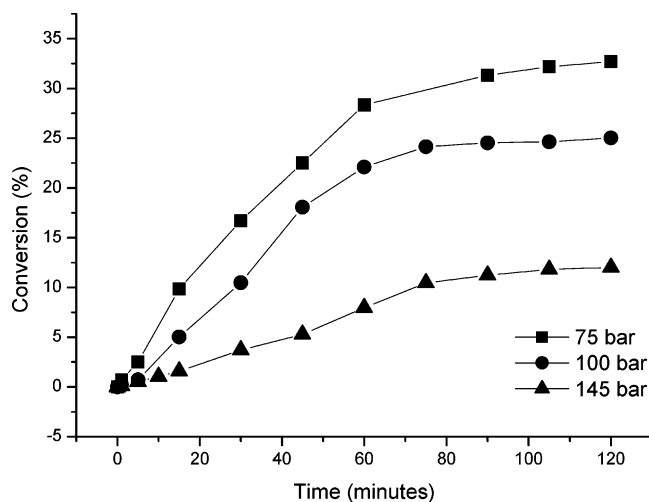
and

$$K_\gamma = \frac{\gamma_C \gamma_D}{\gamma_A \gamma_B} \quad (2)$$

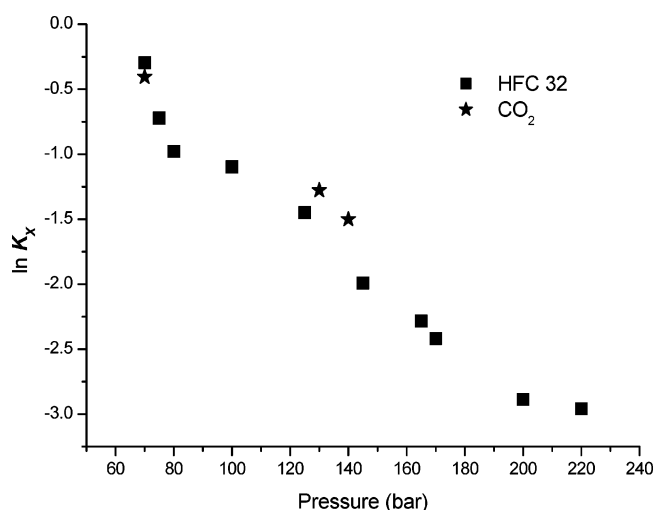
$$K_X = \frac{X_C X_D}{X_A X_B} \quad (3)$$

where  $X_A$ ,  $X_B$ ,  $X_C$ , and  $X_D$  are the mole fractions of species A, B, C, and D under equilibrium conditions, respectively.  $K_X$  is the apparent equilibrium constant, and  $\gamma_A$ ,  $\gamma_B$ ,  $\gamma_C$ , and  $\gamma_D$  are the respective activity coefficients of species A, B, C, and D.

Unfortunately, there is negligible data on activity coefficients in supercritical fluids; hence, only  $K_X$  values can be discussed. Figure 3 shows the variation of  $K_X$  with pressure for the esterification of benzoic acid with 1-butanol.  $K_X$  increases as the pressure decreases, in agreement with the results for esterification reactions by Ellington et al.<sup>8</sup> and Hou et al.<sup>10</sup> A 14-fold decrease in the apparent equilibrium constant is observed when the pressure is increased from 70 bar to 220 bar. The increase in the  $K_X$  value with decreasing pressure signifies that  $K_\gamma$  must be decreasing, because the equilibrium constant ( $K$ ) should be independent of pressure, because the process is performed at constant volume.<sup>16</sup> It can be argued that, at 220 bar, where the solvent-to-solute ratio is ca. 400, the solution solute–solute interactions will be negligible and it can therefore be assumed that  $K_\gamma = 1$  and  $K_X = K$ . Such an assumption could be made for any system where the solutes have a relatively small dipole moment. Making this assumption, values of  $K_\gamma$  can be calculated as a function of pressure. At high pressures, the solvation sheath around the solute will be full and solute–solute



**Figure 2.** Ester conversion with time for a variety of pressures in difluoromethane (HFC 32) at 363 K.



**Figure 3.** Change in  $\ln K_X$  with pressure for the benzoic acid esterification reaction at 363 K.

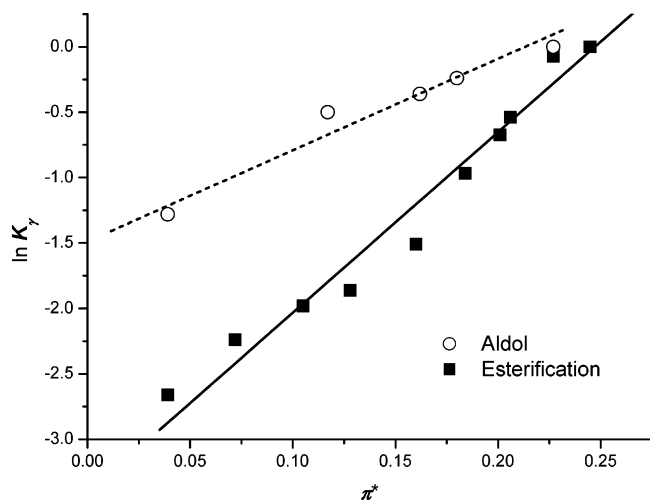
interactions will be negligible, because of the high polarizability of the cybotactic region. At lower pressures, where the solvation sheath may be incomplete, solute–solute interactions will increase and the activity coefficients of the solutes will decrease. By definition,<sup>16</sup>

$$\Delta G = \Delta G^\circ + RT \ln x + RT \ln \gamma \quad (4)$$

and it has been shown that<sup>17</sup>

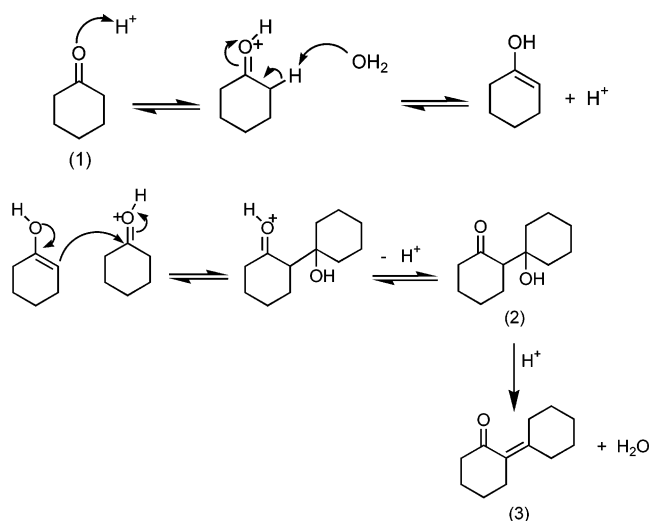
$$\Delta G = \Delta G^\circ + s\pi^* \quad (5)$$

where  $\pi^*$  is the dipolarity/polarizability parameter from the theory of Kamlet and Taft<sup>18</sup> and  $s$  is a susceptibility constant. Therefore, it is logical that the change in  $\ln K_\gamma$  should be related to  $\pi^*$ . Figure 4 shows that the data from Figure 3 for the esterification reaction correlates well with the  $\pi^*$  data published previously.<sup>14</sup> This esterification reaction was also performed in conventional liquid solvents for comparison. The apparent equilibrium constant for this reaction in DCE at 363 K was calculated to be 0.201, which is similar to the  $K_X$  values in HFC 32 at moderate pressures ( $K_X = 0.23$  at 125 bar), where local composition enhancement is less important. The reaction was also performed in cyclohexane (cHex), which has a much lower dielectric constant than DCE or HFC 32 (for cHex,  $\epsilon = 2.02$  at



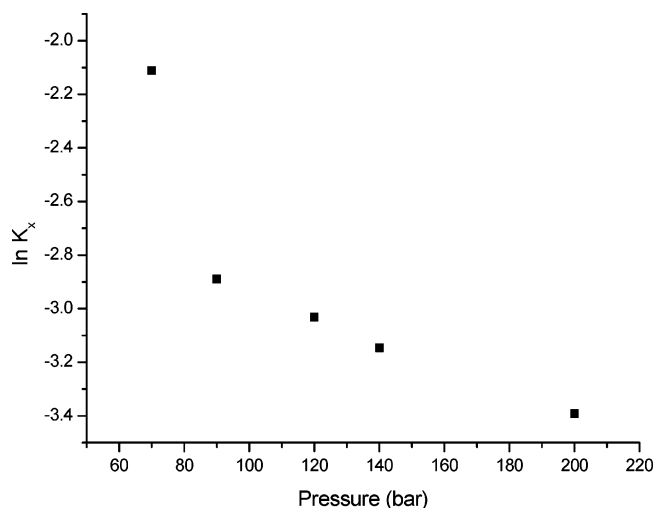
**Figure 4.** Change in  $K_\gamma$  with solvent polarizability ( $\pi^*$ ) for the esterification and aldol reactions.

#### SCHEME 2. The Mechanism for the Acid-Catalyzed Aldol Reaction of Cyclohexanone



273 K). However, the  $K_X$  value was calculated to be 0.192, which is very similar to that in DCE.

To assess whether the dielectric constant of the solution has this effect in a supercritical fluid, the esterification reaction was performed in sc  $\text{CO}_2$  at 363 K (for  $\text{CO}_2$ ,  $\epsilon = 1.2$  at 363 K and 200 bar). Results obtained for  $K_X$  are shown in Figure 3, and it can be seen that the  $K_X$  values are similar to those for HFC 32. This is a remarkable observation, considering the vast differences in dielectric constant between the two solvents. In the low-dielectric media such as cHex and sc  $\text{CO}_2$ , it is surprising that the reaction progresses at all, because the dissociation of the acid catalyst should be negligible. This suggests that either the catalyst activity is not a factor that affects the reaction rate or the reagents affect the dielectric properties of the solution sufficiently to allow dissociation of the acid. The starting dielectric constant of the solution containing all the reagents in  $\text{CO}_2$  was 5.0, which is much higher than the dielectric constant for the pure solvent ( $\epsilon < 2$ ), and significantly, it is not much lower than the value measured for the solution in HFC32, which was 5.48 (at 90 °C and 170 bar), showing that the latter explanation is the cause of the apparent anomalous behavior. Thus, although the reagents are present in a small concentration (1 mol %), they have a marked effect on the dielectric constant of the solution. Hence, it can be seen that the reagents



**Figure 5.** Change in  $\ln K_X$  with pressure for the aldol condensation reaction of cyclohexanone in HFC 32 at 363 K.

themselves have a significant effect on the extent of a reaction negating, to some degree, the effect of the solvent.

**Aldol Condensation Reaction.** In an aldol reaction, it is the  $\alpha$ -carbon of an aldehyde or ketone molecule that adds to the carbonyl carbon of another molecule of the aldehyde or ketone. Base-catalyzed aldol reactions are most common, but acid-catalyzed reactions are known.<sup>19,20</sup> Under acidic conditions, the alcohol almost always undergoes acid-catalyzed dehydration to yield the  $\alpha,\beta$ -unsaturated ketone. Scheme 2 shows the mechanism of the acid-catalyzed reaction of the ketone, cyclohexanone (compound 1), which is used in this work.

Cyclohexanone was chosen because it is a liquid that readily dissolves into solution, which allows the reaction to be followed by dielectrometry, and *p*-Tos acid was once again used as the acid catalyst. Analysis of the product showed that the dehydration product (compound 3 in Scheme 2), rather than the aldol dimerization product (compound 2 in Scheme 2), was isolated. Analogous to the esterification reaction, the dielectrometry technique was observed to give a large change in dielectric constant accompanying the formation of products. Initial experiments followed conversion, as a function of time, and this reaction was observed to reach equilibrium in <2 h.

Figure 5 shows the apparent equilibrium constants for this reaction as a function of pressure. The  $K_X$  values shown in Figure 5 follow the same trend that was observed with the esterification reaction described previously, where  $K_X$  increases as pressure decreases. A sharp increase in  $K_X$  can be seen as the pressure decreases toward the critical pressure  $p_c$ . The arguments applied to the esterification reaction also apply to the results observed here for the aldol reaction, where the increased value of  $K_X$  at low pressures is thought to be due to local composition enhancements.

The change in apparent equilibrium constant with pressure for the aldol reaction is less than that observed for the esterification reaction, showing only a 4-fold increase when decreasing the pressure from 200 bar to 70 bar (cf. the 14-fold change previously discussed). At higher pressures, note that both the esterification and aldol reactions have similar  $K_X$  values; therefore, the main factor in causing only a 4-fold change in rate is due to the much lower  $K_X$  values observed for the aldol reaction at low pressures. Using the same assumption about the ideality of the solution as discussed previously, Figure 4 shows the change in  $\ln K_\gamma$  with  $\pi^*$  for the aldol reaction, and, again, a linear relationship is observed. The decrease in  $K_\gamma$  with  $\pi^*$  is



less pronounced than that for the esterification reaction. The dipole moment of cyclohexanone ( $\mu = 2.97$  D)<sup>21</sup> is larger than that for the aldol product ( $\mu = 2.75$  D) or water ( $\mu = 1.86$  D). Because

$$K_\gamma = \frac{\gamma_{\text{aldol}}\gamma_{\text{water}}}{(\gamma_{\text{ketone}})^2} \quad (6)$$

then the dipole–dipole interactions will increase and the activity coefficients for all of the species will decrease as the polarizability of the supercritical solution decreases. The same is true for the previously mentioned esterification reaction; however, in this case, the dipole moments of the reagents ( $\mu = 1.70$  D for butanol and  $\mu = 2.40$  D for benzoic acid) are similar to those of the products ( $\mu = 2.19$  D for butyl benzoate). Defining a dipole moment ratio for the reaction ( $K_\mu$ ) as

$$K_\mu = \frac{\mu_{\text{aldol}}\mu_{\text{water}}}{(\mu_{\text{ketone}})^2} \quad (7)$$

a value of 1.00 is obtained for the esterification reaction whereas the value for the aldol reaction is 0.58. To account for the trends observed in Figure 4, the decrease in the denominator in eq 7 with solvent polarizability must be proportionately larger than that for the corresponding expression for the esterification reaction (hence,  $K_\gamma$  does not decrease to the same extent with the more-polar reagents). In the absence of any activity coefficient data, this is difficult to quantify; however, interestingly, the ratio of the  $K_\mu$  values for the two reactions (0.58) is very similar to the ratio of the two slopes in Figure 4 (0.52), showing that the change in apparent equilibrium constant with pressure is dependent on the dipolar properties of the reagents. Hence, solute dipolar interactions seem to affect the position of equilibrium, and this observation is consistent with the assumptions made previously<sup>8,10</sup> for similar reactions in supercritical solutions.

## Conclusions

The first examples of an esterification and aldol condensation reaction in supercritical difluoromethane (sc HFC 32) are presented here. Using these reactions as examples, the successful application of the in situ dielectrometry technique to follow equilibrium reactions was demonstrated. The advantages and disadvantages of applying this technique to follow reactions were discussed; however, it could be seen that when this

technique can be applied, it is a quick and simple method. Equilibrium constants were calculated for both reactions, as a function of pressure, and the apparent equilibrium constants decreased as the pressure increased. The enhanced equilibrium constants observed at low pressure were thought to be due to local composition enhancements. The lower observed apparent equilibrium constants for the aldol reaction, compared to those for the esterification reaction, are explained in terms of dipolar interactions.

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## References and Notes

- (1) Jessop, P. G.; Leitner, W. *Chemical Synthesis Using Supercritical Fluids*; Wiley-VCH: Weinheim, Germany, 1999.
- (2) Kimura, Y.; Yoshimura, Y.; Nakahara, M. *J. Chem. Phys.* **1989**, *90*, 5679.
- (3) Kimura, Y.; Yoshimura, Y. *J. Chem. Phys.* **1992**, *96*, 3085.
- (4) Kimura, Y.; Yoshimura, Y. *J. Chem. Phys.* **1992**, *96*, 3824.
- (5) Gupta, R. B.; Combes, J. R.; Johnston, K. P. *J. Phys. Chem.* **1993**, *97*, 707.
- (6) O'Shea, K.; Kirmse, K. M.; Fox, M. A.; Johnston, K. P. *J. Phys. Chem.* **1991**, *95*, 7863.
- (7) Mikami, K.; Matsukawa, S.; Kayaki, Y.; Ikariya, T. *Tetrahedron Lett.* **2000**, *41*, 1931.
- (8) Ellington, J. B.; Park, K. M.; Brennecke, J. F. *Ind. Eng. Chem. Res.* **1994**, *33*, 965.
- (9) Ellington, J. B.; Brennecke, J. F. *J. Chem. Soc., Chem. Commun.* **1993**, 1094.
- (10) Hou, Z.; Han, B.; Zhang, X.; Zhang, H.; Liu, Z. *J. Phys. Chem. B* **2001**, *105*, 4510.
- (11) Abbott, A. P.; Eardley, C. A.; Tooth, R. J. *J. Chem. Eng. Data* **1999**, *44*, 112.
- (12) Abbott, A. P.; Eardley, C. A. *J. Phys. Chem. B* **1998**, *102*, 8574.
- (13) Abbott, A. P.; Eardley, C. A. *J. Phys. Chem. B* **1999**, *103*, 2504.
- (14) Abbott, A. P.; Corr, S.; Durling, N. E.; Hope, E. G. *J. Phys. Chem. B* **2003**, *107*, 10628.
- (15) Abbott, A. P.; Corr, S.; Durling, N. E.; Hope, E. G. *J. Chem. Eng. Data* **2002**, *47*, 900.
- (16) Atkins, P.; de Paula, J. *Physical Chemistry*, 7th ed.; Oxford University Press: New York, 2002.
- (17) Taft, R. W.; Abraham, M. H.; Doherty, R. M.; Kamlet, M. J. *J. Am. Chem. Soc.* **1985**, *107*, 3105.
- (18) Kamlet, M. J.; Abboud, J.-L. M.; Taft, R. W. *J. Am. Chem. Soc.* **1977**, *99*, 6027.
- (19) Mahrwald, R.; Gundogan, B. *J. Am. Chem. Soc.* **1998**, *120*, 413.
- (20) Simth, M. B.; March J. *March's Advanced Organic Chemistry*, 5th ed.; Wiley: New York, 2001.
- (21) Dipole moments calculated using a molecular modeling package (Spartan Pro, Wave Function, Inc., Irvine, CA).