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Short Communication

Exploring the re-evaluated interpretation of hydrophobicity to explain rates of Diels–Alder reactions in aqueous salt solutions

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ABSTRACT: The recently proposed correlation between hydrophobicity and internal pressure offers quantitative support to our understanding on the rate enhancement of Diels–Alder reactions in water and its salt solutions. Copyright © 2002 John Wiley & Sons, Ltd.

KEYWORDS: Diels–Alder reaction; salt effect; reaction rates; hydrophobicity, internal pressure, endo/exo ratios

Hydrophobicity plays a crucial role in several chemical and biological systems.[1] Some of these are stability of proteins and nucleic acids, surfactant aggregation, coagulation, detergent action, mineral floatation, etc. Hydrophobicity is also important in understanding the formation of gas clathrates and the surface phenomena involving wetting, aggregation processes at the air–water interface. The area of hydrophobicity, in spite of intense research over the years, has been a debatable issue.[2] Several attempts have been made to understand hydrophobicity and its correlation to different chemical and biological phenomena.[2b] Very recently, Kodaka[3] re-evaluated hydrophobicity based on the scaled particle theory.[4] He has shown that the hydrophobicity phenomenon is not caused by the small size of the water molecule. He attributed the hydrophobicity to the high packing density of water molecules. The high packing density of water molecules can be expressed[5] in the form of cohesive energy density (CED) and internal pressure P_{int}. For weakly polar or nonpolar solvents, P_{int} is treated approximately equal to CED. From this argument, therefore, it is possible to extend the explanation of hydrophobicity in terms of P_{int} or CED in understanding the kinetic behavior of Diels–Alder (DA) reactions.

Rideout and Breslow[6] were the first to demonstrate that the DA reaction of cyclopentadiene with acrylonitrile could be accelerated when carried out in water. Similarly, anthracene-9-carbinol reacted with *N*-ethylmaleimide about 27 times faster in water compared with in 2,2,6-trimethylpentane, a nonpolar solvent.[7] Since the work from Breslow's school on the special effect of water, several sluggish DA reactions can now be made faster in water. The topic of why the DA reactions go faster in water has been the focus of research of several workers, and a recent review[8] has summarized the topics covered, together with the original references. The solvent polarity, hydrogen bonding, enforced hydrophobic interactions, hydrophobic packing, Lewis acid catalysis, etc., have been termed as possible reasons for the rate enhancement in salt solutions.[8] Breslow[9] proposed that hydrophobic packing of diene and dienophile in the presence of water is a principal force in accelerating the reaction. Later, rate enhancement of DA reactions in aqueous LiCl was ascribed to increased hydrophobic interactions, whereas the decrease in $LiClO_4$ and guanidinium chloride (GnCl) was ascribed to reduced hydrophobic interactions. These suggestions, though significant, were qualitative, however. In our search of possible factors responsible for rate variations to provide quantitative support to the Breslow approach, we demonstrated that the hydrophobic packing of diene and dienophile is greatly facilitated by the internal pressure of water. The internal pressure of water (166.2 MPa) presses the diene and dienophile together in order to realize a DA reaction.

In this work, we wish to strengthen the outcome of Kodaka's work,[3] that the hydrophobicity is strongly correlated with internal pressure. In return, we also demonstrate that this correlation can prove to be a powerful tool to understand the effects of water and its salt solutions on the kinetics of DA reactions.

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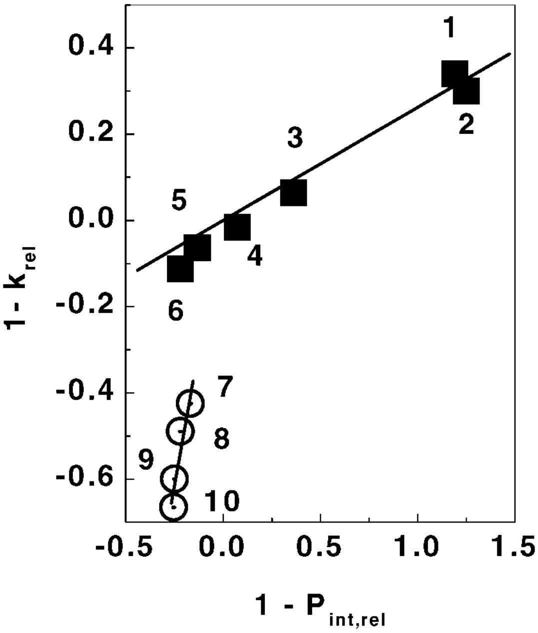

Figure 1. The plots of $(1 - k_{rel})$ versus $(1 - P_{int,rel})$ for the reaction of anthracene-9-carbinol with *N*-ethylmaleimide in sodium (■) salts: (1) NaCl, (2) NaBr, (3) $NaBF_4$, (4) $NaClO_4$, (5) $NaPF_6$, (6) $NaAsF_6$; and in guanidinium (○) salts: (7) GnCl, (8) GnBr, (9) $GnBF_4$, (10) $GnClO_4$. The salt concentration in each reaction is 2 M

It is seen that addition of a salt increases the internal pressure of water $P_{int,w}$ due to the electrostriction process occurring between an ion and water.[5] Our calculations of internal pressures, based upon the thermal expansion α and adiabatic compressibility β of solutions, show that internal pressure increases with the addition of LiCl, NaCl, etc.[10,11] Breslow and Connors called these salts prohydrophobic agents.[12] Salts like $LiClO_4$ and GnCl, on the other hand, decrease the internal pressure of water and are termed antihydrophobic agents. This implies that the salts, which increase internal pressure, also enhance hydrophobic interactions. The opposite is true in the case of the antihydropobic agents. Essentially, the internal pressure of water increases or decreases due to the phenomenon of electrostriction, where an ion, owing to its strong electric field, orients water molecules, thus causing a reduction in volume. This, in turn, raises the internal pressure of water. These effects are a function of salt concentration and depend on the nature of the salt.

At an earlier occasion,[10] we showed this situation to be true in the case of the reaction of anthracene-9-carbinol with *N*-ethylmaleimide carried out in 2 M solutions of NaCl, NaBr, $NaBF_4$, $NaClO_4$, $NaPF_6$, $NaAsF_6$, GnCl, GnBr, $GnBF_4$ and $GnClO_4$ in water using the data of Rizzo.[13] Figure 1 shows $(1 - k_{rel})$ as a function of $(1 - P_{int,rel})$ in the sodium and guanidinium salt solutions for the above reaction. The relative rate constant k_{rel} of the reaction is defined as $k_{rel} = k_s/k_w$, where k_s and k_w are the rate constants in the salt solution and in water respectively. An analogous definition is true for the quantity termed the relative internal pressure, $P_{int,rel} = P_{int,s}/P_{int,w}$, where $P_{int,s}$ is the internal pressure of the salt solution. As k_{rel} indicates the change in rate constant in salt solution over that in pure water, $P_{int,rel}$ the change in hydrophobicity in salt solution over that in pure water in terms of internal pressure. There is a strong linear correlation of k_{rel} with $P_{int,rel}$ for both the salt solutions, as shown by the following relationship:

for sodium salts

$$(1 - k_{rel}) = 0.2626 \pm 0.0092(1 - P_{int,rel})$$

with correlation coefficient $r = 0.998\,56$
for guanidinium salts

$$(1 - k_{rel}) = 2.4505 \pm 0.0285(1 - P_{int,rel})$$

with $r = 0.988\,90$.

Both Fig. 1 and the above correlations follow the condition that if $(1 - P_{int,rel}) = 0$, then $(1 - k_{rel}) = 0$, indicating water as a reference solvent for the reaction.

It should be noted that sodium salts, like $NaBF_4$, $NaClO_4$, $NaPF_6$ and $NaAsF_6$, decrease the internal pressure of water owing to the structure-breaking abilities of these anions, as the large anions have a low charge density. This is the opposite to what one sees in Li^+, Na^+, etc., where cations are the structure-makers. The stronger structure-breaking powers of BF_4^-, ClO_4^-, PF_6^- and AsF_6^- outweigh the structure-making ability of the Na^+ species, resulting in the dominance of the structure-breaking environment. This results in a lowering of the internal pressure of water in a variety of salt solutions. As a matter of fact, the hydration of ions is greatly affected by the structure-making and -breaking abilities of ions. Why does the action of Cl^- differ from that of ClO_4^-? Why do Li^+ and Gn^+ species demonstrate opposite actions in water and other solvents? These issues have been discussed by us in a recent paper.[14] A strong linear correlation suggests hydrophobic packing or unpacking of diene and dienophile in the sodium and the guanidinium salts respectively. As DA reactions are accompanied by negative activation volumes, the increased internal pressure leads to enhancement of reaction rates. In other words, the packing of diene and dienophile is enhanced by a negative activation volume and higher internal pressure. On the contrary, the decreased internal pressure in guanidinium salt solutions (and also in some sodium salt solutions) coupled with a negative activation volume further inhibits the reaction rates, as is evident from Fig. 1. This suggests that packing of diene and dienophile is decreased in aqueous solutions of guanidinium salts. It is interesting that the aqueous solutions of both sodium and guanidinium salts change the internal pressures of water by different magnitudes and signs. Later, we also applied the same concept to delineate the endo/exo stereoselectivity ratios obtained

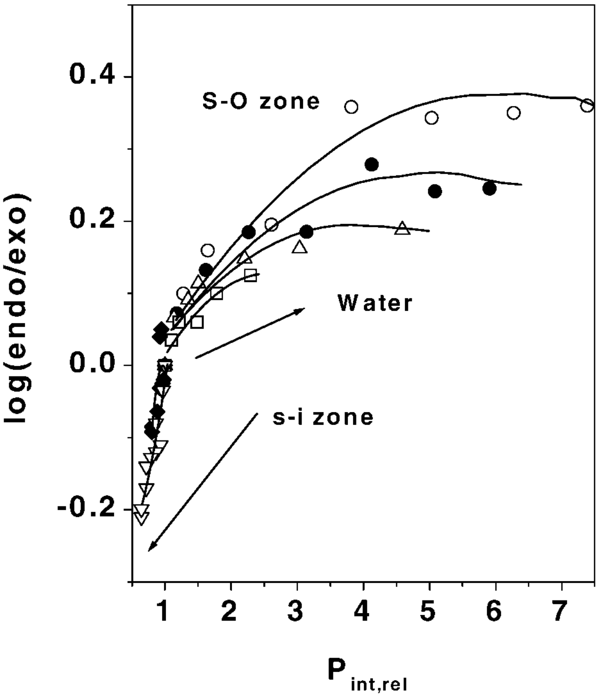

Figure 2. Variation of log(endo/exo) with $P_{\text{int,rel}}$ for the reaction of cyclopentadiene with methyl acrylate in aqueous salt solutions. The salt concentration ranges from 0.5 to 6 M, from Ref. 11; LiCl (○); NaCl (●); NaBr (△); $CaCl_2$ (□); GnCl (◆); $LiClO_4$ (▽)

from the reaction of cyclopentadiene with methyl acrylate in concentrated aqueous LiCl, NaCl, NaBr, $CaCl_2$, $LiClO_4$, and GnCl solutions.[11] The endo/exo ratios of the reaction of cyclopentadiene with methyl acrylate increase in aqueous LiCl, NaCl, NaBr and $CaCl_2$ solutions. $LiClO_4$ and GnCl decrease the endo/exo values for this reaction. As the transition state for the endo stereoisomer is more compact than the exo stereoisomer, the increase in the endo/exo ratios with increase in the concentrations of prohydrophobic salts can be explained on the basis of negative activation volume and high internal pressure. The reduced endo/exo ratios obtained in the GnCl and $LiClO_4$ types of salt explain the inhibition of endo/exo ratios due to weakening of hydrophobic effects as expressed in terms of internal pressure. The log(endo/exo) values when plotted against $P_{\text{int,rel}}$ in various salt solutions of different concentrations are not linear (Fig. 2). At higher $P_{\text{int,rel}}$ values, the log(endo/exo) values taper, suggesting the maximum in hydrophobic effects. Based on $P_{\text{int,w}}$ and $P_{\text{int,s}}$, we have suggested three zones characterizing the variations in reaction rates in salt solutions.[11] These zones are: $P_{\text{int,s}} > P_{\text{int,w}}$ gives rise to salting-out (enhanced relative hydrophobicity with respect to water); $P_{\text{int,s}} < P_{\text{int,w}}$ gives rise to salting-in (reduced relative hydrophobicity with respect to water); $P_{\text{int,s}} = P_{\text{int,w}}$ gives no salt effect (hydrophobic effect due to water alone; see Fig. 2). As internal pressure has been correlated with hydrophobicity, it is possible to correlate these zones in terms of hydrophobicity, and so with the reaction rates. The linear relationship in the case of Rizzo's data plotted in Fig. 1 was possible as the rate data were collected only at a single salt concentration. We have noted these observations to be valid for the reaction of cyclopentadiene with methyl acrylate in solutions of different concentrations of GnCl, GnBr, CH_3COOGn and $GnClO_4$.[15] The (endo/exo) ratios are suppressed in the guanidinium salts, except in Gn_2SO_4. Both the enhancement and inhibition in endo/exo values can be easily explained in terms of the enhanced or reduced hydrophobic effects as expressed by internal pressure.[15] The studies on the above-mentioned guanidinium salts suggest that internal pressure is decreased in the presence of GnCl, GnBr, CH_3COOGn, and $GnClO_4$. Gn_2SO_4, on the other hand, increases the internal pressure. These decreases and increases in internal pressures in these guanidinium salts reflect decreased and increased hydrophobic effects in DA reactions. From our published experimental work,[16,17] the computed P_{int} values decrease on adding GnCl in aqueous NaCl, KCl and $MgCl_2$ solutions, suggesting a reduced hydrophobic effect. We have carried out the reaction of cyclopentadiene with methyl acrylate in mixtures of NaCl–GnCl and noted that the changes in P_{int} or in hydrophobic effect were strongly correlated with the variations in rates and endo/exo values.[15]

Some years ago, we successfully correlated the reaction rates and endo/exo ratios with internal pressures for 20 DA reactions in about 75 organic solvents and their aqueous mixtures.[18] This successful correlation suggests that 'solvophobicity' due to organic solvents can also be described by internal pressure. The role of solvophobicity in DA reactions was first demonstrated by Schneider and Sangwan.[19]

In short, we have demonstrated the immediate use of the new interpretation of hydrophobicity in delineating the effects of water, organic solvents and their salt solutions on the kinetics of DA reactions. From the above, it seems that the relative hydrophobicity can be judged from the relative internal pressure of water and solutions, which is useful in understanding the salt effect on DA reactions. It should be possible to apply the above development to other DA reactions in salt solutions in nonaqueous solvents.[20]

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