Cycloadditions in weakly and highly organized aqueous media

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CHAPTER 7

Epilogue

Cycloadditions in water/cosolvent mixtures as well as in aqueous micellar and vesicular solutions have been the primary subject of interest of this thesis. In this final chapter, the work presented in the previous chapters is briefly reviewed and evaluated. Furthermore, the results are put into perspective in relation to the field of organic reactivity in mixed aqueous media and to the use of mimics for complex microenvironments such as the micellar pseudophase.

7.1 Solvent Effects on Cycloadditions

Relatively little was known about solvent effects on 1,3-dipolar cycloadditions, especially in aqueous media. Therefore, a detailed study of solvent effects on several 1,3-dipolar cycloadditions has been made (Chapter 2). Emphasis was put on the role of the solvent polarity and hydrogen-bond donor (HBD) capacity. Solvent polarity was regarded as the ability to interact via polar interactions (dipole-dipole, dipole-induced dipole, etc.). This includes — in principle — hydrogen bonds. However, the effect of the HBD capacity of the solvent turned out to be rather complex. Sometimes it affected the rate constant in the opposite direction as the polarity did, which distinguishes the HBD capacity from polarity. This deviation — prompted by the kinetic results — was not recognized previously. Nevertheless, functional groups, capable of donating hydrogen bonds, are usually capable of interacting by means of other polar interactions as well, and it is not possible to fully separate these different contributions. (The popular $E_T(30)$-scale, used as a measure of the polarity, does not distinguish between different types of polar interactions, including hydrogen bonds.) Therefore, it was not possible to quantitatively account for the solvent effects. In dipolar aprotic solvents, the observed rate constants deviate from trends found among other solvents, especially if the solvent is a good hydrogen-bond acceptor. These observations indicate that not all factors that influence the rate constants of these reactions are fully understood yet. Interestingly,
different HBD solvents, viz. 1-propanol and 2,2,2-trifluoroethanol (TFE) have a substantially different effect on the rate constant. In 1-propanol, hydrogen bonds affect the dipolarophile more than the 1,3-dipole and the rate constant is relatively high. By contrast, in TFE, the 1,3-dipole is more affected by the hydrogen bonds, which diminishes the rate constant. These results suggest that the nature of the HBD offers a possible source of selectivity.

In order to obtain more detailed information about reactivity in mixed aqueous solvents, in Chapter 3 a number of cycloadditions was studied using aqueous mixtures of ‘hydrophilic’ solvents (methanol, acetonitrile, poly(ethylene glycol)). Previously, hydrophobic cosolvents like 1-propanol have received most attention. However, hydrophilic cosolvents were chosen for the present study, because the tendency of clustering or preferential solvation is greatly reduced in comparison to e.g. 1-propanol. It was found that the kinetic data for aqueous mixtures of these hydrophilic solvents are in qualitative agreement with those for the hydrophobic cosolvent 1-propanol. More importantly, it was found that (in the absence of preferential solvation) activation Gibbs energies depend nearly linearly on the molar concentration or volume fraction of water over large concentration ranges for these binary aqueous solvent mixtures, and characteristic changes in slope appear in a relatively narrow range of concentrations for different cosolvents. This point has received little attention in the literature, because it is more common to present kinetic data in mixed aqueous solvents on a mole fraction scale. The difference between these concentration scales can be substantial for aqueous mixtures, because water is a small molecule in comparison to nearly any other molecule (molar volumes of water, methanol and ethanol are 18, 41 and 59 cm$^3$/mol, respectively). Apart from cycloadditions, a nearly linear dependence of log($k$) on [H$_2$O] has also been observed for several hydrolysis reactions in aqueous mixtures of PEG400 or acetonitrile. The relatively narrow range of concentrations in which these changes in slope occur (at around 40 M of water) emphasizes that the amount of water (per unit volume) plays a role in governing the hydration characteristics of apolar solutes. These changes in slope might be attributed to a transition from water molecules ‘behaving individually’ to clusters of ‘bulk-like’ water.

The kinetic data reflect the thermodynamic parameters of transfer of substrates from water to binary aqueous solvent mixtures. In particular, also Gibbs energies of transfer often show a nearly linear dependence on the molar concentration or volume fraction of water. Unfortunately, a general theory to describe the dependence of transfer parameters on the composition of a solvent mixture is lacking. Fundamental questions regarding solute-solvent interactions and the treatment of the thermodynamics (concentration scales, mixing entropies, volume and size effects) are still unanswered. The picture that emerges from our kinetic data and from Gibbs energies of transfer is that for solvation of a solute, often the number of molecules (of one or perhaps both com-
ponents) per unit volume that is important (emphasized using the molar concentration scale), rather than the relative number of molecules (emphasized using the mole fraction scale). In other words, in the condensed (liquid) phase, the size of molecules plays an important role in the solvation process in solvent mixtures, because this size determines the chances to find solvent 1 or 2 near a solute molecule. One expects for a binary solvent mixture that the less specific the interactions between individual solvent and solute molecules; i.e. the better the solvent mixture can be described as a continuum, the better any property of the solute correlates with volume fraction of the (co)solvent. It is therefore remarkable that this dependence is also found in aqueous mixtures.

The focus on the concentration of water in mixed aqueous systems is of importance for the study of thermodynamics and reactivity in a biological context as well. For example, for the hydrolysis of a dipeptide by \(\alpha\)-chymotrypsin in water/1,4-butanediol mixtures, the logarithms of the initial rate constants varied approximately linearly with volume fraction of water.\(^{15}\) The variation in rate constant was mainly caused by the variation in binding constant \(K_m\), whose logarithm in turn varied linearly with volume fraction of water. Furthermore, the unfolding Gibbs energy change of proteins in mixed aqueous solvents typically depends linearly on the molar concentration of denaturant (linear in volume fraction).\(^{16}\) The amount of water in the cytosol is limited, as the cytosol contains up to 300–500 g/L of non-aqueous material.\(^{17}\) A starting point for the selection of possible cytosol mimics may be the concentration of water, keeping in mind that refinements to this simple model are inevitable.

As \(\log(k)\) depends linearly on the molar concentration of water, it also depends linearly on the number of hydrogen-bond donors in water/acetonitrile mixtures (where water is the only source of hydrogen-bond donors). This pattern is not in full agreement with (strong) hydrogen bond interactions between water and reactant. A dependence reflecting a binding curve, as is seen for \(E_T(30)\)-values in water/acetonitrile, would have been expected. These observations, and the complex effects of hydrogen bonds on the 1,3-dipolar cycloadditions reactions, illustrate that hydrogen bonds are complex interactions and that further research toward a better understanding of these interactions is desired.

### 7.2 Reactivity in Organized Media

In Chapters 4-6, detailed studies of reactivity in micellar and vesicular solutions were reported for a number of cycloadditions. The rates of Diels-Alder (DA) reactions are usually substantially enhanced in water, whereas the 1,3-dipolar cycloadditions (DC) that were studied in this thesis hardly proceed faster in water than in organic solvents. This difference is nicely reflected in the observed kinetics in the presence of micelles.
The DA reactions appear to be hardly affected by the micelles, but the DC reactions are significantly accelerated. The small effect of micelles on the rate constants of DA reactions is the outcome of two factors that affect the rate constant in opposite directions. (1) Binding of the reactants to the micelles leads to locally high concentrations and therefore to an increase in rate constant; this also explains the increased rate constants for the DC reactions. (2) The local reaction environment in the micelle is only slightly aqueous, and part of the rate enhancing effect of water on DA reactions is lost; i.e., the rate constant in the micellar pseudo-phase is much lower than in water. For the DC reactions, the micellar rate constants are close to the aqueous rate constants and the first effect prevails.

Studies of bimolecular processes in the presence of micelles have been limited mainly to reactions involving hydrophilic (counter) ions as one of the reactants. It was therefore of interest to analyze the kinetics of bimolecular cycloadditions involving only neutral substrates (and occasionally one charged substrate) in micellar media. For these bimolecular reactions, the kinetic data could be quantitatively accounted for using the pseudo-phase model (Figure 4.1). In most cases, the assumption of one distinct pseudo-phase suffices to describe the kinetics in the presence of micelles. As long as no charge-charge interactions between reactant and surfactant are involved, there is no need for a subdivision of a micelle into several regions with different affinities of both substrates for the different regions. This means that many substrates partition into similar parts of the micelle, and that it is likely that this includes a large fraction of the micelle; i.e. the binding location is not spatially well-defined. Of course, some properties, such as the amount of water, depend strongly on the position in the micelle. Hence, individual probes may report different average local environments, depending on the property that is monitored. However, for a bimolecular process, not only the average binding location(s), but also the amount of overlap between the distributions of the reactants within the micellar phase is of importance in determining the reactivity. The overlap will be substantial if the distributions are relatively broad, which, at least for neutral substrates, appears to be the case. The micellar rate constant is therefore largely determined by the properties of the local reaction environment in the micelle. In line with this, the rate constant of a (unimolecular) retro-Diels-Alder (RDA) reaction is diminished in the presence of micelles, and the values of the micellar rate constants of both the DA and RDA reactions are fully consistent with a local medium effect, as quantified using a micelle mimic (vide infra).

If one of the reactants is charged, it binds strongly to oppositely charged surfactant aggregates (Chapters 4 and 6). The charge-charge interactions most likely confine the binding region of this reactant to the outer part of the micelle and narrow the width of its distribution. Hence, the possibilities to encounter a neutral reactant are negatively affected (Figure 4.6) and the effective rate constant will be lowered due to this partial mismatch. It was shown in Chapter 6 that no simple relation exists between factors
that are expected to enhance mismatch and observed rate constants. Apart from differences in mismatch, interactions between surfactants and reactants can influence the rate constant. This was found, for example, for the DC reactions with benzonitrile oxide. It is therefore difficult to draw definite conclusions. Nevertheless, for several reactions involving a charged substrate or substrate-catalyst complex, mismatch seems likely and a plausible explanation for the observed kinetics. Large differences in polarity appear necessary for this situation to become significant and induce a substantial effect. For vesicles, the phase (gel state, liquid-crystalline state) seems to affect the extent of mismatch (Chapter 6). There are other indications that the phase of a bilayer can have a significant influence on the observed reaction kinetics. It would therefore be of interest to study bimolecular reactions in the presence of vesicles above and below the main phase transition temperature.

To obtain insight into the reactivity within the local microenvironment of a micelle or vesicle, a simple mimic of this environment can be a useful tool. DA and DC reactions of two uncharged substrates appear to take place in a region of a micelle that is neither highly aqueous nor completely apolar. Indeed, a 15 M water/1-propanol mixture (mimic A) turned out to be a reasonably good mimic of the micellar reaction environment for a variety of cycloadditions in terms of rate constants (Chapters 4–6) and activation parameters ($\Delta^{\ddagger}G^\circ$, $\Delta^{\ddagger}H^\circ$, and $\Delta^{\ddagger}S^\circ$, Chapter 5). It does not fully account for the variation in micellar rate constants, though. In order to evaluate this model, in Figure 7.1, a

FIGURE 7.1: Left: Plot of the logarithm of the relative micellar rate constants vs predicted values using a 15 M water/1-propanol mixture (A). The solid line indicates where $k_m = k_{mimic}$. Different reactions are labeled with numbers and are explained in the notes. Values for CTAB are indicated with crossed circles. Right: A similar plot for a 17 M water/acetonitrile mixture (B).
comparison is made between predicted and measured values of the micellar rate constants (excluding reactions involving a charged substrate). As can be seen, in general, the predictions are fair, but in some cases, the values differ by as much as a factor of 2 (a difference of 0.3 on a log-scale). There are several things to note.

For the DC reactions, slightly aqueous water/1-propanol mixtures behave odd. Whereas for nearly any other DA or DC reaction, the rate would increase upon adding water to 1-propanol, for the reactions of benzonitrile oxide, the rate constant initially decreases and then increases again. This negatively affects the quality of the predictions made using the water/1-propanol micelle mimic for DC reactions. Other cosolvents (methanol, acetonitrile) lack this odd behavior; in hindsight, it would have been better to choose another cosolvent. Based on the results of Chapter 3, a possible alternative mimic is a mixture of water and acetonitrile. Because acetonitrile does not contain any hydrogen-bond donating groups and because the amount of hydrogen-bond donating material (hydrogen-bond donating capacity) is one of the factors that influences the rate constants, the concentration of water, predicted from a water/acetonitrile mixture will be somewhat larger. There are only a few reactions for which data are available. For these reactions, a 17 M water/acetonitrile mixture is evaluated as an alternative micelle mimic (B). The results are presented in Figure 7.1. It appears that this mimic is indeed somewhat better in predicting the micellar rate constants, largely because the values for the DC reaction are now closer to the measured values, as expected.

Interestingly, CTAB micelles are better mimicked than SDS micelle (using mimic A). A general reason why it is more difficult to predict rate constants for SDS micelles is perhaps the smaller size of the aggregates it forms, in comparison to CTAB (which possesses both a larger aggregation number and a longer alkyl tail). The presence of any substrate therefore more easily disturbs the morphology of a SDS micelle. Specific interactions with the headgroups do not play a large role in determining the micellar rate constants for the cycloadditions.23

The micellar reaction environment could be mimicked reasonably well with a water/1-propanol mixture. For other processes, the exact composition of such a mimic may have to be chosen differently.24 Nevertheless, it seems possible to mimic the micellar environment by a mixture of water with a (hydrophobic) cosolvent, and possibly include a salt, to mimic the headgroups, if specific interactions with the headgroups are of importance. This has more general implications. For the study of reactivity, molecular recognition processes, etc. as they take place in a biological cell membrane, or in the cytosol, for instance, simple mimics of these environments may well provide a good approximation.12

The suggestion that the concentration of water can be used to predict (local) medium effects is difficult to examine for the micelle mimic, as the (average) concentration of
water in the micelle cannot be easily measured. Nevertheless, estimates of the water density on the basis of molecular dynamics simulations (Section 1.3) in combination with estimates of the average binding location as determined with NMR (Chapter 4) suggest that the concentration of water in the mimic may well match the average concentration of water in the micellar reaction environment. Note that if substrate-headgroup interactions are of particular importance, the concentration of water no longer suffices to account for the ‘local medium effects’.

It is also of interest to note that prediction of partition coefficients on the basis of these micelle mimics largely fails. Micellar partition coefficients\textsuperscript{25} are invariably larger than the corresponding water/octanol partition coefficients;\textsuperscript{26} a few examples have already been given in the introduction. Micellar partition coefficients may be estimated using transfer Gibbs energies to water/cosolvent mixtures, but values are often a factor of 5–10 smaller than the micellar partition coefficients. In particular, for cyclopentadiene, this difference amounts to a factor of about 5. As cyclopentadiene can be regarded to be fully apolar, a favorable combination of hydrophobic interactions and polar interactions cannot account for the relatively large micellar partition coefficient. The binding process apparently is too complex to be mimicked using a simple water/cosolvent mixture.

7.3 Cycloadditions and Organic Chemistry in Water

Aqueous organic chemistry has become an important field of research, and there are examples where water has proved a practical alternative to organic solvents.\textsuperscript{27} Many of the reactions that have been studied in this thesis actually benefit from the use of water (increased reaction rates). A major drawback of the use of water is the limited solubility of many organic compounds. However, one can perform a reaction under heterogeneous conditions. Alternatively, one can try to enhance the solubility using different types of addenda, of which cosolvents are one example, surfactants another.

Does it help? First, consider cycloadditions in water/cosolvent mixtures. As demonstrated in Chapter 3, changes in rate constant and changes in solubility (changes in $\Delta^\ddagger G^\circ$ and $\Delta_{tr} G^\circ$) in water/cosolvent mixtures follow the same pattern with respect to composition. What is gained in solubility, is lost in rate. It depends on the particular reaction, whether aqueous solvent mixtures exist, that can dissolve the reactants in reasonable amounts and at the same time provide significant rate enhancements. The endo/exo-ratios follow a similar pattern: the usually enhanced endo-selectivity upon increasing the amount of water is accompanied by a decrease in the solubility. Of course, when the primary interest is a high selectivity, one may accept a limited solubility.

Starting from pure water, it appears, that a considerable amount of cosolvent (i.e., up to a volume fraction of 0.2–0.25) may be added to water, before the rate of any
cycloaddition is substantially affected (Chapter 3). This point was not apparent from previous studies, as data have always been presented on a mole fraction basis. It is an important observation, though: if reactants are structurally modified in order to be reasonably water-soluble, and behave similarly to the cosolvents that have been studied, fair amounts of reactants may be dissolved without losing much of the rate-enhancing properties of water. Perhaps the best way to benefit from the aqueous accelerations of cycloadditions is to use structurally modified, water-soluble reactants.\textsuperscript{28,29}

With aqueous surfactant solutions, the situation is slightly different. Within limits, the intrinsic lower reactivity in the micellar phase is compensated for by a concentration effect. To establish this situation, one still needs a relatively large volume of water, in comparison to the amount of reactant. Endo/exo-ratios appear to be not highly affected by the use of surfactants,\textsuperscript{30} although further experiments would be desirable. Furthermore, micelles or vesicles can have other beneficial effects. For instance, for 1,3-dipolar cycloadditions, in particular the ones for which water does not accelerate the reaction with respect to \textit{n}-hexane, the use of aqueous surfactant solutions may substantially enhance the reaction rate, as was shown in Chapter 5. Another example is the combination of a catalyst and a micellar or vesicular aggregate, that can lead to efficient catalysis, largely because of enhanced binding of the catalyst to the substrate (Chapter 6). A similar approach was found useful for other transformations as well.\textsuperscript{31,32} In summary, a micellar solution can be a useful aqueous medium for organic transformations.

References and Notes

\[1\] Part of Chapter 2 will be published: \textit{Solvent Effects on 1,3-Dipolar Cycloadditions of Benzonitrile Oxide}. Rispens, T., Engberts, J. B. F. N. \textit{submitted for publication}.

\[2\] Part of Chapter 3 will be published: \textit{Cycloadditions in Mixed Aqueous Solvents: Hydrophilic Cosolvents}. Rispens, T., Engberts, J. B. F. N. \textit{submitted for publication}.


\[4\] Part of Chapter 5 has been published: \textit{A Kinetic Study of 1,3-Dipolar Cycloadditions in Micellar Media}. Rispens, T., Engberts, J. B. F. N. \textit{J. Org. Chem.}, 2003, 68, 8520–8528.


\[6\] \textit{Kinetics of Hydrolysis of p-Methoxyphenyl-2,2-dichloroethanoate in Binary Water-Cosolvent Mixtures; the Role of Solvent Activity and Solute-Solute Interactions}. Rispens, T., Cabaleiro Lago, C., Blandamer, M. J., Engberts, J. B. F. N. \textit{to be published}.

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[13] Nevertheless, in highly aqueous media, kinetic medium effects can be explained in terms of the concentration of nucleophilic water molecules in the direct vicinity of the ester carbonyl functionality.7


[21] (1) cyclopentadiene + N-n-butylmaleimide, SDS; (2) 2,4-hexadienol + N-ethylmaleimide, CTAB; (3) 2,4-hexadienol + N-ethylmaleimide, SDS; (4) cyclopentadiene + N-ethylmaleimide, SDS; (5) nitrosobenzene + cyclohexadiene, SDS; (6) cyclopentadiene + N-benzylmaleimide, SDS; (7) retro DA (Scheme 6.1), SDS; (8) retro DA (Scheme 6.1), CTAB; (9) benzonitrile oxide + N-n-butylmaleimide, SDS; (10) benzonitrile oxide + N-n-butylmaleimide, C_{12}E_{23}; (11) benzonitrile oxide + N-n-butylmaleimide, C_{12}E_{8}, C_{16}E_{20}; (12) benzonitrile oxide + N-n-butylmaleimide, CTAB; (13) benzonitrile oxide + N-ethylmaleimide, SDS; (14) benzonitrile oxide + N-ethylmaleimide, CTAB.
Data from previous chapters. A value for the micellar rate constant for the reaction of sorbyl alcohol with \( N \)-ethylmaleimide in CTAB was obtained from a fit of the pseudo-phase model to the data of Figure 4.4 using the value of \( P_{\text{ethylmaleimide}} \) from Table 5.2.

For the DC reactions with benzonitrile oxide, the difference in \( k_m \) for SDS and CTAB is reflected in part in the rate constants in concentrated solutions of SMS and TMAB. However, for the nonionic poly (ethylene glycol) surfactants, \( k_m \) should be highest according to the rate constant in concentrated PEG solutions. An alternative explanation has been given in Chapter 5, based on possible interactions for the most plausible orientations of benzonitrile oxide in the different micelles.


