Kinetic and Thermodynamic Measurements for the Facile Property Prediction of Diels–Alder-Conjugated Material Behavior

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The Diels–Alder (DA) reaction between maleimide and furan moieties possessing various substitutions was performed as a means for developing predictive capabilities for temperature and conversion-dependent material properties in networks comprised of DA moieties. Using HNMR spectroscopy, the reactions of maleimide- and furan-containing molecules further functionalized with carboxylic acids were monitored to ascertain the impact that substitutional changes had on the thermodynamic and kinetic behavior of the DA reaction. The reaction rate and equilibrium conversion of the furan and maleimide increased when the carboxylic acid functional group directly connected to the furan ring was moved from the two to the three position. When an aliphatic two-carbon spacer was used, such that the π-electrons of the carboxylic acid and furan were no longer conjugated, the reaction rate increased further. We also report the reactivity effect on the distance between the carboxylic acid functional group and the maleimide, which yielded little impact on the reaction rate but exhibited increased equilibrium conversion with increasing distance. Additionally, the impact on the kinetic and thermodynamic properties of coupling the carboxylic acid to another molecule, tert-*butyl glycine, was also determined. When the carboxylic acid was coupled to an amine, the DA reaction between the furan and maleimide was generally found to have similar kinetic and thermodynamic behavior as compared to their uncoupled, carboxylic acid equivalents. Thus, the characterized and tabulated kinetic and thermodynamic data presented herein enables the prediction of a broad set of temperature-dependent chemical and material properties. Finally, we discuss practical limitations and nuances of the DA reaction, such as the potential for the maleimide to ring-open in aqueous media via hydrolysis.* © 2012 American Institute of Chemical Engineers *AIChE J,* 58: 3545–3552, 2012

Keywords: Diels–Alder reactions, self-healing polymer networks, thermoreversible reactions

Introduction

The Diels–Alder (DA) reaction is one of the premier ‘‘click’’ reactions[1] owing to its exceptional ability to efficiently and orthogonally form carbon–carbon bonds.[2] For example, the direct organic synthesis of several natural products, such as oseltamivir phosphate,[3] utilizes the DA reaction to create carbon–carbon linkages. While in much of conventional organic synthesis, it is desirable for the diene and dienophile pair (D/P in Scheme 1) to be essentially irreversible and favor the forward reaction to the exclusion of any significant reversibility, frequently, the DA adduct possesses the capability to revert back to the starting diene and dienophile pair at elevated temperatures via the retro DA (rDA) reaction.

Recently, several research groups have utilized the DA and the subsequent rDA reaction for several applications, ranging from protection/deprotection of functional groups to the formation of thermoreversible crosslinks in polymer networks.[4–6] For example, the DA and rDA reactions have been used to protect maleimides, which are used in a variety of

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Additional Supporting Information may be found in the online version of this article.

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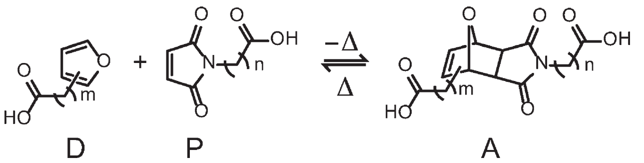


Scheme 1. The DA carboxylic acid species studies here, where furan (*D*iene) and maleimide (dieno*P*hile) species react to form the DA *A*dduct.

Low temperatures promote the forward reaction to form the DA adduct while elevated temperatures cause reversion to the initial diene and dienophile pair. The nature of the forward and reverse reactions and their thermoreversibility are controlled by the diene and dienophile chemical structure.

applications, including fluorescent staining, antibody coupling, and surface functionalization.[7–9] As the maleimide readily reacts in the presence of free radical species and organic bases,[5,10,11] the DA adduct formed by the reaction with a diene moiety is used to prevent undesired side-reactions during synthetic transformations.[10,12] After synthesis, the maleimide is reformed and isolated by simply heating the product and liberating the diene moiety.

Thermoreversible polymers have also been produced from multifunctional diene and dienophile monomers or oligomers.[13,14] Unlike conventional polymeric network materials, covalent networks composed of DA adduct crosslinks are capable of complete structural reversion, including having the capacity to depolymerize completely. Such materials have found prominent applications in covalent adaptable networks, allowing for the creation of various technologies, including removable coatings, recyclable polymers, and self-healing materials.[6,15]

Current applications that utilize the forward and reverse DA reaction typically use a trial and error process to select the diene and dienophile pairs that exhibit the desired thermodynamic and kinetic properties. The examination and understanding of thermodynamic and kinetic properties for furan and maleimide pairings would facilitate informed selection of the correct DA functionalities for a given application. As these species exemplify the archetypal DA thermoreversible characteristics over moderate temperatures (from room temperature to 100°C), the DA reaction between maleimide and furan is commonly exploited throughout the literature in a range of applications, such as those mentioned above.[6,15] In particular, our studies will focus on carboxylic acid functionalized maleimide and furan molecules. The carboxylic acid forms of the maleimide and furan are readily available either commercially or by means of simple synthetic measures. In addition, the carboxylic acid provides a convenient synthetic handle through which the furan or maleimide is incorporated into other structures or materials having amines and hydroxyl groups, such as polymer networks and peptides, via well-developed coupling chemistries.

Herein, a comprehensive set of kinetic and thermodynamic data are presented and discussed, enabling the selection of furan and maleimide functional groups for the *a priori* design of functional materials and other applications, including self-healing networks and protecting groups. To accomplish this outcome, the impact of systematic substitutional changes on the thermodynamic and kinetic parameters of the DA reaction between the furan, a diene, and the maleimide, a dienophile, functional carboxylic acids was evaluated. Additionally, to investigate the role that solvent plays in the DA reaction, thermodynamic and kinetic data were collected from experiments conducted in two solvents, namely dimethylformamide (DMF) and water.

Experimental

Materials

The following compounds were purchased from the specified vendor and, unless otherwise indicated, directly used without further purification. Dienes used in this study, 2-furoic acid, 3-furoic acid, and 3-(2-furyl) propionic acid, were all purchased from Sigma–Aldrich. To remove a brown discoloration and any impurities, 3-(2-furyl) propionic acid was recrystallized from hexanes (30–50°C).[16] Maleic anhydride and the amino acid precursors: β-alanine, glycine, and 6-aminohexanoic acid involved in the synthesis of the maleimides considered in this investigation were purchased from Fisher Scientific and Sigma–Aldrich, respectively. To investigate the amine coupling of furan and maleimide, thionyl chloride was purchased from Sigma–Aldrich and glycine *tert*-butyl ester HCl was acquired from AK Scientific. Deuterated solvents, DMF-d7 and deuterium oxide, d2, for use in NMR spectroscopy were acquired from Cambridge Isotope Laboratories.

Synthesis

Information pertaining to the materials synthesized for this investigation, including the maleimide species (glycine, β-alanine, and caproic maleimides) as well as furan and maleimide functionalized *tert*-butyl glycine, is found in the Supporting Information.

NMR spectroscopy

NMR spectroscopic measurements were acquired using a Varian 500MHz NMR spectrometer equipped with a Nalorac probe. Samples studied via NMR spectroscopy were prepared by measuring equimolar quantities of the diene and dienophile under consideration directly into a 5-mm NMR tube. Immediately following the addition of deuterated solvent, an NMR spectrum was acquired to serve as a reference point in equilibrium measurements and the first time point in kinetic studies. To control the temperature while spectra were acquired, samples were kept in a heating block between NMR experiments. As the NMR experiments took ~1 min to complete and as the DA and rDA reactions between the dienes and dienophiles are relatively slow at ambient temperature with half-lives of hours to days, the subsequent reaction during this interim was deemed negligible. The progress of the DA reaction was monitored by measuring the consumption of the furan and maleimide functionalities while subsequently monitoring the formation of the adduct peaks in the NMR spectrum. The location of each peak in the spectrum (diene, dienophile, or adduct) depended on the particular furan and maleimide reacted and the deuterated solvent used. A singlet associated with the maleimide carbon–carbon double bond was observed around 7 ppm, multiplets corresponding to the furan could be found from 6 to 7.5 ppm, and characteristic peaks of the endo and exo isomers of the adduct were typically located between 4.5 and 5.5 ppm. Detailed spectra cataloguing the endo and exo forms of adduct may be found in the Supporting Information.

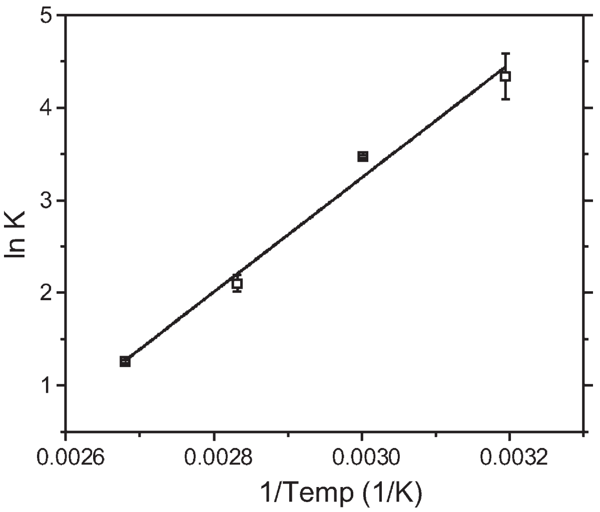


Figure 1. Arrhenius plot for the reaction of 3-(2-furyl) propionic acid with β-alanine maleimide acid allowing for determination of ΔH_{rxn} and ΔS_{rxn} from the slope and intercept, respectively.

Analysis

To determine the thermodynamic and kinetic properties, the DA reaction between the various maleimide and furan functionalized molecules (Scheme 1) was monitored as a function of temperature using NMR spectroscopy. NMR spectroscopy enabled the monitoring of maleimide and furan moiety consumption while simultaneously permitting the observation of adduct formation. Each DA reaction studied was monitored via NMR until equilibrium was achieved, allowing for thermodynamic and kinetic parameter determination. A given reaction mixture was considered to have reached equilibrium when the conversion of maleimide and furan remained constant over multiple time points.

Once known, the equilibrium conversion in conjunction with the initial reactant concentration is used to calculate the equilibrium constant, K_c, which may be expressed in terms of diene conversion as

$$K_c = \frac{X_{\text{Diene}}}{C_{0,\text{Diene}}(1 - X_{\text{Diene}})\left(\frac{1}{r} - X_{\text{Diene}}\right)}, \tag{1}$$

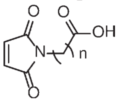
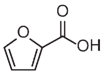
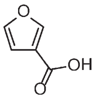
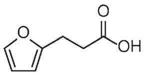
where r is the stoichiometric ratio of the initial diene to dienophile concentrations (i.e., $r = C_{0,\text{Diene}}/C_{0,\text{Dienophile}}$, where $r = 1$ as all studies performed herein used a stoichiometric equivalent of furan to maleimide), and X_{Diene} is the equilibrium diene conversion. Calculation of the equilibrium constant at several temperatures provides sufficient data to determine ΔH_{rxn} and ΔS_{rxn} from the Van't Hoff equation

$$\ln K_c = \frac{\Delta S_{\text{rxn}}}{R} - \frac{\Delta H_{\text{rxn}}}{RT}. \tag{2}$$

Once the equilibrium constant, and thus the ratio of the forward and reverse rate constants, is known, the time-dependent diene concentration is used to determine the forward and reverse rate constants. Where the mass balance on dienes is

$$\frac{dD}{dt} = -k_f[D][P] + k_r[A], \tag{3}$$

Table 1. Summarized Furan and Maleimide Carboxylic Acid Enthalpies in DMF (kJ/mol)

Dienophile 	*n*		
	1	2	5
Diene			
	−48 ± 3	−42 ± 6	−43 ± 2
	−34 ± 6	−53 ± 2	−56 ± 2
	−59 ± 2	−51 ± 3	−40 ± 3

where D, P, and A denote the diene, dienophile, and adduct concentrations, respectively. As with determination of the thermodynamic properties, NMR spectroscopy allows the simultaneous monitoring of diene and dienophile functional group conversion as well as the adduct formation over time. To determine the individual rate constants, the integral form of Eq. 3 was used to obtain a best fit of the data over the experimental time range.

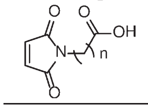
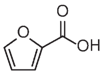
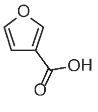
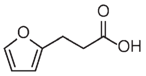
Results and Discussion

Thermodynamic experiments

A linear regression of the natural logarithm of K vs. $1/T$, as depicted in an Arrhenius plot (for example, Figure 1), yielded both the enthalpy and the entropy of reaction from the slope and intercept, respectively, via the Van't Hoff equation (2), for each of the maleimide–furan combinations studied here.

The entropies and enthalpies for the reaction between the carboxylic acid functionalized maleimide and furan are presented in Tables 1 and 2. Using the Van't Hoff equation, these data are used to calculate the equilibrium conversion for a given furan–maleimide pair throughout the temperature range studied (40–100°C). The ability to predict the temperature-dependent equilibrium conversion is critical in the design of DA-based materials. For example, these

Table 2. Summarized Furan and Maleimide Carboxylic Acid Entropies in DMF (J/mol K)

Dienophile 	*n*		
	1	2	5
Diene			
	−167 ± 6	−150 ± 20	−139 ± 12
	−80 ± 20	−128 ± 7	−138 ± 10
	−154 ± 7	−138 ± 8	−95 ± 8

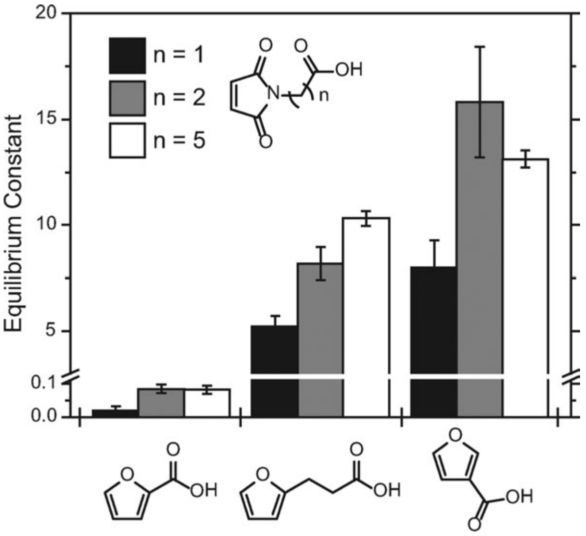


Figure 2. Furan and maleimide carboxylic acid equilibrium constants at 80°C in DMF.

Each clustered group presents one of the furoic acids considered in the study. Each of the furans was reacted with one of the three maleimides with different hydrocarbon spacers.

thermodynamic parameters enable the prediction of temperature-dependent phenomena such as the gel point conversion and crosslink density in thermoreversible covalent adaptable networks.[15]

To emphasize trends in the thermodynamic properties resulting from substitutional changes in the maleimide and furan carboxylic acids, Figure 2 presents the equilibrium constants at 80°C for the DA reaction between each of the possible diene and dienophile combinations considered in this study. 2-Furoic acid has the smallest equilibrium constant, regardless of the dienophile and measured temperature, which is attributed to the strong electron-withdrawing capacity of the carbonyl group in the two-position of the furan ring. Delocalization of the electron density of the furan ring to the carbonyl of the carboxylic acid reduces the electron donating potential[17] and retards the DA reaction. Shifting the carboxyl electron-withdrawing group to the three-position (i.e., 3-furoic acid) or adding a hydrocarbon spacer (i.e., 3-(2-furyl propionic acid)) favors the DA adduct given by the higher equilibrium constants.

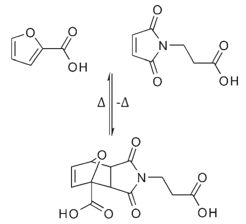
In addition to electron-withdrawing effects, the furan side chain can have steric effects that may impact the progress of the reaction. In order for the DA reaction to occur, the furan molecule must be able to form a bridgehead; thus, the rigidity of 2-furoic acid may also contribute to the reduced equilibrium constant. In contrast, 3-furoic and 3-(2-furyl) propionic acids with increased distance of the carboxyl group from the reactive center would have less steric hindrance to form the DA adduct.

Changing the hydrocarbon chain length between the carboxylic acid and maleimide ring also had an impact on the equilibrium constant. For each of the furans studied, the equilibrium constant increased, when the hydrocarbon chain length between the maleimide nitrogen and carboxylic acid was increased. A larger increase in equilibrium conversion was observed, when the hydrocarbon spacer on maleimide was increased from 1 to 2 atoms than from 2 to 5. This trend either owes to unfavorable steric intermolecular interactions with the furan or intramolecular interactions that stabilize the maleimide. With a carbon spacer of $n = 1$, the maleimide species has the capacity to form hydrogen bonds between the carboxylic acid hydrogen and a carbonyl oxygen on the maleimide heterocycle, resulting in a seven-membered ring configuration. When the maleimide carbon spacer length increases to 2 or 5, a less stable eight- or eleven-membered ring would be necessary to achieve this intramolecular arrangement.

An interesting observation is that the solvent plays a considerable role in the equilibrium conversion of the DA reaction.[14,18,19] While we observed a very low equilibrium constant for the reaction between 2-furoic acid and β-alanine maleimide in DMF (Figure 2), the equilibrium constant in water was at least two orders of magnitude greater. As shown in Table 3, the water has a significant effect on the entropy of reaction.

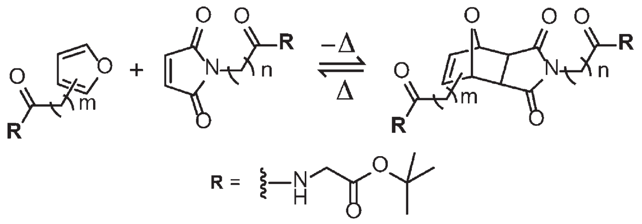
This increase in reaction entropy most likely stems from hydrophobic interaction between the solvent and reactants—the diene and dienophile. To minimize free energy, the solvent/reactant system arranges itself such that hydrophobic components are in close proximity to other hydrophobic entities and similarly with hydrophilic groups. While the diene and dienophile considered in this study possess hydrophobic character, the carboxylic acid moiety promotes hydrogen bonding. Hydrogen bonding most likely enhances the electron donating capacity of the diene, which may also explain the increase in conversion. Water hydrogen bonds well with the carbonyl and hydroxyl groups of a carboxylic acid such as those present in the furans studied. Hydrogen bonding to the carbonyl oxygen of the carboxylic acid likely delocalizes the extended conjugation of the furan ring and the carbonyl, which for a compound like 2-furoic acid enables the electrons of the furan ring to participate more readily in the DA reaction. The conversion for the reaction 3-(2-furyl) propionic acid with β-alanine maleimide also increased in water; however, it achieves nearly complete conversion for each

Table 3. Thermodynamic Data Comparison and Equilibrium Constant Comparision



	ΔH (kJ/mol)	ΔS (J/mol K)
(a) *Thermodynamic data comparison*		
DMF	−42 ± 8	−160 ± 20
Water	−41 ± 3	−110 ± 10
Temperature (°C)	DMF	Water
(*b*) *Predicted Equilibrium constant comparision*		
25	0.10	27
80	0.01	2.1

Solvent comparison of thermodynamic parameters—reaction of 2-furoic acid with β-alanine maleimide. (a) presents the experimentally determined thermodynamic parameters of the DA reaction, whereas (b) illustrates the predicted equilibrium constants at 25 and 80°C using the empirical parameters. The reaction scheme is presented on the top of the table.



Scheme 2. Summarized *tert*-butyl glycine-coupled DA reaction.

temperature, making the determination of thermodynamic parameters impractical using this method. An irreversible side reaction was found to dominate the study concerning 3-furoic acid and β-alanine maleimide ("Side reactions" section).

In a large number of materials applications, the DA species are incorporated by covalently coupling these reactive functional groups into the material. As stated earlier, the carboxylic acid functional group is a convenient handle, as it is readily coupled to amine functional groups to form an amide bond, which are found in a large set of commercially available materials, including proteins and DNA. As a result, we also explored the thermodynamic and kinetic differences between coupled and uncoupled furan and maleimide functional groups. With the exception of 2-furoic acid, which as noted earlier does not participate extensively in the DA reaction, the maleimides and furans were coupled to the amine of *tert*-butyl glycine. Upon their incorporation onto *tert*-butyl glycine, the diene and dienophile (Scheme 2) were permitted to react at various temperatures in DMF allowing for the analysis of the thermodynamic properties presented in Figure 3.

Maleimides with a hydrocarbon spacer exceeding two carbon units exhibited similar entropy and enthalpy values for both coupled and noncoupled carboxylic acids (Supporting Information). Likewise, when the furan hydrocarbon spacer was increased beyond one, amide coupling had a negligible effect on the entropy and enthalpy (right bars in Figures 3a, b). In contrast, the entropies and enthalpies of maleimides with a single carbon spacer were significantly different, when an amide was coupled to the 3-furoic acid (left bars in Figures 3a, b). As the carbonyl in a three-substituted furan is in resonance within the furan ring, it is perhaps not surprising that a change in electronegativity (amide vs. carboxylic acid) has a significant effect on the equilibrium conversion. For example, the enthalpy and entropy found for the 3-furoic acid were −53 ± 2 kJ/mol and −128 ± 7 J/(mol K), respectively, compared to −18 ± 0 kJ/mol and −37 ± 1 J/(mol K) for their glycine-coupled equivalents. The more positive enthalpy and entropy illustrate that the electron-withdrawing group and its proximity to the diene or dienophile significantly influence the DA reaction and the properties of materials that incorporate these moieties. With the electron-withdrawing group far enough removed from the diene and/or dienophile functionalities, the furan and maleimide exhibit similar thermodynamic properties.

Kinetic experiments

While the thermodynamic parameters provide information about the maximum extent of reaction, the reaction rate is often critical in using DA-based synthetic strategies or designing DA-based materials. For example, the healing kinetics of a covalent adaptable network must be on a time scale dictated by the application and the rheological behavior of polymer networks that incorporate DA structures is directly controlled by the thermoreversion kinetics.[6] Here, rate constants were determined as a function of temperature using Eq. 3, as discussed above, which enabled the determination of the activation energy and pre-exponential terms via an Arrhenius plot (Tables 4 and 5). Expressing the reaction kinetics in terms of activation energy and a pre-exponential term enables the rate constants to be estimated over the entire experimental range of temperatures. The ability to estimate the rate at which adducts form or revert back to the diene and dienophile will facilitate the *a priori* design for new materials.[15] In particular, knowing these rates will be of great benefit when designing a mendable material or a protecting group, as this determines the rate of material healing and reaction time, respectively.

To visualize better the trends in the data, the reverse reaction rate constant at 80°C is shown in Figure 4. The

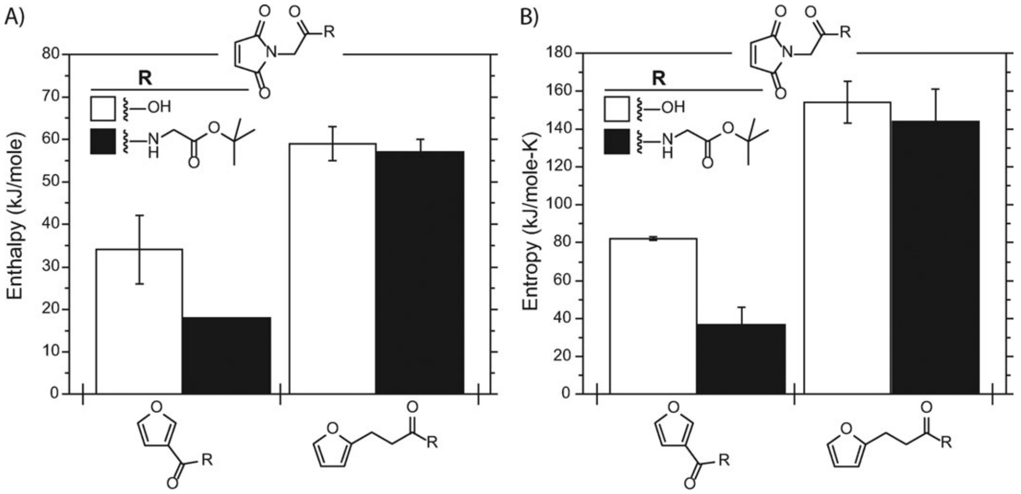
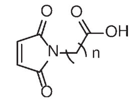
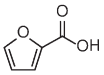
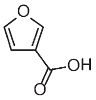
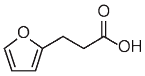


Figure 3. Summarized *tert*-butyl glycine-coupled furan and maleimide enthalpies (A) and entropies (B) in DMF (kJ/mol) compared to their carboxylic acid equivalents for the case where the maleimide spacer, *n*, equals 1.

The side-by-side bars show the uncoupled (carboxylic acid, open bars) and coupled (amide, dark bars) species (left to right, respectively).

Table 4. Kinetic Parameters Associated with Adduct Formation (Forward Reaction)

	Activation Energies (kJ/mol)			Frequency Factor (h^{-1})		
Acid Dienophile 	*n*			*n*		
	1	2	5	1	2	5
Acid diene						
	69 ± 7	24 ± 11	57 ± 6	$(4 \pm 7) \times 10^8$	30 ± 70	$(1 \pm 1) \times 10^7$
	55 ± 13	69 ± 3	55 ± 5	$(2 \pm 4) \times 10^7$	$(6 \pm 3) \times 10^9$	$(4 \pm 4) \times 10^7$
	44 ± 6	23 ± 7	60 ± 4	$(3 \pm 4) \times 10^6$	$(3 \pm 6) \times 10^5$	$(1 \pm 1) \times 10^9$

hydrocarbon spacer in the maleimide has a similar effect on the DA equilibrium constant as the reaction rate. Specifically, once the hydrocarbon spacer is greater than one carbon, the reaction rate is dictated by the furan structure. In a trend opposite to that observed with the equilibrium constant, as the carboxylic acid is shifted from the two- to three-position on the furan ring, there is a significant decrease in the reaction rate (i.e., the equilibrium constant was largest for the 3-furoic acid, whereas 3-furoic acid had the slowest reverse rate constant). While this behavior is at least partially explained by the differences in the position of the carbonyl electron-withdrawing group, steric hindrance may also play a significant role. Thus, the location of the electron-withdrawing group is more significant to the reverse reaction rate than any benefits resulting from the distance between the ring and the carboxylic acid.

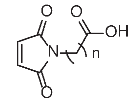
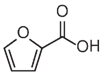
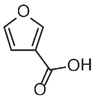
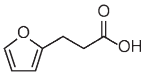
As observed with the equilibrium constant in the previous section, the solvent has a significant effect on the reaction rate. When water was utilized as the solvent, the forward reaction rate was seen to increase markedly. For instance, the forward reaction rate constant for the 2-furoic acid with β-alanine maleimide in water was found to be 0.36 ± 0.02 L/(mol h) compared to a forward rate constant of 0.002 ± 0.001 L/(mol h) for the same reaction in DMF. As stated earlier, water has the capacity to hydrogen bond with the carbonyl oxygen, which could potentially make 2-furoic acid a more reactive diene in the DA reaction. Additionally, hydrophobic effects also have the potential to bring the nonpolar diene and dienophiles into close proximity to one another in a hydrophilic environment, which could allow for a greater number of collisions and therefore chances to form the adduct.

The reverse kinetic parameters associated with furan and maleimide coupled to another species (glycine) compared to their carboxylic acid equivalents were also considered. It was found that the reverse rate constants for the carboxylic acids were very similar to their glycine-coupled equivalents (Figure 5). When the carbon chain length on the maleimide was increased, the trend of similar reverse rate constants in the carboxylic acids compared to the glycine-coupled counterparts held true (Supporting Information).

Side reactions

Monitoring the reactions considered in this study via NMR in lieu of other techniques, such as Fourier Transform Infrared Spectroscopy, allowed the detection of the DA

Table 5. Kinetic Parameters Associated with Adduct Degradation (Reverse Reaction)

	Activation Energies (kJ/mol)			Frequency Factor (h^{-1})		
Acid Dienophile 	*n*			*n*		
	1	2	5	1	2	5
Acid diene						
	115 ± 11	62 ± 28	99 ± 7	$(1 \pm 4) \times 10^{17}$	$(3 \pm 20) \times 10^8$	$(2 \pm 3) \times 10^{14}$
	89 ± 6	123 ± 2	110 ± 6	$(3 \pm 4) \times 10^{11}$	$(1.8 \pm 0.6) \times 10^{17}$	$(4 \pm 4) \times 10^{14}$
	107 ± 7	74 ± 4	95 ± 4	$(8 \pm 10) \times 10^{14}$	$(1 \pm 1) \times 10^{10}$	$(1 \pm 1) \times 10^{13}$

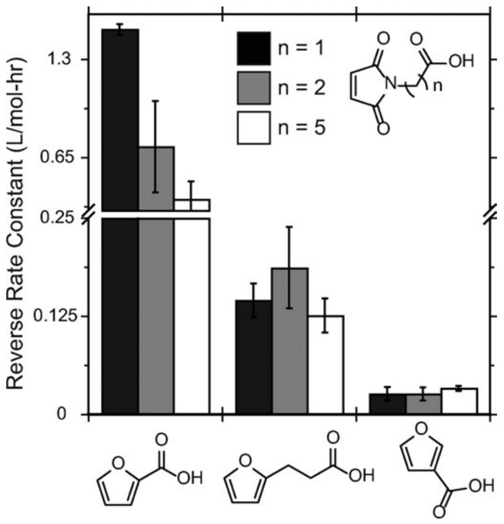


Figure 4. The reverse reaction rate constant at 80°C for the DA reaction of maleimide and furan carboxylic acids possessing various substitutional positions.

adduct as well as the formation of other products. The reactions involving 3-furoic acid and 3-furan functionalized *tert*-butyl glycine were observed to undergo an irreversible side reaction to a limited extent. Although the DA adduct was still the dominant product, the peaks of the new material were present in the NMR spectrum. The side reaction was only observed after extended periods of time and was more prominent at higher temperatures. Figure 6 depicts the structure of 3-furoic acid and 2-furoic acid with β-alanine maleimide in the adduct form. One possible explanation is that the 3-furoic acid forms a conjugated electron poor vinyl bond, which may be susceptible to nucleophilic attack. It has been well documented that maleimides and vinyl or acrylate species react readily with one another.[20,21]

In addition, a separate side reaction was found to occur when the reaction was examined in water. This side reaction was observed to occur with all diene and dienophile pairs at higher temperature. A control study was conducted where the dienes and dienophiles were prepared separately in D_2O and placed in separate NMR tubes. The study revealed that the furan alone did not undergo a side reaction. NMR of the maleimide dienophiles, however, illustrated the formation of a new compound. HNMR spectra are presented in the Supporting Information for 3-furoic acid and β-alanine maleimide carboxylic acids illustrating their stability, or lack there of, upon exposure to water at elevated temperatures.

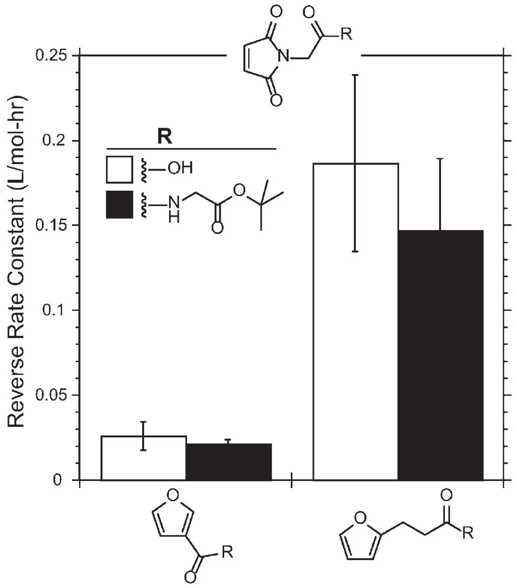


Figure 5. Comparison of the reverse rate constant at 80°C for carboxylic acids and their coupled glycine equivalents.

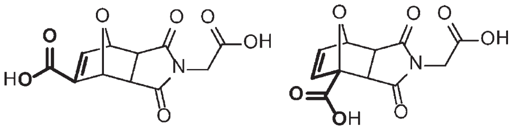


Figure 6. Adducts of 3-furoic acid and 2-furoic acid with β-alanine maleimide.

The structure on the left, an adduct with 3-furoic acid, possesses a conjugated electron poor vinyl functional group (in bold) while the structure on the left does not.

This side reaction has also been reported in the literature where maleimide has been shown to hydrolyze (ring open) when subjected to basic conditions.[22] An analogous mechanism whereby the maleimide hydrolyzes in acidic environments is also a potential pathway.

Conclusions

Systematically varying the substitutional position of the carboxylic acid moieties on the furan and maleimide substitued molecules allowed for the thermodynamic and kinetic properties of several different DA pairs to be considered. The thermodynamic and kinetic data presented in this study facilitate the selection and implementation of furan and maleimide carboxylic acid derivatives for various polymeric materials applications. From this study, it appears that the location of an electron-withdrawing group and the solvent system greatly impact the outcome of the DA reaction. For instance, placing an electron-withdrawing group on the 2-position on furan hinders the DA reaction. Changing the solvent was shown to influence the extent to which the electron withdrawing on the 2-position on furan hindered the formation of the DA adduct. Conversely, this study illustrates that steric effects seem to play a much less significant role in the DA reaction as the carboxylic acids had similar properties to their larger, glycine-coupled equivalents.

Ultimately, selection of a substituent and a hydrocarbon spacer on the furan and maleimide depends on the final target application and the specific requirements of that application. An abridged list of criteria that may come into play when selecting the appropriate furan and maleimide includes: reversibility of the DA reaction, the desired time scale for the reaction, and the final conversion achieved for the forward and reverse reactions. Given that the thermodynamic and kinetic properties of the carboxylic acid functionalized furan and maleimide molecules are similar once incorporated into other molecules, the data presented in this study grant some guidance for selection of the proper DA pair. For instance, construction of a mendable polymer material would require thermodynamic properties that maintain a high conversion (high-adduct population) at the desired normal operating temperature, providing an acceptable tolerance above and below this point. At the same time, if the material sustains damage, the reaction behavior must also allow reversion back to near complete diene and dienophile species upon heating above some threshold temperature to allow for healing to take place. In addition to these thermodynamic properties, the selected system for a mendable material must also have desirable kinetics; the system must be able to reach its final forward and reverse conversion on a reasonable time scale. In terms of the carboxylic acids dienes and dienophiles considered here, a large ΔH and small ΔS value (both in magnitude, not in sign) would be desirable to achieve the desired reaction behavior and enable formation of a mendable material. Additionally, the solvent system selected can also act as a handle to tune the reaction behavior. For instance, aqueous conditions drive the DA reaction to higher conversion faster than if the reaction were carried out in an aprotic solvent like DMF, providing a protection/deprotection strategy based solely on changing solvents.

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Literature Cited

1. Kolb HC, Finn MG, Sharpless KB. Click chemistry: Diverse chemical function from a few good reactions. *Angew Chem-Int Ed.* 2001;40(11):2004–2021.
2. Loudon GM. *The Diels–Alder reaction.* In: *Organic Chemistry*, 4th ed. ed: Oxford: University Press, Inc.: New York, NY, 2002:648–651, 1190.
3. Shibasaki M, Kanai M. Synthetic strategies for oseltamivir phosphate. *Eur J Org Chem.* 2008;2008(11):1839–1850.
4. Adzima BJ, Kloxin CJ, Bowman CN. Externally triggered healing of a thermoreversible covalent network via self-limited hysteresis heating. *Adv Mater.* 2010;22(25):2784–2787.
5. Dispinar T, Sanyal R, Sanyal A. A Diels–Alder/retro Diels-Alder strategy to synthesize polymers bearing maleimide side chains. *J Polym Sci Part A: Polym Chem.* 2007;45(20):4545–4551.
6. Bergman SD, Wudl F. Mendable polymers. *J Mater Chem.* 2008;18(1):41–62.
7. Chow CF, Lam MHW, Leung MKP. Fluorescent sensing of homocysteine by molecular imprinting. *Anal Chim Acta.* 2002;466(1):17–30.
8. Sun XL, Stabler CL, Cazalis CS, Chaikof EL. Carbohydrate and protein immobilization onto solid surfaces by sequential Diels–Alder and azide-alkyne cycloadditions. *Bioconjug Chem.* 2006;17(1):52–57.
9. Huwyler J, Wu DF, Pardridge WM. Brain drug delivery of small molecules using immunoliposomes. *Proc Natl Acad Sci USA.* 1996;93(24):14164–14169.
10. Mantovani G, Lecolley F, Tao L, Haddleton DM, Clerx J, Cornelissen J, Velonia K. Design and synthesis of N-maleimido-functionalized hydrophilic polymers via copper-mediated living radical polymerization: a suitable alternative to PEGylation chemistry. *J Am Chem Soc.* 2005;127(9):2966–2973.
11. Kojima K, Yoda N, Marvel CS. Base-catalyzed polymerization of maleimide and some derivatives and related unsaturated carbonamides. *J Polym Sci Part A-1: Polym Chem.* 1966;4(5PA1):1121–1134.
12. Conley NR, Hung RJ, Willson CG. A new synthetic route to authentic N-substituted aminomaleimides. *J Org Chem.* 2005;70(11):4553–4555.
13. Chujo Y, Sada K, Saegusa T. A novel nonionic hydrogel from 2-methyl-2oxazoline.4. reversivle gelation of polyoxazoline by means of Diels–Alder reaction. *Macromolecules.* 1990;23(10):2636–2641.
14. Wei HL, Yang Z, Chu HJ, Zhu J, Li ZC, Cui JS. Facile preparation of poly(*N*-isopropylacrylamide)-based hydrogels via aqueous Diels–Alder click reaction. *Polymer.* 2010;51(8):1694–1702.
15. Kloxin CJ, Scott TF, Adzima BJ, Bowman CN. Covalent adaptable networks (CANS): a unique paradigm in cross-linked polymers. *Macromolecules.* 2010;43(6):2643–2653.
16. Arena G, Cali R, Maccarone E, Passerini A. Thermodynamics of protonation of some 5-membered heteroaryl-carboxylates, heteroaryl-alkanoates and heteroaryl-trans-propenoates. *J Chem Soc–Perkin Tran* 2. 1993;(10):1941–1945.
17. Gupta RR, Kumar M, Gupta V. *Heterocyclic Chemistry II: Five-Membered Heterocycles.* Springer: Germany, 1998:114–115.
18. Lubineau A, Auge J, Queneau Y. Water-promoted organic-reactions. *Synthesis.* 1994;1994(8):741–760; Referenced:743–748.
19. Rideout DC, Breslow R. Hydrophobic acceleration of Diels–Alder reactions. *J Am Chem Soc.* 1980;102(26):7816–7817.
20. Jia XQ, Pang YW, Huang JL. Copolymerization of ethyl alpha-(hydroxymethyl)acrylate with maleimide and characterization of the resulting copolymer. *J Polym Sci Part A: Polym Chem.* 1998;36(8):1291–1299.
21. Decker C, Morel F, Jonsson S, Clark S, Hoyle C. Light-induced polymerisation of photoinitiator-free vinyl ether maleimide systems. *Macromol Chem Phys.* 1999;200(5):1005–1013.
22. Knight P. Hydrolysis of p-nn′-phenylenebismaleimide and its adducts with cysteine—implications for cross-linking of proteins. *Biochem J.* 1979;179(1):191–197.

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