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Predictions of Substituent Effects in Thermal Azide 1,3-Dipolar Cycloadditions: Implications for Dynamic Combinatorial (Reversible) and Click (Irreversible) Chemistry

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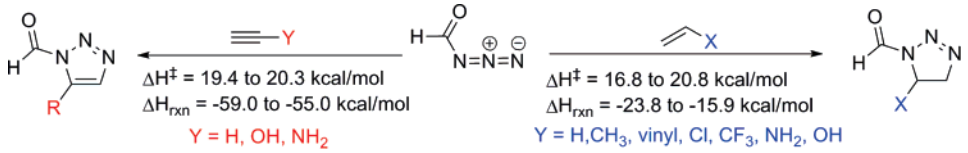

Substituent effects in 1,3-dipolar cycloadditions of azides with alkenes and alkynes were investigated with the high-accuracy CBS-QB3 method. The possibilities for noncatalytic activation and the reversibility or irreversibility of these reactions was explored; the possibilities for uses in dynamic combinatorial chemistry (DCC) or click chemistry were explored. The activation enthalpies for reactions of ethylene and acetylene with hydrazoic acid, formyl, phenyl-, methyl-, and methanesulfonylazides exhibit modest variation, with $\Delta H^{\ddagger}$ ranging from 17 to 20 kcal/mol. A detailed study of formylazide cycloadditions with various alkenes and alkynes reveals a narrow range of activation enthalpies (17−21 kcal/mol). The activation enthalpies for the reactions of azides with alkenes and alkynes are similar. FMO theory and distortion/interaction energy control have been used to rationalize the rates and regiochemistries of cycloadditions involving alkene dipolarophiles. Significantly, triazoles, formed from alkynes, are 30−40 kcal/mol more stable than tetrazolines formed from alkenes. On the basis of initial reactant concentrations, kinetic and thermodynamic values are suggested for the identification of reversible reactions that approach equilibrium over 24 h, as well as for fast irreversible reactions. Although azide cycloadditions are suitable for irreversible chemistry and are typically unsuitable for reversible applications, theoretical procedures established by these studies have provided guidelines for the prediction of useful reversible libraries.

Introduction

The thermodynamic stabilities of products and the kinetic control of selectivities are generally exploited principles in synthetic applications. Click chemistry, a concept which emerged during the past decade, is firmly grounded on these principles.[1] This concept utilizes the high selectivities and thermodynamic stabilities of products to facilitate synthetic applications in such diverse fields as biological chemistry, host−guest design, and supramolecular chemistry.

By contrast, dynamic combinatorial chemistry (DCC),[2] which also emerged during the past decade, is founded on a different philosophy. Here kinetic selectivities are immaterial, and the reversibility and thermodynamic control of the reaction are important. DCC also possesses vast potential in biological science and materials chemistry.

The aim of this study is to use a computational approach to explore substituent effects in azide 1,3-dipolar cycloadditions.

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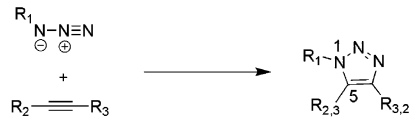
SCHEME 1. Catalyzed Azide−Alkyne Cycloadditions



(i) R_2 = H, R_3 = alkyl; Cu(I) or Mg(II) catalysts
(ii) R_2, R_3 = H, alkyl or aryl; Ru(II) catalysts

The goal of such an approach is to predict reactions that will undergo reversible exchange, appropriate for DCC, and to make predictions on the type of substituents that compounds must contain to facilitate reversible exchange, especially in systems where reversibility has not yet been demonstrated. In addition, reactions will be identified that are expected to be irreversible and may thus be suitable for investigations in which product stability is desired, such as click chemistry.

Background. Click chemistry, as formulated by the Sharpless group, utilizes rapid, modular reactions operating under a large thermodynamic driving force.[1a] These reactions involve the use of readily available starting materials and must be insensitive to reaction conditions. A number of reactions have been used in click chemistry including (1) cycloaddition reactions, usually involving 1,3-dipoles,[1] (2) nucleophilic substitution chemistry,[1a] usually involving ring-opening ring reactions of strained heterocyclic compounds, and (3) oxidative addition to carbon−carbon multiple bonds, usually involving dihydroxylation, aziridination, and sulfenyl halide addition.[1a]

1,3-Dipolar cycloaddition reactions are the most widely utilized examples of click chemistry. The copper-catalyzed 1,3-dipolar cycloaddition reaction of azides with terminal acetylenes is the poster child of Sharpless's click chemistry methodology (Scheme 1).[1,3] These reactions predominately form 1,4-disubstituted adducts, whereas both 1,4- and 1,5-disubstituted adducts are formed in the corresponding thermal reactions. Notably, only terminal alkynes can be used in the copper-catalyzed version, but more recent studies have shown that copper catalysts based on N-heterocyclic carbene (NHC) templates are capable of catalyzing azide cycloadditions involving both terminal and internal alkynes.[4] Ruthenium catalysts have also been used to promote azide 1,3-dipolar cycloadditions involving internal alkynes.[5]

Click chemistry has been applied in a number of diverse fields including combinatorial chemistry[1a,6,7] and materials chemistry,[8−11] as well as drug discovery and molecular biology.[1a,c−f,3j] Notably, potent inhibitors of carbonic anhydrase,[12] acetylcholine esterase (AChE),[13] and HIV-1 protease[14] have been synthesized in situ by the 1,3-dipolar cycloadditions of azides with alkynes, proceeding without the catalytic benefit derived from added copper. Remarkably, triazole adducts formed in AChE induce femtomolar inhibitory activity.[13] These results have in turn inspired studies utilizing copper-free conditions for in vivo labeling of proteins and cell surfaces.[15−17]

In dynamic combinatorial chemistry (DCC),[2] dynamic combinatorial libraries (DCLs) are generated from components that react reversibly via covalent bond formation or noncovalent interactions to provide dynamically interconverting molecules. Several potential applications of DCC have been identified. These include (a) the selection of the most stable structure from a DCL comprising members with different conformational properties (foldamers) based on internal noncovalent properties,[18] (b) the selection of a host by a guest from a DCL of potential host molecules, a particularly promising strategy for drug discovery, and (c) the selection of a guest by a host from a library of potential guest molecules.

The type of reaction used to generate a DCL is dependent on several requirements,[2] including (a) reversibility on a reasonable time scale, (b) availability of diverse building blocks, (c) mild reaction conditions (temperature, pressure, concentration) to prevent disruption of the interactions involved in molecular recognition, (d) all library members being soluble at equilibrium, (e) the reaction being able to be stopped so that library members can be isolated and characterized, (f) the reversible reaction being compatible with the experimental conditions used in the selection process, for example, aqueous solution in the case of drug discovery, and (g) the library members being nearly isoenergetic to prevent the formation of a thermodynamic trap under which equilibration is unattainable.

The reversible formation of C═N bonds from reactions of amines, hydroxylamines, or hydrazines with carbonyl groups is the most popular type of reaction used to generate DCLs.[2k,19] The search for new types of reversible reactions for use in DCC continues to be of great interest.[20]

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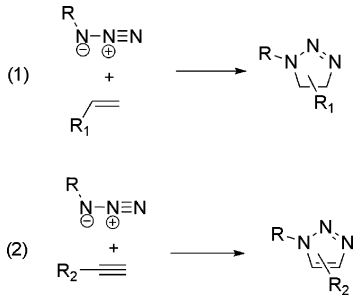
SCHEME 2. Thermal Cycloadditions of Azides with (1) Alkenes and (2) Alkynes



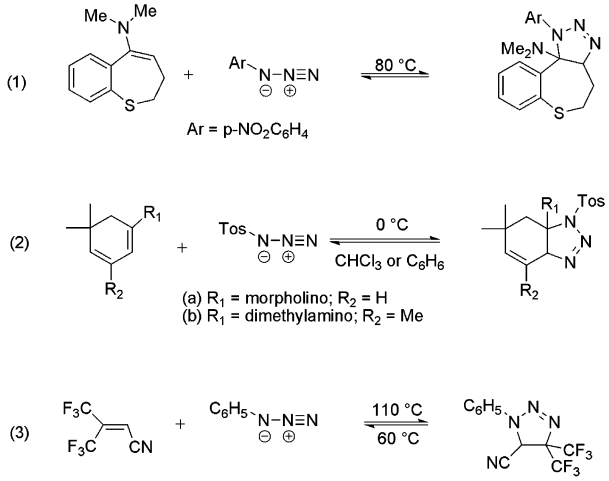
The irreversibility of azide−alkyne reactions as click chemistry paradigms prevents their use in DCC, but the library concept is achieved by the use of a library of reactants (azides and alkynes) and kinetic acceleration of one reaction by an active site.[1,2] The modularity of the azide−alkyne 1,3-dipolar cycloaddition suggests that incorporation of reversibility could expand the utility of DCC involving azide cycloadditions.

We have explored a variety of azide 1,3-dipolar cycloadditions involving alkenes and alkynes (Scheme 2) with high-accuracy computational methods to determine whether substitution patterns might be useful for DCC or click chemistry.

Although azide−alkene cycloadditions are usually irreversible, examples of reversibility are known,[21] usually involving cycloadditions of electron-deficient azides with enamines (Scheme 3, eqs 1[22] and 2[23]). Reactions of conjugated azides with highly electron-deficient alkenes may also be in dynamic equilibrium with triazoline adducts (cf. eq 3[24]).

These results are particularly encouraging in light of the fact that previous studies have noted the high reactivities of enamines in 1,3-dipolar cycloadditions of azides with alkenes.[25−27] More generally, azides are ambiphilic (type II) dipoles which exhibit characteristic substituent effects in 1,3-dipolar cycloadditions involving alkenes.[27] These substituent effects have been rationalized by FMO theory.[28] For example, in 1,3-dipolar cycloadditions of phenylazide with various alkenes, a plot of log k_2 versus alkene IPs gives a U-shaped activity curve, typical of ambiphilic 1,3-dipoles.[29] The rates for 1,3-dipolar cycloadditions

SCHEME 3. Examples of Experimentally Observed Reversible Azide Cycloadditions



of both electron-rich ($HOMO_{dipolarophile}$−$LUMO_{dipole}$ gap smallest) and electron-deficient ($HOMO_{dipole}$−$LUMO_{dipolarophile}$ gap smallest) alkenes are approximately similar and are greater than the rates of 1,3-dipolar reactions involving alkenes of intermediate polarity (large HOMO−LUMO gaps). Of course, the U-shaped curve may become asymmetrical in cycloadditions involving markedly electron-deficient dipoles due to the much larger reactivity of such dipoles with electron-rich alkenes than with either electron-poor or conjugated alkenes.[27]

General rules have been developed for the reactivities and regioselectivities of reactions of various 1,3-dipoles with alkenes with the use of FMO theory[30] and by the direction of electron migration.[31] Hard and soft acid and base (HSAB) theories based on conceptual density functional theory[32] have recently been used to make predictions of reactivities and regioselectivities in 1,3-dipolar cycloaddition reactions.[33−37] Houk and Ess have more recently developed a general distortion/interaction energy control theory for the reactivities of 1,3-dipolar cycloadditions.[38] This theory describes the correlation between distortion energies and the activation barriers for 1,3-dipolar cycloadditions of various 1,3-dipoles with alkenes and alkynes. These studies revealed that reactivity differences between dipoles are controlled by the distortion energies of the reactants (the energy required to distort the ground state of the reactants to their transition state geometries), rather than by frontier molecular orbital (FMO) interactions or reaction thermodynamics. FMO interactions do influence interaction energies between the 1,3-dipole and the dipolarophile at the transition state and differentiate dipolarophile reactivities.

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The Supporting Information that accompanies this article provides a detailed description of guidelines for the identification of reversible reactions from the energetic parameters of each reaction studied herein. From these predictions, it was possible to assign reactions suitable for proof-of-principle studies (those having millimolar concentrations of reactants) as having ΔH_{rxn} values in the range of −17 to −20 kcal/mol with an optimal value being approximately −18 kcal/mol. Enthalpic barriers below 10 kcal/mol are suitable for reactions that have $t_{1/2}$ on the order of 24 h at these concentrations. Those suitable for in situ investigations (micromolar reactant concentrations) are proposed to have predicted ΔH_{rxn} values in the range of −21 to −24 kcal/mol with an optimal value of approximately −23 kcal/mol. Activation enthalpies lower than 5 kcal/mol are required for fast reactions at micromolar reactant concentrations. These are, of course, very restrictive ranges that make the predictions of appropriate reactions very difficult and also make catalysis necessary in most cases.

Computational Methods

All calculations were performed with the Gaussian03 suite of programs.[39] All calculations were performed with the CBS-QB3 compound method.[40] CBS-QB3 involves optimizations with the B3LYP method and the 6-311G(2d,d,p) basis set. A series of higher level calculations are performed with this geometry, giving energies within ±1 kcal/mol of experimentally determined values for the G2 data set. Calculations with the conductor-like polarizable continuum model[41] with the self-consistent reaction field, CPCM-SCRF, were performed with the HF/6-31+G(d) method to address aqueous solvation effects of all stationary points found with CBS-QB3.[42] Energies and distances are given in units of kcal/mol and angstroms, respectively. All optimizations were done in the gas phase at standard temperature and pressure.

Results and Discussion

Reactions of Substituted Azides with Ethylene and Acetylene. Initial studies were performed on the cycloadditions of hydrazoic acid with ethylene and acetylene. Detailed descriptions of the transition structures and energies for these reactions were addressed in a previous publication.[43] The most important features of that study are summarized here, and new results are reported for the cycloadditions of formyl-, methyl-, phenyl-, and methanesulfonylazides with both dipolarophiles.

The activation enthalpies for the reactions of hydrazoic acid with ethylene and acetylene are the same, 19 kcal/mol (Table 1). The reaction enthalpy for the cycloaddition of hydrazoic acid with ethylene is −22 kcal/mol in the gas phase. In contrast, the reaction involving the triple-bonded acetylene results in the formation of an aromatic adduct which is more than 40 kcal/mol more exothermic than that for the reaction of hydrazoic acid with ethylene which forms a nonaromatic adduct. The activation energies of all five cycloadditions are only modestly increased, 4 kcal/mol or less in water, but the products of all cycloadditions are significantly stabilized by 4−7 kcal/mol in water.

Substitution of the azide with electron-withdrawing, electron-donating, and conjugating substituents has a negligible effect on both activation barriers and heats of all reactions in comparison with hydrazoic acid: the reactions of ethylene and acetylene with formyl-, methanesulfonyl-, phenyl-, and methylazides all have activation enthalpies ranging from 17 to 19 kcal/mol. The reaction enthalpies of these cycloadditions also follow trends that are similar to activation enthalpies. Reactions of formyl-, methanesulfonyl-, phenyl-, and methylazides with ethylene have similar reaction enthalpies ranging from −22 to

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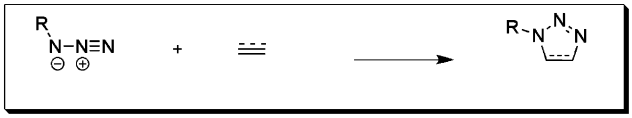
TABLE 1. Activation Enthalpies and Reaction Enthalpies for the 1,3-Dipolar Cycloadditions of Ethylene with Substituted Azides as Determined by the CBS-QB3 Method (Numbers in Parentheses are Energies Corrected with Aqueous Solvation Energies)



	Ethylene				Acetylene			
Azide	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$	ΔH_{rxn}	ΔG_{rxn}	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$	ΔH_{rxn}	ΔG_{rxn}
OHC–N≡N	19.3 (16.3)	30.8 (27.5)	-22.0 (-35.3)	-9.8 (-23.1)	20.1 (17.6)	30.5 (28.0)	-57.7 (-68.2)	-45.3 (-55.6)
H–N≡N	19.0 (21.0)	30.3 (32.3)	-21.5 (-28.5)	-9.1 (-16.1)	19.0 (21.6)	29.1 (31.8)	-63.7 (-71.1)	-51.7 (-59.1)
Me–N≡N	16.9 (18.6)	28.6 (30.1)	-25.6 (-31.9)	-12.3 (-18.7)	17.3 (18.5)	27.8 (28.9)	-69.0 (-77.0)	-56.8 (-64.5)
Ph–N≡N	16.7 (18.1)	28.1 (29.4)	-24.1 (-30.2)	-13.2 (-18.0)	17.3 (19.2)	27.6 (29.6)	-66.0 (-70.7)	-53.6 (-58.3)
MeO_2S–N≡N	16.4 (18.5)	28.4 (30.3)	-24.9 (-29.4)	-11.5 (-16.0)	17.3 (19.4)	28.3 (30.2)	-60.7 (-64.1)	-47.7 (-51.0)

−25 kcal/mol. All acetylene cycloadditions are 36−42 kcal/ more exothermic than reactions involving ethylene.

The observation that alkenes and alkynes have similar activation enthalpies in 1,3-dipolar cycloadditions although the thermodynamics are so drastically different has not been rationalized by FMO theory. This has recently been rationalized by Ess and Houk by the observation that reactions of various 1,3-dipoles with both types of dienophiles possess identical distortion energies.[38] As a result, activation enthalpies are identical for 1,3-dipolar cycloadditions involving ethylene and acetylene.

The activation enthalpies for most of these reactions exhibit modest (1−2 kcal/mol) increases in water. The lone exceptions are for the cycloadditions of formylazide with ethylene and acetylene for which the activation enthalpies decrease by about 3 kcal/mol. In contrast, the exothermicities of these reactions increase by larger amounts, 5−11 kcal/mol.

Examination of the energetics of these cycloadditions leads to the following observations on the suitability of these reactions for use in synthetic applications which require the use of reversible or irreversible reactions: (1) The barriers for all azide 1,3-dipolar cycloadditions with ethylene and acetylene are similar; however, reactions involving acetylenes are exothermic by 60−70 kcal/mol. As demonstrated by Sharpless and others, these are attractive candidates for synthetic applications relying on reactions which are irreversible at all concentrations.[1,3] The barriers for the 1,3-cycloadditions of *terminal* alkynes have been shown to be significantly lowered by the use of copper catalysts.[44−46] Activation enthalpies for alkyne cycloadditions are also significantly lowered by their introduction into a ring.[15−17] Herein, we report investigations on substituent effects on the activation enthalpies of these reactions to examine the likelihood of designing reactions based on these templates that may be fast at ambient temperatures in the absence of catalyst or without the incorporation of ring strain. (2) The reaction enthalpies for most azide−alkene 1,3-dipolar cycloadditions are within the range targeted for reversibility at micromolar, −21 to −24 kcal/mol (see Supporting Information for details), but the activation enthalpies are too high for the reactions to proceed at a reasonable rate. Because of the similarities of the energies obtained for the cycloadditions involving all azides, it seemed reasonable to perform additional computational studies on 1,3-dipolar cycloadditions of selected azides with various alkenes and alkynes to evaluate whether these reactions could be fast at ambient temperatures and reversible at various concentrations. Formylazide and methanesulfonylazide were selected because of their relatively small sizes (appropriate for computational studies with high-accuracy methods) and because of the previously observed reversibility of reactions of electron-deficient azides with electron-rich alkenes (Scheme 3). It also seemed that the barriers of these reactions of alkenes with these electron-deficient azides could be easily modified by the appropriate use of alkene substituents. Note that aliphatic azides are promoted as being stable to a variety of functional groups and to a variety of synthetic conditions.[1a] Aromatic azides have also been frequently used in various investigations.[25,26]

Reactions of Substituted Alkenes with Formylazide. Gas-phase energies and energies corrected with aqueous solvation energies were computed for the reactions of formylazide with substituted alkenes. Table 2 shows the energies for these reactions subdivided into three classes comprising electron-rich alkenes, conjugated alkenes including ethylene, and electron-deficient alkenes.

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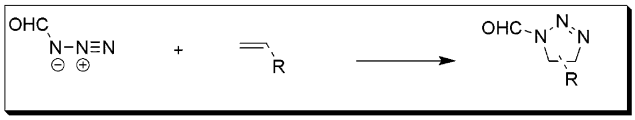
TABLE 2. Activation Enthalpies and Reaction Enthalpies for the 1,3-Dipolar Cycloaddition Reactions of Formylazide with Substituted Alkenes as Predicted by CBS-QB3 (Numbers in Parentheses are Energies Corrected with Aqueous Solvation Energies)



	Alkene	1,5-disubstituted $\Delta H^{\ddagger}$	1,5-disubstituted $\Delta G^{\ddagger}$	1,5-disubstituted ΔH_{rxn}	1,5-disubstituted ΔG_{rxn}	1,4-disubstituted $\Delta H^{\ddagger}$	1,4-disubstituted $\Delta G^{\ddagger}$	1,4-disubstituted ΔH_{rxn}	1,4-disubstituted ΔG_{rxn}
Electron-rich	NH_2	16.8 (6.2)	29.2 (18.6)	-19.9 (-32.2)	-6.3 (-18.6)	20.9 (20.1)	33.2 (32.4)	-17.4 (-30.3)	-5.0 (-17.9)
	OH	19.9 (15.8)	32.4 (28.3)	-23.8 (-34.7)	-10.0 (-20.9)	21.8 (21.5)	34.0 (33.7)	-20.0 (-31.3)	-6.8 (-18.1)
Conjugated		19.0 (16.3)	30.3 (27.5)	-21.5 (-35.3)	-9.1 (-23.1)				
	Me	19.1 (18.2)	31.5 (30.7)	-23.7 (-34.3)	-9.8 (-20.4)	19.4 (19.1)	31.9 (31.5)	-23.2 (-33.7)	-9.8 (-20.4)
		19.6 (18.1)	31.9 (30.4)	-19.7 (-30.1)	-6.4 (-16.8)	20.5 (19.2)	32.7 (31.4)	-18.3 (-29.6)	-5.2 (-16.5)
	Cl	20.7 (21.2)	33.2 (33.7)	-23.8 (-35.4)	-9.9 (-21.5)	21.4 (21.0)	33.8 (33.4)	-20.6 (-33.1)	-6.8 (-19.3)
Electron-deficient	CF_3	18.7 (20.2)	31.6 (33.2)	-22.5 (-33.9)	-8.4 (-19.8)	19.3 (19.5)	31.8 (32.0)	-21.0 (-32.9)	-7.1 (-19.1)
	CN	20.8 (20.8)	33.2 (33.2)	-15.9 (-27.8)	-2.6 (-14.4)	20.3 (17.7)	32.6 (30.0)	-15.2 (-27.9)	-1.9 (-14.6)

1,5-Disubstituted triazolines are kinetically favored over 1,4-disubstituted triazolines by about 1 kcal/mol for all but the strongest electron-withdrawing substituent in acrylonitrile.

Within the subset of reactions involving electron-rich alkenes, the cycloaddition of vinylamine with formylazide has an activation enthalpy of 17 kcal/mol, 3 kcal/mol less than the cycloaddition involving vinylalcohol. The exceptional reactivity of enamines in 1,3-dipolar cycloadditions with azide dipoles has been noted.[25−27] The activation enthalpies for cycloadditions involving conjugated alkenes and ethylene range from 19 to 21 kcal/mol, increasing in the order ethylene < propene < butadiene < chloroethylene. These results are in keeping with previous observations on the regioselectivities and reactivities of cycloadditions of azides with alkenes.[25−27,30,33h]

The lowest-energy transition structures for these reactions (Figure 1) show that the cycloaddition involving vinylamine is quite synchronous; the forming bonds have bond distances of 1.92 Å (N3−C4) and 2.46 Å (N1−C5). All other transition structures are more synchronous, having bond distances ranging from 2.0 to 2.2 Å. The bonds being formed between N3 and C4 are shorter than the bonds formed between N1 and C5 in almost all cases. The lone exception is for the TS of the reaction between formylazide and acrylonitrile which favors formation of the 1,4-disubstituted regioisomer. Unsurprisingly, the bond between N1 and C5 is shorter than that between N3 and C4 since now the interaction of the nucleophilic terminus of the azide with the electrophilic terminus of acrylonitrile is most important in the transition state.

The trends in the activation enthalpies of these reactions are best understood by analysis of the charge separations in the transition structures of these reactions as shown in Table 3. The largest charge transfer is observed for the reaction involving vinylamine; 0.36*e* is transferred to formylazide from the alkene, consistent with the low activation enthalpy of this reaction in comparison with the others. The amount of charge transferred from formylazide to the alkene falls off sharply for more electron-deficient alkenes.

The activation enthalpies for the 1,3-dipolar cycloadditions of formylazide with these alkenes lie in a narrow range of values, from 17 to 21 kcal/mol. More remarkably, if the reaction involving vinylamine is disregarded, the activation enthalpies only range from 19 to 21 kcal/mol. The HOMO and LUMO energies for formylazide are −8.3 and −0.2 eV, respectively. The dominant interaction for all reactions is between the HOMO of the alkene and the LUMO of the azide. These separations are smaller, by as much as 6 eV, than the opposite combination, involving interactions between the HOMO of formylazide and the LUMO of the alkene. The HOMO energy of vinylamine is −5.4 eV; the HOMO energies of the other alkenes are larger, ranging from −6.2 to −8.2 eV. The smallest Kohn−Sham HOMO−LUMO gap (3.6 eV) is for the reaction of formylazide

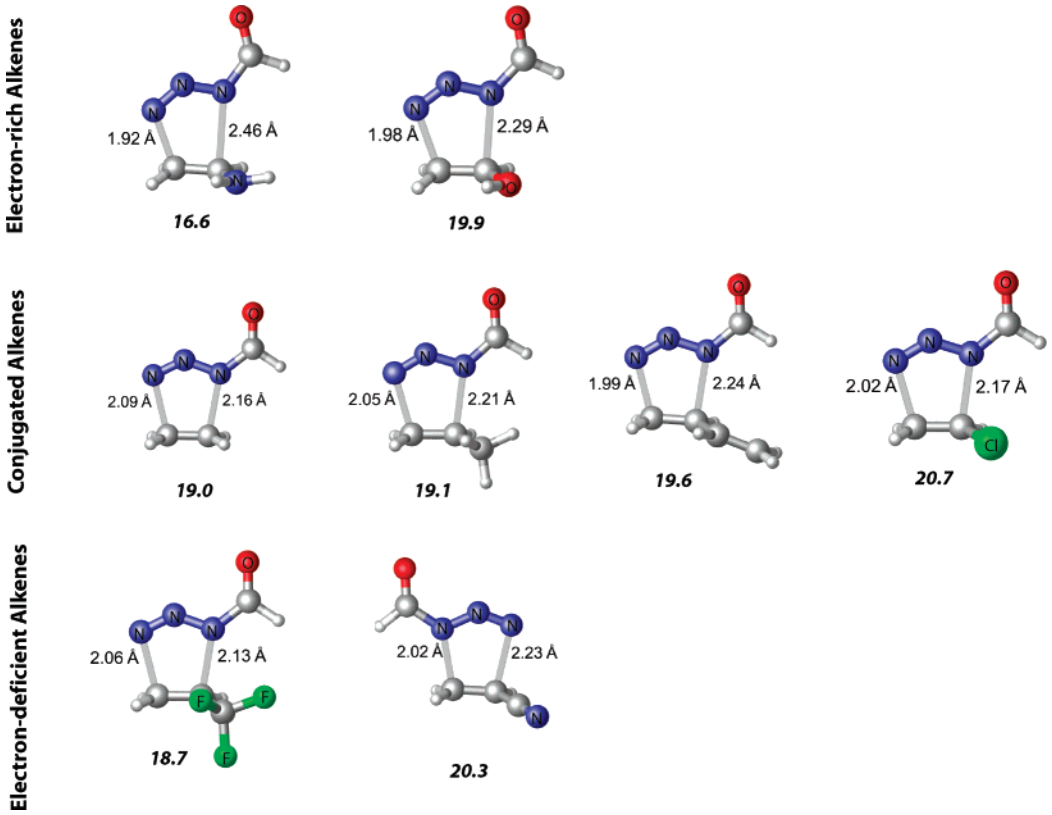
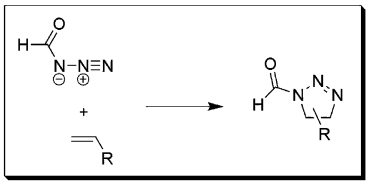


FIGURE 1. CBS-QB3 low-energy transition structures, forming bond distances, in Å, and activation enthalpies, in italics, for 1,3-dipolar cycloadditions of formylazide with alkene dipolarophiles.

TABLE 3. Activation Enthalpies, HOMO−LUMO Separations in Electronvolts, and Sum of Mulliken Charge, *Q*, in Units of *e*, on the Atoms of Dipolarophiles at the Transition Structures for 1,3-Dipolar Cycloadditions of Formylazide with Alkene Dipolarophiles



	Alkene	*Q*	$HOMO_{alkene}$	$LUMO_{alkene}$	$\Delta H^{\ddagger}$
Electron-rich	NH_2	0.36	-5.4	1.4	16.6
	OH	0.25	-6.2	1.1	19.9
Conjugated		0.15	-7.2	0.5	19.0
	Me	0.18	-6.6	0.8	19.1
		0.17	-6.2	-0.6	19.6
	Cl	0.12	-7.1	0.0	20.7
Electron-deficient	CF_3	0.09	-8.1	-0.5	18.7
	CN	0.06	-7.9	-1.5	20.3

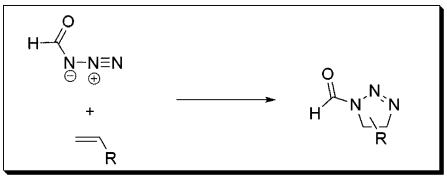
with vinylamine, consistent with the comparatively low activation enthalpy.

Further evidence for the exceptional reactivity of vinylamine in these cycloadditions in comparison with all other alkenes is provided by an analysis of the distortion and interaction enthalpies of these cycloadditions. The distortion enthalpy is the energy required to distort the ground state of the reactants to the transition state geometry. The total distortion, $\Delta H_d^{\ddagger}$, and interaction, $\Delta H_i^{\ddagger}$, enthalpies are related to the activation enthalpy of the reaction by $\Delta H^{\ddagger} = \Delta H_d^{\ddagger} + \Delta H_i^{\ddagger}$. Table 4 shows predicted activation, $\Delta H^{\ddagger}$, distortion, $\Delta H_d^{\ddagger}$, and interaction, $\Delta H_i^{\ddagger}$, enthalpies for the series of reactions.

The total distortion enthalpies for all reactions lie in a narrow range, just 28−34 kcal/mol; this is consistent with the narrow range of activation enthalpies predicted for these reactions. The total distortion enthalpies for all reactions are greater than the corresponding activation enthalpies, and as a result, the interaction enthalpies are stabilizing. Notably, the trends found for alkene reactivities in these cycloadditions follow closely with the derived interaction enthalpies. The reaction involving vinylamine has the largest interaction enthalpy, −17 kcal/mol, while the other reactions have interaction enthalpies that only range from −9 to −13 kcal/mol. This is consistent with the charge separations observed at the transition states of these reactions: the azide transfers the greatest amount of charge from vinylamine; significantly less charge is transferred from other alkenes. Similar generalizations have been made by Ess and Houk regarding the interaction energy control in reactions of a 1,3-dipole with a series of alkene dipolarophiles.[38]

Overall, the reactivity trends observed in these reactions are rationalized by the insights provided by FMO theory and by the analysis of the distortion and interaction energies of these reactions: 1,3-dipolar cycloadditions of formylazide are fastest

TABLE 4. Activation, $\Delta H^{\ddagger}$, Distortion, $\Delta H_d^{\ddagger}$, and Interaction, $\Delta H_i^{\ddagger}$, Enthalpies Predicted by CBS-QB3 for the 1,3-Dipolar Cycloadditions of Formylazide with Alkene Dipolarophiles



Alkene	$\Delta H^{\ddagger}$	$\Delta H_d^{\ddagger}$	$\Delta H_i^{\ddagger}$
	16.8	33.8	-17.0
	19.9	32.5	-12.6
	19.3	27.8	-8.5
	19.1	30.0	-10.9
	19.6	31.3	-11.7
	20.7	31.7	-11.0
	18.7	30.2	-11.6
	20.3	31.7	-11.4

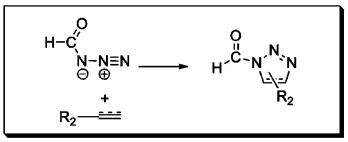
with electron-rich alkenes, while reactions involving all other alkenes are slow; these trends are typical of electrophilic dipoles. These contrast with reactivities previously identified for phenylazide cycloadditions, which are typical of ambiphilic dipoles.[29]

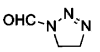
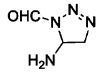
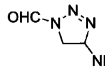
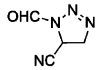
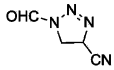
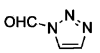
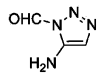
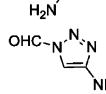
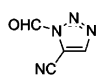
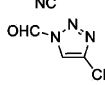
The reaction enthalpies for these formylazide cycloadditions range from −15 to −24 kcal/mol. The reaction involving cyanoethylene is at least 5 kcal/mol less exothermic than other reactions. Notably, reaction enthalpies do not follow the trends found in activation enthalpies. For example, although the reaction involving vinylamine has the lowest activation enthalpy, it is not as exothermic as the reaction involving vinylchloride, which has one of the largest activation enthalpies.

Activation enthalpies for most of these cycloadditions in water are within 1−4 kcal/mol of gas-phase activation enthalpies. The activation enthalpies for reactions involving vinylchloride and trifluoromethylethylene increase in water, but all others are modestly lowered. The reaction of trifluoromethylethylene with formylazide is the only reaction in which formation of the 1,5-disubstituted triazoline regioisomer is favored in the gas phase but is disfavored in water, although by only 1 kcal/mol. Collectively, the changes in the activation enthalpies for these reactions are not as dramatic as that seen for the reaction of formylazide with vinylamine. The activation enthalpy for the reaction decreases from 17 kcal/mol in the gas phase to 6 kcal/mol in water, a remarkable 11 kcal/mol reduction in the barrier of the reaction. Water significantly stabilizes all reactions by an additional 10−14 kcal/mol, so much so that the reaction of cyanoethylene, which is nearly thermoneutral in the gas phase, becomes exergonic by −15 kcal/mol in water.

Reactions of Substituted Alkynes with Formylazide. The energies for the reactions of formylazide with selected alkynes and their alkene analogues are compared in Table 5. Activation enthalpies and reaction energies corrected with aqueous solvation energies are also shown. The activation enthalpies for the

TABLE 5. Activation Enthalpies and Reaction Enthalpies for the 1,3-Dipolar Cycloaddition Reactions of Formylazide with Substituted Alkenes and Alkynes as Determined by CBS-QB3 (Numbers in Parentheses are Energies Corrected with Aqueous Solvation Energies)



		$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$	ΔH_{rxn}	ΔG_{rxn}
Alkene	**Product**				
		19.0 (16.3)	30.3 (27.5)	-21.5 (-35.3)	-9.1 (-23.1)
		16.8 (6.2)	29.2 (18.6)	-19.9 (-32.2)	-6.3 (-18.6)
		20.9 (20.1)	33.2 (32.4)	-17.4 (-30.3)	-5.0 (-17.9)
		20.8 (20.8)	33.2 (33.2)	-15.9 (-27.8)	-2.6 (-14.4)
		20.3 (17.7)	32.6 (30.0)	-15.2 (-27.9)	-1.9 (-14.6)
Alkyne	**Product**				
		20.1 (17.6)	30.5 (28.0)	-57.7 (-68.2)	-45.3 (-55.6)
		20.8 (17.3)	32.3 (28.8)	-59.0 (-65.9)	-44.9 (-51.8)
		19.4 (21.7)	31.3 (33.6)	-61.3 (-66.3)	-47.1 (-52.1)
		20.3 (22.6)	31.1 (33.4)	-55.0 (-57.5)	-42.0 (-44.5)
		21.4 (21.7)	32.1 (33.6)	-55.9 (-66.3)	-43.0 (-52.1)

reactions of formylazide with most alkynes are similar to reactions involving the corresponding alkene analogues. Also evident is the ∼40 kcal/mol greater thermodynamic stability of all triazoles in comparison with triazolines. Similar observations were made for the reactions of substituted azides with ethylene and acetylene.

Activation enthalpies corrected with aqueous solvation energies are within 3 kcal/mol of gas-phase activation enthalpies for most reactions, with the noteworthy exception of the reaction involving vinylamine. Notably, in the gas-phase cycloaddition of formylazide with ynamine, the 1,4-disubstituted adduct is predicted to be favored by 1 kcal/mol, but the regioselectivity switches in water to favor the 1,5-disubstituted adduct by 4 kcal/mol.

For cycloadditions involving amine-substituted alkenes and alkynes, the activation enthalpies leading to formation of the 1,4-disubstituted adducts are only moderately lowered in water; therefore, reactant destabilization in water does not seem to be a likely scenario. The transition states leading to formation of the 1,5-disubstituted adducts must be strongly stabilized by water. The dipole moments of these transition structures provide an indication of the source of these trends. The transition states

for formation of 1,4-disubstituted adducts have dipole moments of 1.2 D; however, the transition states leading to formation of 1,5-disubstituted adducts have larger dipole moments of 3.1 D and are likely to be more stabilized in the strongly polar aqueous environment.

Generation of Triazoline Libraries from Enamines and Ketene Acetals. All of these reactions possess high barriers and would be slow at room temperature. In addition, the 1,3-dipolar cycloadditions of formylazide with the alkenes studied here would most likely be unsuitable for the generation of reversible libraries under the thermodynamic guidelines outlined at the outset.

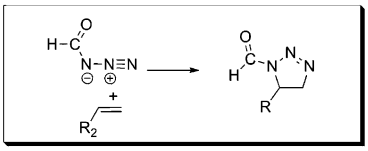
The focus has been shifted to reactions involving the electron-rich alkenes, vinylamine and vinylalcohol. With reference to target energies for reversibility shown in the Supporting Information that accompanies this article, the gas-phase reaction enthalpies for these cycloadditions (−22 and −24 kcal/mol, respectively) are within the desired range for the establishment of a dynamic equilibrium at micromolar concentrations of reactants. At concentrations of 0.1−10 μM, the gas-phase activation enthalpies required for the completion of one half-life in 24 h would be in the range of 3−5 kcal/mol. However, the activation enthalpies for the cycloadditions of formylazide with vinylamine and vinylalcohol in the gas phase are 17 and 20 kcal/mol, respectively. As a result, these activation enthalpies would have to be reduced by some 12−17 kcal/mol to be attractive candidates for the reversible generation of adducts from azides and enamines or enols in the gas phase or other relatively nonpolar solvent. Nevertheless, reduction of the $HOMO_{alkene}-LUMO_{formylazide}$ gap (and, consequently, the activation barrier) may be possible by increasing the electron-donating character of the enamine or the electron-withdrawing character of the azide. Equations 1 and 2 (cf. Scheme 3) illustrate where such effects might have played a significant role in previous observations of reversibility in azide−enamine 1,3-dipolar cycloadditions. Particularly attractive, especially from a kinetic perspective, is the prospect of performing the reaction of azides with enamines and vinylalcohol derivatives in the aqueous phase.

The activation enthalpies for the reaction of formylazide with vinylamine and vinylalcohol in water are predicted to be 6 and 16 kcal/mol, respectively. The reaction involving vinylamine is within the target for reactions completing one half-life at 10−100 μM concentration of reactants, while the reaction involving vinylalcohol would be slow at even 1 M concentration of reactants (see Supporting Information for details). The largest obstacle, though, is that the exothermicities for both reactions increase to −32 and −35 kcal/mol in water. As a result, the reversibility of both reactions is limited even at nanomolar concentrations of reactants.

The cycloadditions of azides with enamines have been studied in an effort to simulate, as realistically as possible, conditions for which the reversibility of these reactions may be experimentally demonstrated under DCC conditions. Reactions of enamines in aqueous media are impractical in many cases, owing to obstacles associated with tautomerism and hydrolysis.[47]

The cycloadditions of azides with ketene acetals have also been explored. The main obstacle to the incorporation of vinyl ethers in generating triazoline libraries is the relatively high barrier for reaction with formyl azide. We surmised that the presence of an additional hydroxyl substituent on the ethylene moiety should increase the reactivity of vinyl ethers in dipolar cycloadditions with azides, thereby offering the possibility of their entry into generation of triazoline libraries. The stability of these reactants in water is an additional advantage over reactions involving enamines.

TABLE 6. Activation Enthalpies and Reaction Enthalpies for the 1,3-Dipolar Cycloaddition Reactions of Formylazide with Enamine and Enol Determines (Numbers in Parentheses are Energies Corrected with Aqueous Solvation Energies)



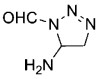
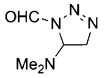
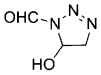
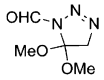
Alkene	Product	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$	ΔH_{rxn}	ΔG_{rxn}
		16.8 (6.2)	29.2 (18.6)	-19.9 (-32.2)	-6.3 (-18.6)
		12.8 (3.9)	25.0 (16.0)	-22.1 (-31.4)	-7.8 (-17.1)
		19.9 (19.9)	32.4 (28.3)	-23.8 (-34.7)	-10.0 (-20.9)
		15.3 (9.1)	28.5 (22.3)	-23.9 (-30.4)	-10.0 (-16.5)

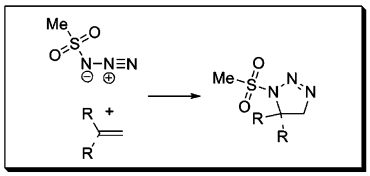
Table 6 shows predicted activation enthalpies, free energies of activation and reaction energies for 1,3-dipolar cycloadditions of formylazide with enamines and vinylalcohol derivatives. Replacement of the amino substituent on the alkene with a dimethylamino substituent lowers the activation barrier from 17 to 13 kcal/mol in the gas phase, but the reaction enthalpy remains essentially unchanged at −22 kcal/mol. Similarly, *O*,*O*-dimethyl substituents on the alkene lowers the barrier from 20 kcal/mol, for the reaction involving vinylalcohol, to 15 kcal/mol. The reaction enthalpy of −24 kcal/mol also remains essentially unchanged.

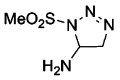
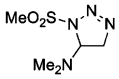
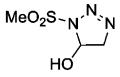
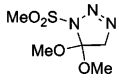
The reduction of the activation enthalpies of these reactions in water is even more remarkable. In the enamine series, introduction of the dimethylamino substituent lowers the barrier from 6 kcal/mol, for vinylamine, to 4 kcal/mol. The activation enthalpy is lowered from 20 kcal/mol for vinylalcohol to 10 kcal/mol for *O*,*O*-dimethyl keteneacetal. Although the reactions become slightly more endothermic in water, the reaction enthalpies are still too exothermic at −30 kcal/mol to be reversible at even nanomolar concentrations.

The reactivity trends for cycloadditions involving methanesulfonylazide are expected to be similar to those of formylazide. In addition, methanesulfonylazide, being more electron-deficient than formylazide, should exhibit enhanced reactivities with these alkenes. This is indeed the case. The use of methanesulfonylazide instead of formylazide in these cycloadditions lowers activation enthalpies by 2−6 kcal/mol in the gas phase (Table 7). The activation enthalpies for cycloadditions involving vinylamine and *N*,*N*-dimethylvinylamine are 13 and 8 kcal/mol. For reactions involving vinylalcohol and dimethylketeneacetal,

(47) *The Chemistry of Enamines*; Rappaport, Z., Ed.; John Wiley & Sons: New York, 1994.

TABLE 7. Activation Enthalpies and Reaction Enthalpies for the 1,3-Dipolar Cycloaddition Reactions of Methanesulfonylazide with Enamine and Enol Determines (Numbers in Parentheses are Energies Corrected with Aqueous Solvation Energies)



Alkene	Product	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$	ΔH_{rxn}	ΔG_{rxn}
		13.0 (8.1)	25.8 (20.8)	-24.8 (-28.6)	-10.4 (-14.2)
		7.6 (7.2)	20.7 (20.3)	-23.3 (-28.0)	-8.2 (-12.9)
		17.5 (15.9)	30.3 (28.7)	-28.7 (-31.9)	-13.4 (-16.6)
		9.3 (11.5)	23.3 (25.5)	-26.0 (-26.2)	-10.4 (-10.5)

the activation enthalpies are 18 and 9 kcal/mol, respectively. The reaction enthalpies, approximately −24 kcal/mol, are slightly more exothermic than the corresponding formylazide cycloadditions.

The gas-phase energies for the cycloaddition of methanesulfonylazide with *N*,*N*-dimethylvinylamine ($\Delta H^{\ddagger} = 8$ kcal/mol and $\Delta H_{rxn} = -23$ kcal/mol) are fairly satisfactory for reversibility at micromolar reactant concentrations. The activation enthalpy is still slightly larger than the range of barriers targeted for a reaction completing one half-life within 24 h at this concentration (less than 5 kcal/mol), but the reaction enthalpy is within the range targeted for reversibility (−21 to −24 kcal/mol). However, the fact that only one of the reactions studied meets the conditions suggests that the generation of libraries of compounds based on this template would, more than likely, suffer from an inability to utilize diverse building blocks. Another significant obstacle in using this template is the inability to use this template in aqueous conditions because of the large exothermicity of the reaction. In addition, enamines such as *N*,*N*-dimethylvinylamine reversibly form mixtures of amines and aldehydes in water. It is unclear how exactly this equilibrium would affect the equilibrium of the desired reaction between the azide and the enamine. The use of this reaction for reversible chemistry would require nonpolar aprotic solvents.

Conclusion

The high-accuracy CBS-QB3 method has been used to study substituent effects in azide 1,3-dipolar cycloadditions with alkenes and alkynes. Alkene and alkyne cycloadditions with azides have similar barriers, but the products formed from alkynes are about 40 kcal/mol more exothermic than those formed from alkenes. The activation enthalpies for 1,3-dipolar cycloadditions of very electron-deficient azides, such as formylazide and methanesulfonylazide, with various monosubstituted alkenes range from 17 to only 21 kcal/mol. Cycloadditions involving electron-rich alkenes with these azides have lower activation enthalpies than cycloadditions involving electron-deficient and conjugated alkenes. These findings are rationalized by analyses provided by FMO theory and distortion/interaction energy control.

We have extended these findings to examine reversibility and irreversibility in these reactions and their implications for methods such as DCC and click chemistry. On the basis of initial reactant concentrations, theoretical procedures have been established for the prediction of kinetic and thermodynamic values that will be useful for the identification of reversible reactions that approach equilibrium over 24 h, as well as for fast irreversible reactions. Clearly, azide cycloadditions with alkynes are very exothermic and are therefore irreversible; they are ideal for click chemistry, as discussed by Sharpless. Under guidelines established to identify reactions which are fast and reversible at various concentrations. A single example has been detected, the reaction of methanesulfonylazide with *N*,*N*′-dimethylvinylamine, which could proceed rapidly and may be reversible at micromolar reactant concentrations. However, because of the instability of related enamines in water, experimental conditions utilizing these examples are likely to be impractical.

Acknowledgment. This work was supported by the National Science Foundation (CHE-0548209 to K.N.H.) and the National Institutes of Health (GM36700 to K.N.H.). This research was facilitated through the Partnerships for Advanced Computational Infrastructure (PACI) through the support of the National Science Foundation. The computations were performed on the National Science Foundation Terascale Computing System at The National Center for Supercomputing Applications (NCSA) and on the UCLA Academic Technology Services (ATS) Hoffman Beowulf cluster. The authors wish to thank Professor Jean-Marie Lehn and Dr. Alexey Eliseev for helpful discussions.

Supporting Information Available: Detailed analysis of target energies for reversibility, B3LYP/6-311G(2d,d,p) Cartesian coordinates, and CBS-QB3 energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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