Reversible Diels−Alder Reactions for the Generation of Dynamic Combinatorial Libraries
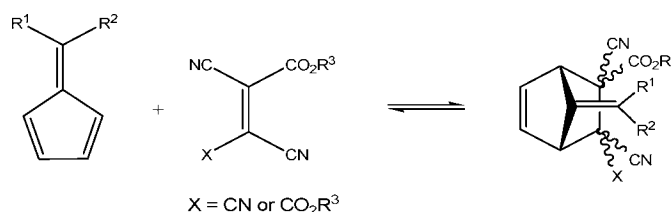
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ABSTRACT

X = CN or CO_2R^3

Condensation reactions between various dienes and dienophiles have been screened for reversibility. Functionalized fulvenes, bearing in particular biological groups, and cyanolefins have been found to react rapidly and reversibly, in the temperature range from −10 to +50 °C. These results pave the way for the development of dynamic combinatorial libraries based on reversible Diels−Alder chemistry.

Constitutional dynamic chemistry (CDC) introduces adaptive behavior in both molecular and supramolecular chemistry by giving access to dynamic diversity through reversible covalent reactions and noncovalent interactions, respectively.[1] On the molecular (covalent) level[2] it is embodied in the burgeoning field of dynamic combinatorial chemistry (DCC) and opens new perspectives for both drug discovery and materials science.[3−5] DCC relies on target-driven selection of a given (optimal) species from a dynamic combinatorial library (DCL) whose covalent constituents are generated by exchange of their components. DCLs have been realized using a variety of reversible reactions including different types of amine/carbonyl condensations,[6] transesterifications,[7] disulfide exchange,[8] peptide exchange,[9] boronic ester formation,[10] and olefin metathesis.[11] The search for other reversible reactions is of paramount importance for unlocking the potential of the conceptual framework of covalent CDC.

The Diels−Alder (DA) reaction is of special interest, as it possesses the particularly attractive features of (1) yielding a three-dimensional structure upon reaction of two planar reactants; (2) belonging to the class of self-contained

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reversible reactions,[12] where all atoms present in the starting materials are also present in the products; and (3) being amenable to easy generation of structural and functional diversity. There has been no demonstration of its use in DCC at this time, and our focus has been to engineer reversible DA reactions that would be dynamic at room and moderate temperatures. The retro DA reaction has been known since the discovery of the forward DA itself.[13] Such retro reactions, however, usually require elevated temperatures.[14] Furans and maleimides react at room temperature and undergo a retro DA reaction at about 110 °C,[15,16] the equilibrium being reached only slowly in organic solvents, although it is faster in water, as is known for other DA processes.[17] In the case of 3-furfuryl alcohol and N-methyl maleimide, the half-life of the reaction was found to be about 1 h at 33 mM in aqueous solution, whereas it was on the order of days in chloroform.
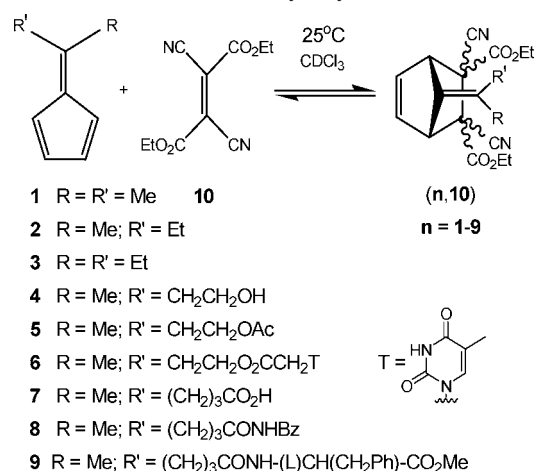
We have uncovered a series of DA reactions that are dynamic between 25 and 50 °C and present efficient kinetics, reaching equilibrium in a matter of 1 min or less at 25 °C and 100 mM concentration. In the course of our search for reversible DA reactions involving in particular fulvenes, it was reported that 2,2-bis(trifluoromethyl)-1,1-dicyanoethylene and 6,6-dimethylfulvene, 1, reacted in toluene at 20 °C, with an equilibrium constant (K_{eq}) of 11.2 M^{-1}.[18] This example of a DA reaction equilibrating at room temperature led us to explore the condensation between fulvenes and cyanoolefins presenting functionalities with potential for expanded chemistry. It was found that 6,6′-disubstituted fulvenes, such as 1−9, engage in reversible DA reactions with two types of cyanoolefincarboxyesters, the dicyano 10−13[19] and the tricyano 14−16[20] compounds, in organic medium.

The introduction of functional groups, as in the fulvene derivatives 4−9, offers the possibility for expanded chemistry in this dynamic system. Thus, the fulvenes bearing thymine 6 and amino acid (L-phenylalanine) 9 groups have been synthesized and reacted with the cyanolefins to establish a room-temperature reversible DA process. The synthesis of 9 involved the condensation of 5-ketohexanoic acid with (L)-phenylalaninemethylester using diisopropylcarbodiimide as coupling reagent (57% yield). The resulting amide was reacted with cyclopentadiene in the presence of pyrrolidine,

following the procedure described in the literature,[21] giving 9 in 87% yield. This procedure provides a general access to fulvenes decorated with various biological fragments or other functional groups, which may be engaged in reversible (or nonreversible) DA reactions. The compounds 4, 7, and 8 have been obtained by the same procedure. Compound 5 resulted from acetylation of 4 and compound 6 from condensation of 4 with N(1)-thymineacetic acid also using diisopropylcarbodiimide. The full synthetic details will be given in a full paper.

The addition of an equimolar amount of the fulvenes 1−9 to diethyldicyanofumarate 10 in chloroform yields an equilibrium mixture of product (1−9,10) and starting materials (Scheme 1). Thermodynamic equilibrium was reached within

Scheme 1. Reversible Diels−Alder Reactions between Fulvenes 1−9 and Diethyldicyanofumarate 10

1 R = R′ = Me   10

2 R = Me; R′ = Et

3 R = R′ = Et

4 R = Me; R′ = CH₂CH₂OH

5 R = Me; R′ = CH₂CH₂OAc

6 R = Me; R′ = CH₂CH₂O₂CCH₂T

7 R = Me; R′ = (CH₂)₃CO₂H

8 R = Me; R′ = (CH₂)₃CONHBz

9 R = Me; R′ = (CH₂)₃CONH-(L)CH(CH₂Ph)-CO₂Me

seconds after mixing. Two isomeric compounds are obtained in different proportions with the unsymmetrically substituted fulvenes 2 and 4−9 (for instance, about 44% and 56% at 25 °C in the case of 4 and 10, respectively). Removal of the solvent for the 1 + 10 mixture gave a solid adduct, which regenerated the equilibrium mixture on redissolution.

The equilibrium constants for the reaction of 1 and 10 were determined to be 63 M^{-1} [33% of 1 and 10; 67% of

(12) Other reactions of this type are cycloadditions in general, the Michael addition, aldol formation, etc., and their retro processes. Conversely, reactions such as imine formation, liberating an ancillary water molecule, are not self-contained. The latter may be manipulated or affected by acting upon the ancillary compound, whereas the former respond to physicochemical parameters (temperature, medium).

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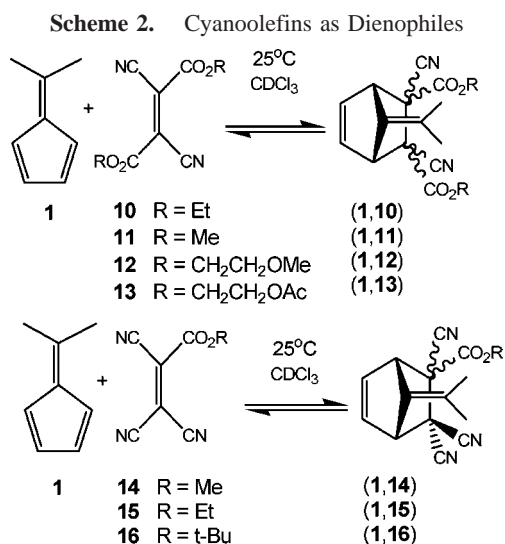
Table 1. Equilibrium for Diels−Alder Reactions in Chloroform

diene	dienophile	equilibrium constants (M^{-1})[a]	
		25 °C	50 °C
1	10	63 ± 3	11 ± 1
3	10	72 ± 2	13 ± 2
1	11	99 ± 6	17 ± 1
1	12	43 ± 2	10 ± 1
1	13	158 ± 3	16 ± 1
1	14	2345 ± 40	140 ± 6
3	14	1616 ± 30	39 ± 3
1	15	581 ± 13	44 ± 4

[a] Determined by ^{1}H NMR signal integration in CDCl₃.

(**1,10**) at 100 mM] at 25 °C and 11 M^{-1} [61% of **1** and **10**; 39% of (**1,10**) at 100 mM] at 50 °C. The equilibrium constants for the cycloadditions of some fulvenes with cyanoolefins were determined at 25 and 50 °C and are listed in Table 1.

Comparing the reactions with 6,6-dimethylfulvene **1** (Scheme 2), it is seen that the tricyanoethylenecarboxylates

Scheme 2. Cyanoolefins as Dienophiles

1	**10** R = Et	(**1,10**)
	11 R = Me	(**1,11**)
	12 R = CH$_2$CH$_2$OMe	(**1,12**)
	13 R = CH$_2$CH$_2$OAc	(**1,13**)
	14 R = Me	(**1,14**)
	15 R = Et	(**1,15**)
	16 R = t-Bu	(**1,16**)

14−16 display higher equilibrium constants, i.e., higher reactivity, favoring the adducts more than the dicyanofumarates **10−13**. The equilibrium constant for the reaction of methyl tricyanoethylenecarboxylate **14** with **1** was found to be 2345 and 140 M^{-1} at 25 and 50 °C, respectively.

Lowering the temperature increases the value of the equilibrium constant. Although there are no kinetic constraints to the reaction of diethyldicyanofumarate **10** at room temperature (thermodynamic equilibrium is reached in a matter of seconds), at temperatures in the −10 to 0 °C range it is necessary to wait on the order of hours for the solution to reach equilibrium. For example, the reaction between **1** and **10** at a concentration of 100 mM produces 94% DA adduct after 6 h at −10 °C.

The equilibrium constants K_{eq} for the reactions of fulvene **1** with the dicyanodiester **10** and tricyanomonoester **14** dienophiles have been determined as a function of temperature. The results plotted in Figure 1 provide the corresponding thermodynamic data. The slope of the graphs of $-\ln(K_{eq})$ versus the inverse absolute temperature T^{-1} (in K^{-1} units) gives $\Delta H/R$ and the intercept gives $-\Delta S/R$. The enthalpies for the equilibria (**1 + 10**) and (**1 + 14**) are calculated to be, respectively, −13 and −22 kcal·mol^{-1}, and the entropies of reaction are, respectively, −36 and −57 cal·gmol^{-1}·K^{-1}.

The dynamics and reversibility of the present DA reactions were studied by performing diene exchange experiments. The process was followed by ^{1}H NMR spectroscopy. For instance, when 5 equiv of **1** was added to the equilibrating mixture of
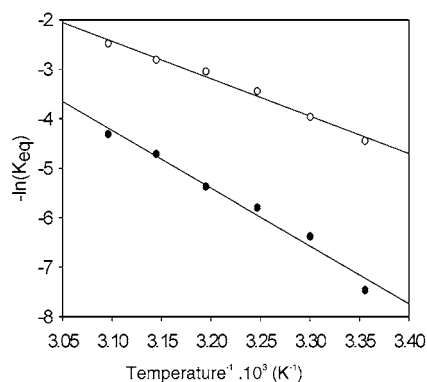
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Figure 1. Plots of the equilibrium constants $-\ln(K_{eq})$ as a function of inverse temperature T^{-1} (K) for the DA reactions of **1** with **10** (○) and of **1** with **14** (●) in CDCl$_3$ at 100 mM concentration.

adduct (**3,10**) and components **3** and **10**, virtually all of (**3,10**) was displaced in favor of the (**1,10**) adduct in approximately a minute or less at 25 °C (Scheme 3).

Indeed the signal at 1.05 ppm, which corresponds to the protons of the terminal methyl of the bridge ethyl group of adduct (**3,10**), has almost completely disappeared after the addition of 5 equiv of **1** (Figure 2).
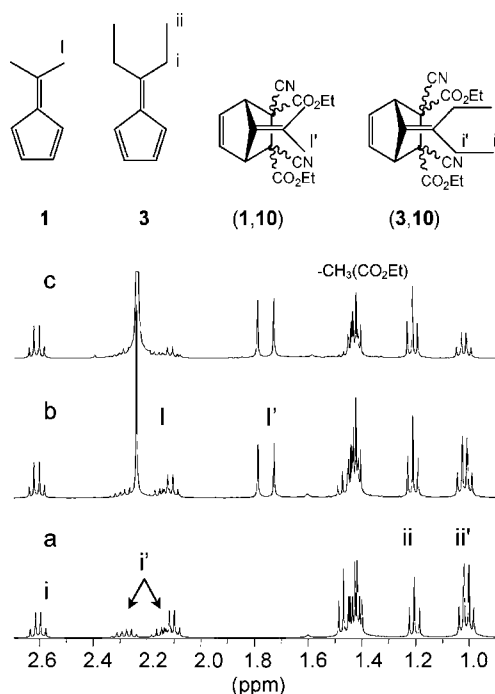
Figure 2. ^{1}H NMR observation of component exchange indicating the dynamic nature of the Diels−Alder reaction between fulvenes and dicyanofumarate esters: (a) 1/1 mixture of diethyl dicyanofumarate **10** (100 mM) and diethylfulvene **3** (100 mM) in *d*-chloroform; (b) mixture obtained after addition of 1 equiv of dimethylfulvene, **1**, to solution (a); (c) mixture obtained after addition of 5 equiv of dimethylfulvene, **1**, to solution (a). The broad signal around 1.6 ppm is due to residual water.

Scheme 3. Fulvene Exchange Diels−Alder Reaction
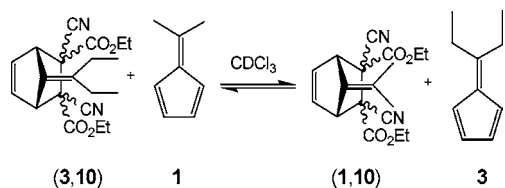
Similarly, the reactions of the alkyl tricyanoethylenecar-boxylates **14**−**16** with dimethylfulvene **1** also exhibit reversibility, as was shown both by the temperature-dependent change in equilibrium concentrations and by competition experiments (Scheme 4). Establishing the two equilibria

Scheme 4. Equilibria and Component Exchange, Starting Either from (**1,10**) and **14** or from (**1,14**) and **10**
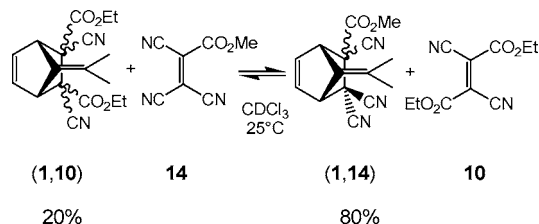
starting either from [(**1,10**) + **14**] or from [(**1,14**) + **10**] (Scheme 4) led to the same final mixture, indicating that thermodynamic equilibrium was reached at room temperature. The adduct (**1,14**) was favored over (**1,10**) in a 4/1 ratio, and this preference increased with temperature (see also Figure 1). On lowering back to room temperature, the ratio of adducts returned to the same value as prior to heating.

In summary, we have found a series of reactive diene and dienophile Diels−Alder building blocks that display both variable reactivity and reversibility. It has further been demonstrated that these building blocks, which are involved in reversible chemistry, undergo exchange in adduct formation, generating dynamic DA diversity. These features provide a basis for the implementation of the reversible Diels−Alder reaction in DCC, toward the discovery of both biologically active substances and mendable materials. In particular, the expanded DA chemistry based on variously functionalized substituted fulvenes and cyanoolefin esters opens the door for the development of reversible dynamic polymers (dynamers)[5] and other dynamic materials. Such extensions are being pursued.

Supporting Information Available: Protocol for studying reversibility and component exchange in the Diels−Alder reactions, as well as selected ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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