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Heavy Atom Effects Reveal Diradical Intermediates. I. An Aqueous Diels-Alder Reaction[1]

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Abstract- The aqueous Diels-Alder reaction between 2-methylfuran and maleic acid in water is 99.9% stereospecific. Addition of heavy but not light atom salts to the retrodiene reaction reduces the degree of stereospecificity significantly. Taking into account the relatively low concentration (3.5-7 M) of heavy atoms, and the rapid fall off of the heavy atom effect with distance, these results show that a large portion, if not all of the Diels Alder occurs *via* diradical intermediates. © 1999 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

Keywords: Cycloadditions, Diels-Alder reactions, stereospecificity.

We report the first example of an external heavy atom effect (HAE) altering the course of a symmetry-allowed pericyclic reaction, namely the Diels-Alder (DA) reaction. The significance is that it shows that a diradical intermediate must exist in a substantial portion if not all the reactive events.

Stereospecificity is a focal point in the controversy between concerted and stepwise diradical mechanisms for the DA reaction.[2] If the cycloaddition is concerted, both new bonds must form simultaneously and there is no opportunity for rotation in the dienophile, so that substituents in a *Z*-olefin must remain *cis* in the cycloadduct and *E* substituents must remain *trans*. On the other hand, if the two new bonds form one at a time and a diradical intermediate intervenes, then rotation in the dienophile portion might allow interconversion of *Z* and *E* before formation of the second bond. It has heretofore been generally held that rotation in diradicals must occur, and that therefore stereospecificity is a sign of concert.[3]

Rotations of this sort are rare in DA reactions, in keeping with the concerted mechanism which presently holds sway.[1] However, stereospecificity also fits the diradical mechanism, provided that rotation, fast though it must be, is slow in comparison with other events, in particular cyclization to cycloadducts and reversion to reactants.[4] These events are indeed faster than rotation, but whether they overwhelm it by a sufficient margin to account for stereospecificity within detectable limits is controversial.

A number of almost-but-not-completely stereospecific reactions have been reported since 1965.[3c,5] These could arise from a completely diradical pathway in which rotation is much slower than cyclization and reversion. Alternatively, there might be competition between a predominantly concerted pathway and a tiny fraction of diradicals that rotate rapidly. Heretofore, most authors have chosen the latter interpretation, which is difficult to challenge because singlet diradicals that do not rotate cannot be easily observed. It must be recognized that

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the percent rotation signifies not less than double that percent as the diradical component, in the extreme case of ultrafast rotation. The slower rotation is relative to cyclization, the greater the diradical component, which rises to 100% when the conditions of eq. (1) are met.[3b]

$$\text{Nonrotated/rotated product} = k_{\text{cycliz.}}/k_{\text{rotation}} + 1 \qquad (1)$$

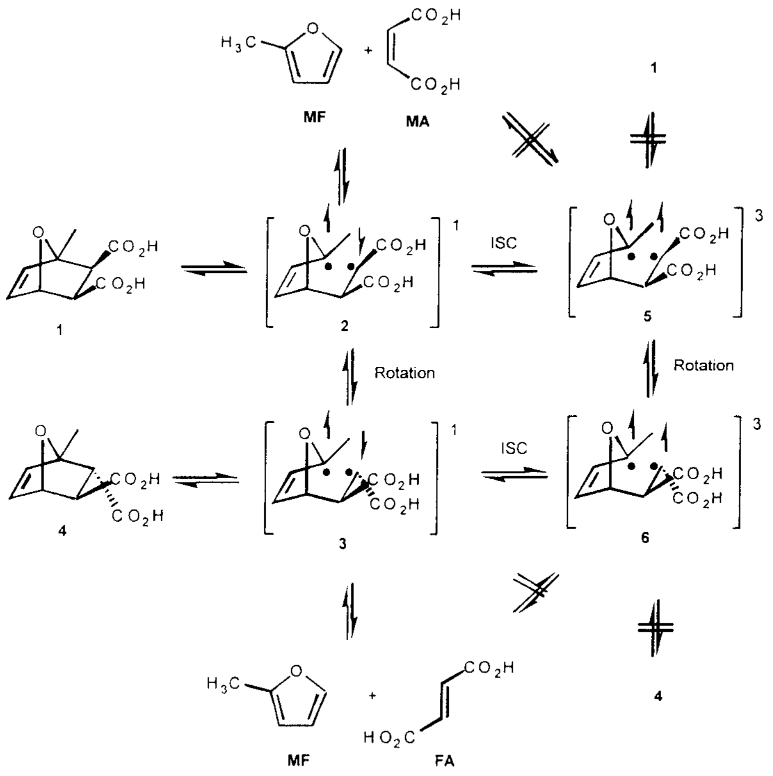
One possible way to show the intervention of singlet diradicals is through the HAE.[4b,c] A heavy atom (defined as any below the first complete row in the periodic table) near a radical center, whether bonded to it or not, is capable of inducing spin inversion of the radical *via* a spin orbit coupling mechanism (SOC). Thus a nearby heavy atom could facilitate intersystem crossing (ISC) of the first-formed diradical, an obligatory singlet, to its triplet counterpart. The triplet is incapable of either cyclizing or reverting to reactants, but it retains the ability to rotate. If it does this at a rate commensurate with ISC back to the singlets, then rotated cycloadduct will begin to appear.

It is noteworthy that several cases of highly nonstereospecific DA reactions are known.[5,6] In each, there is at least one heavy atom (chlorine or sulfur) at or bonded directly to a radical center. We pointed out that the heavy atoms could be revealing the operation of a previously stereochemically silent diradical mechanism, since a diradical must already exist before the HAE can function.[4b,c]

A possible counter to this argument is that perhaps the heavy atoms are not *revealing* pre-existing diradicals, but rather are *creating* them by stabilizing them, thus changing the mechanism from concerted in the light-atom cases to diradical in their heavy-atom counterparts. In our view, this altered-mechanism scenario is not tenable, because chlorine atoms are poor radical stabilizers compared with first-row substituents that typically do *not* induce massive rotation during DA reactions. A case in point is cycloadditions to hexachlorocyclopentadiene,[6a] where only chlorine atoms in the dienophile induce massive rotation while methyl, carbomethoxy, cyano and phenyl induce much less, despite their superior radical-stabilizing power.[7] We conclude then, that the heavy atoms are indeed revealing diradicals that already exist even in the light-atom cycloadditions.

Another and more powerful way of laying to rest the question of HAE-induced mechanistic alteration is by using an *external* instead of internal HAE. With the heavy atom outside of the reacting molecules there is no possible way it could induce a change in mechanism from concerted to diradical. An external HAE is more difficult to observe because an external heavy atom cannot approach the radical center as closely as one bonded to it, and the HAE is strongly attenuated by distance.[8] Thus the HAE is attenuated by a factor of *ca.* 16 by doubling the chlorine atom's distance from the radical site, as would occur by moving from a bonding to a van der Waals distance, and even more if the solvent does not present heavy atoms exclusively. Nevertheless, there exists an important example of an external HAE on the behavior of a diradical created thermally, although not *via* the DA. Methyl methacrylate reversibly dimerizes to a diradical, which initiates polymerization in competition with reversion to monomer.[9] External heavy atoms (Cl, Br, I, Xe) increase the polymerization rate, presumably *via* ISC to triplet diradicals that can initiate polymerization but cannot revert to singlets until a second ISC occurs. Thus the steady-state concentration of diradicals in raised by the HAE.

The first publication of a non-stereospecific DA, in 1965, was that cycloaddition of maleic acid (MA) to 2-methylfuran (MF) occurs with a trace of rotation.[10] This was confirmed by a careful study, which also established that trivial mechanisms such as ions or free radicals were not involved. Rotation was reported to occur in about 0.1% of transition states (TS's).[11] It was concluded that a dual mechanism was functioning, principally concerted but with a tiny diradical component, which cannot be less than 0.2% but could be much more *(vide supra)*. We chose this as a test case because it was already securely poised on the brink of significant rotation, with the object of showing that not only the nonstereospecific, but also much if not all of the *stereospecific* portion of the cycloadditions occurs *via* diradicals.



Scheme 1: Complete Matrix of Singlet and Triplet Diradicals in the Diels-Alder Cycloaddition of Maleic Acid and 2-Methylfuran.

The complete reaction matrix, assuming a pure diradical mechanism, is depicted in Scheme 1. In the DA between MA and MF, the first-formed *cis* diradical **2** may (1) close without rotating to *cis*-cycloadduct **1**, or (2) rotate to singlet *trans*-diradical **3** and then close to *trans*-cycloadduct **4**, or (3) revert to reactants. Normally, closure is 1000 times faster than rotation, so only 0.1% **4** is obtained. If heavy atoms are present, however, ISC from **2** to triplet *cis* diradical **5** competes with the other possible events. Diradical **5** is unable to close to **1** or revert to reactants, so it has a chance to rotate to triplet *trans* diradical **6.** Intersystem crossing (ISC)of **5** and **6** then produces singlet **2** and **3** respectively, but with a greater proportion of *trans*-singlet diradical **3** than is obtained in the purely singlet manifold. This leads to increased production of *trans* cycloadduct **4** as a result of the HAE. In the retrodiene direction the HAE gives rise to a greater proportion of MA from **4**, or of FA from **1**, than normally occurs.

RESULTS

Following Seltzer *et al.*,[11] we studied the reaction in the retrodiene direction for ease of analysis. Microscopic reversibility ensures that the mechanism is the same in both directions. Cycloadduct **1** was heated in water at 35°C without and with added sodium chloride. Both sodium and chlorine are heavy atoms. It should be borne in mind that even at the highest NaCl concentration (3.5M), only about 11% of the particles encountered by singlet diradicals are heavy atoms.

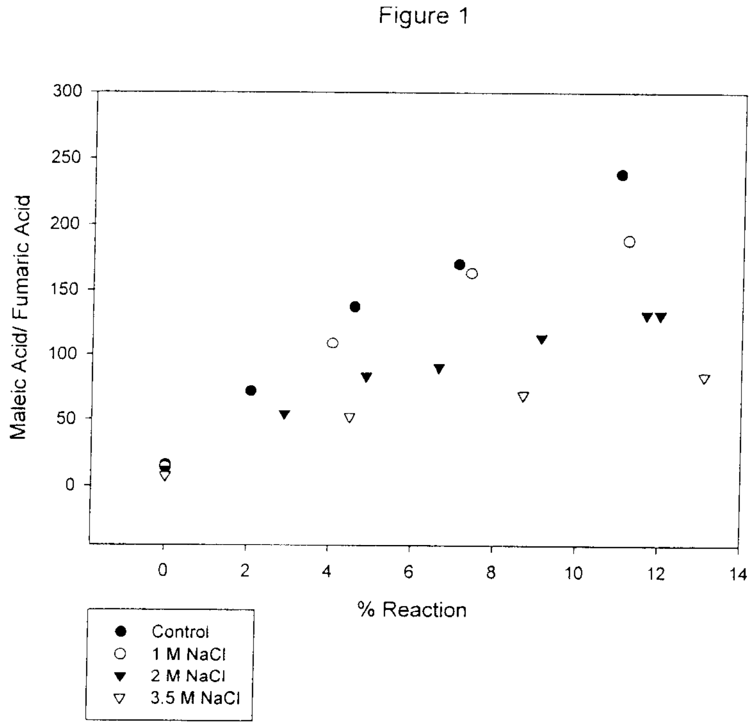


Figure 1: MA/FA *vs*. Retrodiene Reaction of **1**; Effect of NaCl at Varying Concentrations

Figure 2

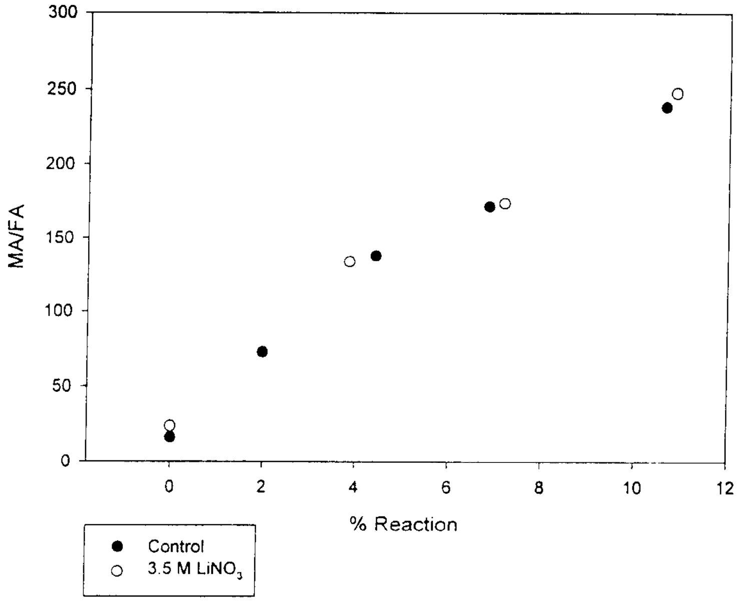


Figure 2: MA/FA *vs.* % Retrodiene Reaction of **1**; Effect of $LiNO_3$.

The results of the first experiment are in Fig. 1. The MA/FA ratio begins at an arbitrary point and represents an inevitable trace of impurity in **1**. It quickly rises as MA is released. In order to be sure that all runs were assayed after the same number of reactive events, the rate with each concentration of salt was measured, and the abscissa is given as percent reaction rather than time. It is clear that the heavy-atom salt NaCl induces the formation of excess FA in a concentration-dependent way, beginning at the earliest time points. In contrast, the light-atom salt $LiNO_3$ at 3.5M induces no rotation (Fig. 2). All other heavy-atom salts also bring about rotation.

The percent rotation induced by each heavy-atom salt was determined separately. In order to minimize the intrusion from the forward Diels Alder reaction, runs were made at 3.5M to only 4% reaction. The forward Diels Alder reaction has a rate constant 350 times that of the retrodiene, but since it is second order while retrodiene is first order, at the concentration employed forward reaction velocity was <1% of retrodiene up to 4% reaction. Runs without and with salt began from the same data point. All data points are given as MA/FA. The amount of *salt-induced* rotation, as a fraction of the total reaction product, is given by $1/(S+1) - 1/(C+1)$, where C is for control and S is for salt. All experiments were duplicated. The experimental results (1 set) are presented in Fig. 3. From Fig. 3 and the duplicates, MA/FA values at 4% reaction were obtained graphically, and are given in Table 1 along with the percent of salt-induced rotation.

Salt	MA/FA$_0$	MA/FA$_4$	% Rotation	Average	MA$_0$	MA$_4$	FA$_4$
Control	3.06	28.8			0.46	4.46	0.15
LiCl	3.06	24.8	0.520				
Control	4.14	37.0			0.62	4.62	0.12
LiCl	4.14	32.7	0.336	0.428±.092			
Control	2.57	28.1			0.39	4.39	0.16
$NaNO_3$	2.57	23.1	0.713				
Control	4.24	37.8			0.64	4.64	0.12
$NaNO_3$	4.24	29.8	0.669	0.691±.022			
Control	12.48	55.1			1.87	5.87	0.11
NaCl	12.48	34.0	1.07				
Control	1.85	35.5			0.28	4.28	0.12
NaCl	1.85	25.5	1.03	1.05±.02			
Control	3.55	30.4			0.53	4.53	0.15
NaBr	3.55	20.4	1.49				
Control	3.26	34.5			0.49	4.49	0.13
NaBr	3.26	23.0	1.35	1.42±.07			
Control	3.13	34.0			0.47	4.47	0.13
KCl	3.13	29.5	0.422				
Control	3.11	29.3			0.47	4.47	0.15
KCl	3.11	25.8	0.431	0.427±.006			
Control	12.07	41.9			1.81	5.81	0.14
KBr	12.07	29.5	0.948				
Control	3.26	34.0			0.49	4.49	0.13
KBr	3.26	26.2	0.819	0.884±.065			

Table 1: Dienophile Rotation During Retrodiene Reaction of **1** with and without External Heavy Atoms

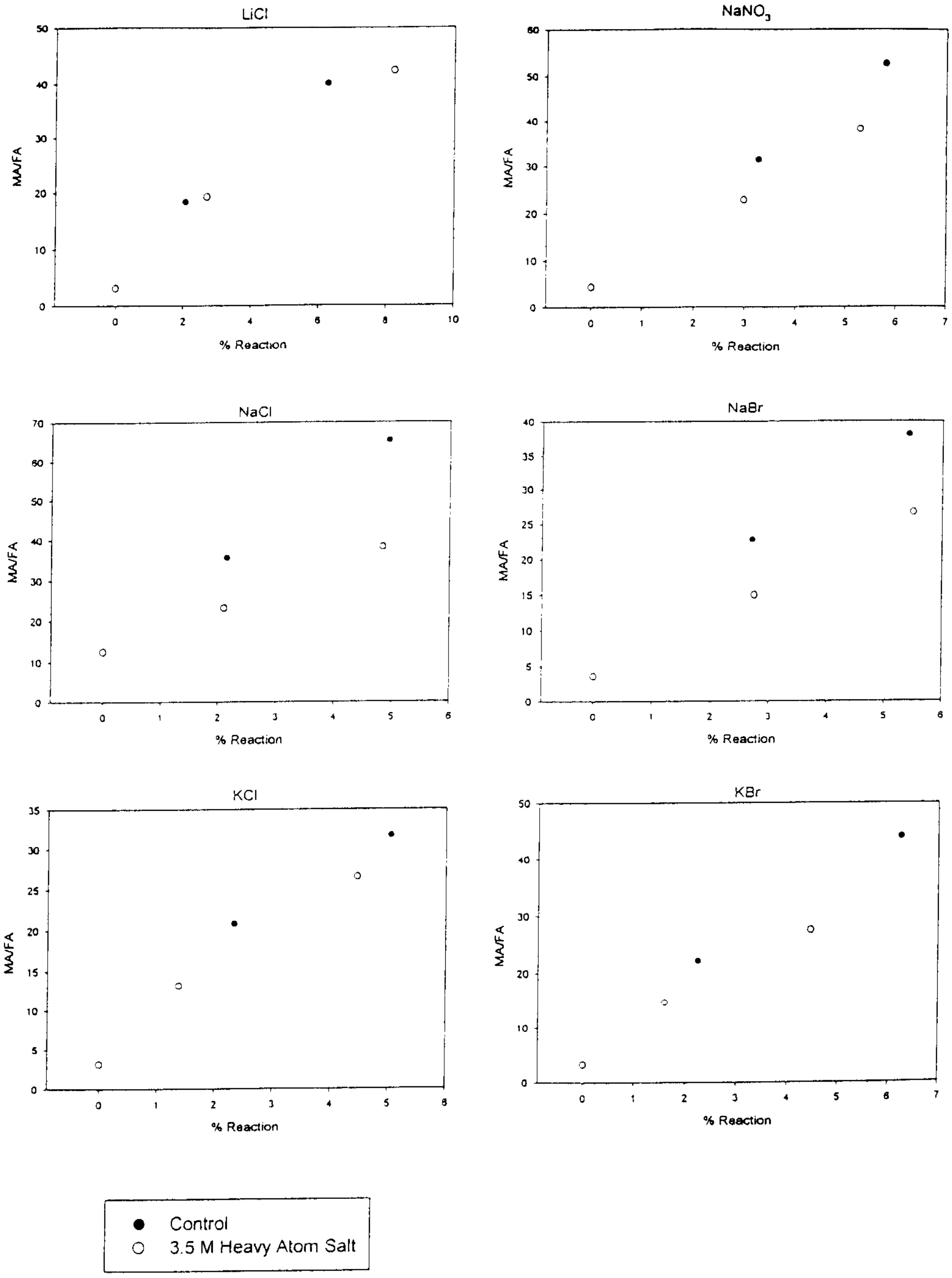


Fig. 3: MA/FA *vs.* % Retrodiene Reaction of **1**; Effect of six different salts.

Clearly there is a significant increase in rotation induced by the presence of external heavy, but not light atoms. As expected, in ability to cause rotation, $Br^- > Cl^- > NO_3^-$, and $Na^+ > Li^+$, but $Na^+ > K^+$ was a bit of a surprise. These rotations are most reasonably attributed to an external HAE on *pre-existing* diradicals. Thus, there must be a significant diradical component in the stereospecific portion of this cycloaddition. The minimum percents diradical component would be twice the rotation value if rotation were much faster than closure or reversion, but are undoubtedly much greater because rotation is not that fast, heavy atom encounters are relatively few, and the HAE is so distance dependent.

Salt	Concentration, M	Rate, min $^{-1}$	Rel. Rate
None		9.32×10^{-4}	1
$NaNO_3$	3.5	8.52×10^{-4}	0.91
NaCl	1.0	7.62×10^{-4}	0.82
NaCl	2.0	7.99×10^{-4}	0.86
NaCl	3.5	9.16×10^{-4}	0.98
NaBr	3.5	9.47×10^{-4}	1.02
$LiNO_3$	3.5	1.80×10^{-3}	1.93
LiCl	3.5	1.23×10^{-3}	1.32
LiBr	3.5	1.81×10^{-3}	1.94
KCl	3.5	5.50×10^{-4}	0.59
KBr	3.5	6.66×10^{-4}	0.71

Table 2: Effect of Salts on the Rate of Retrodiene Reaction of **1**.

Control experiments established that the phenomenon has no trivial explanation. The effects of the salt additives on the rate are small (Table 2), indicating no mechanistic alteration among them. Some lithium salts showed a modest acceleration, which is not surprising since lithium is known to behave as a Lewis acid catalyst,[12] although a very weak one in hydroxylic *vis-à-vis* aprotic solvents. Neither excess **1** nor any of the salts at 3.5 M isomerizes MA into FA during >9 times 4% reaction time. However, iodides do isomerize MA and therefore could not be used. The possible agency of adventitious free radicals in isomerizing MA into FA was also excluded by adding hydroquinone (36 mole %) to a 3.5 M NaCl run; the results were unchanged. No isomerization of *cis*-cycloadduct **1** to *trans*- cycloadduct **4** is detectable under the reaction conditions, either without[11] or with 3.5 M NaCl. Oxygen is normally carefully excluded, but in a few cases where it was not, the results were identical. Therefore, rotation of the dienophile moiety occurs *during,* and not before or after, the retrodiene step.

In each experiment, unavoidable variation in the MA content at time zero occurs owing to adventitious retrodiene reaction during sample preparation. However, the FA content should be invariant over a considerable period. The sample of **1** used to obtain the data in Table 1 was assayed by HPLC, and found to contain 0.15% of FA. From this number and MA/FA at the zero and 4% time points was obtained FA at 4% for each run (Table 1), which was 0.134±0.013. Thus within the limits of our experimental precision there was no detectable spontaneous rotation in the absence of heavy atom additives, in agreement with the very low rotation reported.[11]

DISCUSSION

There is a clearly discernible heavy atom effect that increases the formation of FA in the retrodiene reaction of **1**. By microscopic reversibility, the mechanism must be the same in both the forward and retrodiene directions. All salts containing Na^+, K^+, Cl^- and Br^-, but not $LiNO_3$, are effective.

Diradicals rather than zwitterions are indicated as intermediates because the reaction partners are insufficiently substituted with electron withdrawing and donating groups to form zwitterions, and there is no interception of zwitterions by water[12] as normally seen in hydroxylic solvents[14]. Only heavy atoms give rise to rotation in the dienophile, whereas had a zwitterion mechanism been in effect, one would have expected heavy and light atoms to behave alike. Furthermore, large variations in the salt concentrations have little effect on the rate.

The external HAE cannot alter the mechanism in favor of diradicals, and the HAE cannot operate unless diradicals already exist. As discussed earlier, encounters with heavy atoms at 3.5M in water occur only about 11% of the time, and at van der Waals distance the probability of SOC is only about 1/16 that at covalent distance. Thus the ostensibly small HAE-induced rotations in Table 1 translate into possibly 100% of stereospecific events. This demonstration of an external HAE on a DA reaction can easily account for the 40% rotation of the isomer bearing chlorine at both diradical centers in the dimerization of chloroprene,[5] and shows that our previous proposal of an internal HAE in this reaction is eminently reasonable.[4b] These observations show that a significant fraction and perhaps all of the *stereospecific* portion of the DA reaction between MF and MA occurs *via* diradical intermediates. Stereospecificity, therefore, cannot be regarded as proof of concert.[4c]

While a concerted component can never be experimentally ruled out, if there is one the energy of concert must be very small. Since energy of concert is the bedrock of the Woodward-Hoffmann rules ("A chemical reaction will proceed more readily, the more *bonding* may be maintained throughout the transformation"),[15] it is now possible to doubt the coexistence of a concerted component in this transformation.

Glossary: HAE, heavy atom effect; DA, Diels-Alder; SOC, spin-orbit coupling; ISC, intersystem crossing; MA, maleic acid; FA, fumaric acid; MF, 2-methylfuran; TS, transition state.

EXPERIMENTAL SECTION

General Methods. Starting materials were obtained from commercial sources (Aldrich or VWR) and unless otherwise noted, used without further purification. Reactions were run in HPLC grade water. HPLC analyses were performed on a system equipped with a 15 cm C_{18} Aquasil column from Keystone scientific, a UV/vis detector set to $\lambda = 210$ nm and a mobile phase of 0.1 M $NH_4H_2PO_4$ at pH 2.5 run at 1.25 ml min^{-1}. Kinetic analyses and NMR spectra were obtained on a 400 MHz NMR spectrometer.

HPLC Reactions. An appropriate amount of each salt was weighed into a vial and dissolved in 3.9 ml of HPLC grade water A second vial of 3.9 ml of HPLC grade water was prepared also. **1**, (25 mg) was weighed out into a 1 ml volumetric flask and diluted to the mark with HPLC grade water. 100 µl of the solution was syringed into both vials such that the total volume was 4 ml. An addition 50 µl of the **1** solution was syringed into a vial and diluted with H_2O (3 ml) for HPLC analysis. Dinitrogen was bubbled through the solution in this vial for at least 5 minutes to remove atmospheric oxygen. The vials were placed in a constant temperature bath at 35 °C. Samples (150 µl) were removed together periodically, diluted with H_2O (3 ml) and analyzed by HPLC. Samples that could not be analyzed immediately were stored in an ice bath at approximately 0°C. All samples were analyzed within 20 minutes of their removal from the solution.

NMR Reactions. An appropriate amount of salt and approximately 10 mg of **1** was weighed out into a 1 ml volumetric flask and diluted to the mark with D_2O. After all the solids dissolved at room temperature, the solution was transferred *via* pipet to a 5 mm nmr tube. The tube was placed in a 35 °C NMR probe. The temperature of the probe was confirmed at the start and finish of the kinetic run with ethylene glycol. Spectra were taken periodically with a 4 second relaxation delay between pulses. Because there was overlap between the olefinic signals of **1** and MA, the methyl signals of **1** and MF were integrated in order to evaluate the reaction kinetics.

***exo*-4-Methyl-7-oxabicyclo-[2.2.1]-2-heptene -5,6-dicarboxylic acid 1.** Maleic anhydride (26 g, 0.28 mol) was dissolved in warm diethyl ether. 2-methylfuran (25 ml, 28 mmol) was added with stirring at room temperature. The reaction mixture was stirred for 12 hours and then cooled to -20 °C. After 24 hours, the crystals of pure *exo*-4-methyl -7-oxabyclo-[2.2.1]-2-heptene-5,6-dicarboxylic acid anhydride are filtered away from the mother liquor.

The crystals were then dissolved in water with one drop of concentrated HCl. The water was removed under vacuum, then by lyophilization, and the slightly yellow crystals washed with very cold (cooled in a —78 °C *i*PrOH/dry ice bath) ethanol until they were perfectly white. Their NMR spectrum matched that in ref. 11, with no detectable *trans* isomer **4**. They were stored in the freezer under N_2 and used without further purification as long as they remained perfectly white, and the NMR spectrum remained unchanged. Over many months, traces of fumaric acid did build up in the sample, even in the freezer under a nitrogen atmosphere. Therefore all the reported results were obtained on freshly purified samples of **1**.

Maleic Acid Isomerization Controls. Maleic acid, 200 mg, was weighed out into a 50 ml volumetric flask and diluted to the mark with HPLC grade water. 250 µl of this maleic acid solution was syringed into a vial with 3.5 ml of an appropriate 4 M salt solution and 250 µl of water. The resultant solution was deoxygenated by bubbling dinitrogen through it for at least 5 minutes, then an initial aliquot (200 µl) was removed, and diluted in 3 ml of water for HPLC analysis and the vial was incubated in a 35 °C constant temperature bath. Subsequent samples were diluted similarly, and the isomerization was monitored for several hours. The ratio of maleic acid to fumaric acid was evaluated by HPLC after at least 3 hours.

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