

Unusual Stability of *N*-Methylmaleimide Cycloadducts: Characterization of Isobenzofuran Retro-Diels-Alder Reactions

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Many years ago Diels and Thiele noted the unusual stability of maleic anhydride cycloadducts and employed this feature in scavenging anthracene generated in a retro-[4 + 2] reaction. *N*-methylmaleimide, although nearly identical to maleic anhydride in rates of Diels-Alder reactions, forms even more stable cycloadducts. The rate constants for the four reactions that characterize the furan/*N*-methylmaleimide system were measured under the conditions used by Lee and Herndon to study the furan/maleic anhydride system. Comparison of the two dienophiles indicates that *N*-methylmaleimide adducts are ca. 3 kcal·mol⁻¹ more stable than the corresponding *exo*- and *endo*-maleic anhydride adducts. Somewhat larger (ca. 4 ± 0.5 kcal·mol⁻¹) differences in stability were found for the cycloadducts of the much more reactive diene isobenzofuran. *N*-Methylmaleimide is used as a diene scavenger to obtain rate constants for retro-Diels-Alder reactions of isobenzofuran adducts with maleic anhydride and some substituted analogs. The rates of retro-Diels-Alder reactions of substituted *N*-methylmaleimide adducts were also determined by an alternative method. The substituents examined enhance the rates of *exo* retro-Diels-Alder reactions by factors of 15-40, while *endo* adduct retro-Diels-Alder rates are only slightly affected. Calculations were done at the MP2/6-31G*//HF/6-31G* level to compare the heats of hydrogenation of maleic anhydride and maleimide. The reduction of maleimide is calculated to be 2.5 kcal·mol⁻¹ more exergonic, supporting the experimental observations.

Introduction

Over 50 years ago Diels and Thiele used maleic anhydride (MA) as a scavenger of anthracene generated in a retro-[4 + 2] reaction.¹ Experience had shown that MA gave unusually stable cycloadducts; coupled with its high reactivity, MA has the requisites of a useful scavenger. A few analogous applications of MA to trap anthracene formed in the syntheses of different dienophiles have been reported,^{2,3} but the technique is not widely used. Extension of this method to other dienophiles is limited by the inability to predict the relative stabilities of cycloadducts. Organic chemists are generally comfortable with the concept of relative dienophilicity, but the effects of structure and substituents on the rate of retro-Diels-Alder (rDA) reactions are less thoroughly studied.⁴ A highly reactive diene that affords cycloadducts amenable to chemical modification and subsequent facile rDA reaction would be quite useful in synthesis. Our search for such a diene has provided the first clear demonstration of base-catalysis of DA reactions, with 9-anthracenol oxyanion

serving as the diene.⁵ It enters into room-temperature DA reactions with moderately reactive dienophiles, e.g., those which bear a single electron-withdrawing group, but extension to less activated olefins has proven difficult. For this reason, the much more reactive isobenzofurans⁶ (IBFs) and their analogs continue to be of interest. Although rDA steps figure prominently in several preparative methods for the parent unsubstituted IBF, these reactions usually involve the formation of an especially stable aromatic "diene" as coproduct.⁷ An exception involving expulsion of ethylene is found in the flash vacuum pyrolysis method of Wiersum and Mijs.⁸ Since IBF has very desirable reactivity features (e.g., room-temperature cycloaddition with cyclohexene, which we estimate to be 10¹⁰ less reactive than MA or NMM as a LUMO component dienophile), its potential for use as an olefin protecting group is worth exploration. The present study was initiated with the goal of learning more about the temperatures needed for rDA reactions of IBF cycloadducts involving common dienophiles.

N-Methylmaleimide (NMM) is a preferred dienophile in our laboratory. NMM and MA react at very similar rates, with dienes that span a million-fold reactivity range.⁹

* Abstract published in *Advance ACS Abstracts*, October 15, 1993.

(1) Diels, O.; Thiele, W. E. *Chem. Ber.* 1938, 71, 1173. This paper describes the first example of the useful synthetic procedure consisting of Diels-Alder reaction, modification of the cycloadduct, and retro-Diels-Alder reaction to recover the modified dienophile. In this early work the desired product was the bis acid chloride of acetylenedicarboxylic acid. The yield of this product was enhanced by the addition of MA at the retro-Diels-Alder stage. The authors suggested the word "avidity" to describe the combination of properties, high reactivity and product stability, that is embodied in useful scavengers.

(2) Buck, C. J. *J. Polym. Sci., Polym. Chem. Educ.* 1978, 16, 2475.

(3) (a) De Keyser, J.; De Cock, C. J. C.; Poupaert, J. H.; Dumont, P. *J. Org. Chem.* 1988, 53, 4859. (b) De Keyser, J.; De Cock, C. J. C.; Poupaert, J. H.; Dumont, P. *J. Labelled Compd. Radiopharm.* 1989, 27, 909.

(4) Chung, Y.; Duerr, B. F.; McKelvey, T. A.; Nanjappan, P.; Czarnik, A. W. *J. Org. Chem.* 1989, 54, 1018. This extensive study of substituent effects on retro-Diels-Alder reactions of anthracenes is an exception and provides a benchmark for future comparisons.

(5) (a) Koerner, M.; Rickborn, B. *J. Org. Chem.* 1989, 54, 6. (b) Koerner, M.; Rickborn, B. *J. Org. Chem.* 1990, 55, 2662. (c) Koerner, M.; Rickborn, B. *J. Org. Chem.* 1991, 56, 1373.

(6) Rickborn, B. *Adv. Theor. Interesting Mol.* 1989, 1, 1.

(7) (a) Fieser, L. F.; Haddadin, M. J. *Can. J. Chem.* 1965, 43, 1599. (b) Wege, D. *Tetrahedron Lett.* 1971, 2337. (c) Warrenner, R. N. *J. Am. Chem. Soc.* 1971, 93, 2346.

(8) Wiersum, U. E.; Mijs, W. J. *J. Chem. Soc., Chem. Commun.* 1972, 347.

(9) Relative rates (NMM/MA) have been determined as follows: (a) 3, with anthracene in chlorobenzene at 132 °C;¹⁰ (b) 0.71, with cyclopentadiene in dioxane at 30 °C;¹¹ (c) 1.5, with isobenzofuran in ether at 25 °C (this work); (d) 0.86, for *exo* attack of furan; the ratio for *endo* attack of furan is anomalous (see Figure 1).

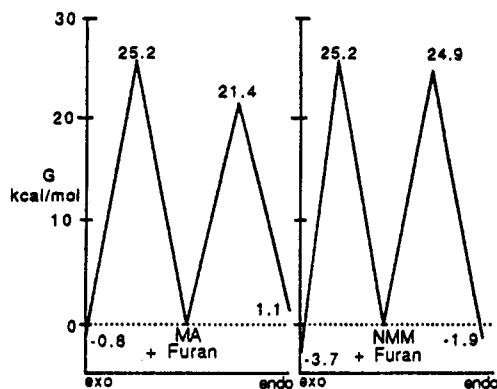
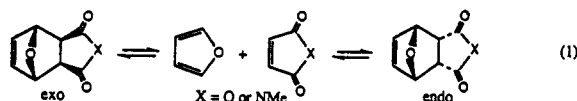


Figure 1. Free energy comparisons for the systems MA + furan (left) and NMM + furan (right) in MeCN at 40 °C.

NMM has the added advantages over MA of forming cycloadducts that are less susceptible to hydrolysis, and the *N*-Me substituent provides a useful signal for NMR analyses. The present study shows that, even though the rates of DA reaction are similar, *the adducts of NMM are considerably more stable than those of MA.* We make use of this property to determine the rate constants of some rDA reactions that would be difficult to obtain by alternative means.

Results and Discussion

One of the few DA/rDA cycles that is amenable to complete kinetic characterization at a single temperature is that of furan and MA (eq 1, X = O), as detailed in the

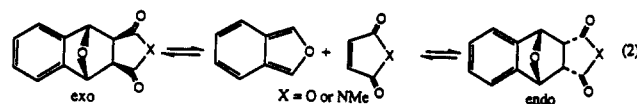


elegant study by Lee and Herndon.¹² The reaction sequence was examined at 40 °C in acetonitrile solvent. For ease of viewing, we display their data in the form of a free energy plot (see Figure 1), with the usual caveat regarding comparison of second-order (DA) and first-order (rDA) processes.¹³ The distinctive features of the MA/furan system are the much more rapid formation of endo (relative to exo) product, the instability of endo cycloadduct relative to the educts, and the thermodynamically favored status of the exo adduct.

We examined the reaction of furan with NMM (eq 1, X = *N*-Me) under the same conditions (acetonitrile, 40 °C), and the results are plotted (Figure 1, right). Some

interesting comparisons with the MA reaction can be made: (a) the rates of formation of both exo isomers are identical; (b) the exo cycloadduct is more stable than the endo isomer in each system, with essentially identical ΔG° values (1.8 and 1.9 kcal·mol⁻¹); (c) both the exo and endo cycloadducts of NMM are *relatively* more stable than those of MA, by ca. 3 kcal·mol⁻¹. The educt energy levels in both systems are arbitrarily assigned $G = 0$, as shown in Figure 1.

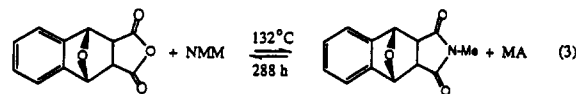
Unlike furan, the forward and reverse reactions of IBF with reactive dienophiles cannot be studied conveniently at a single temperature. In addition to being much more reactive, IBF forms more thermally stable adducts than furan, and thus considerably higher temperatures are needed to effect rDA reactions. Refluxing chlorobenzene (132 °C) provides a convenient temperature for examination of the rDA reactions of IBF adducts of some typical dienophiles, e.g., MA (eq 2, X = O). The endo and exo



MA cycloadducts were separately heated at this temperature for 38 h; equilibrium was established at an endo/exo ratio of 5/95 ($\Delta G^\circ = 2.4$ kcal·mol⁻¹ at 132 °C). The equilibrium constant resembles that of the furan/MA system, and the position of equilibrium does not appear to be strongly affected by variation in temperature.¹⁴

The greater stability of NMM adducts became evident when attempts were made to equilibrate the IBF-NMM cycloadducts. These reactions are much slower than those of the IBF-MA analogs, and the equilibrium position is not attained even after heating at 132 °C for 3 months! From endo starting material, a mixture (endo/exo = 15/85) was formed, while exo starting material gave a 5/95 ($\pm 1\%$) ratio. The exo isomer is thus favored at equilibrium by a value between 85 and 96%; an endo/exo equilibrium ratio of 5/95 was assumed for purposes of calculating the rate constant for the rDA reaction of the endo isomer, from measurements taken over the 3-month period of heating.

Two experiments that directly compare the stability of NMM and MA adducts were carried out (eq 3). In one,



an equimolar mixture of exo IBF-MA adduct and NMM was heated at 132 °C for 288 h. This resulted in a mixture of adducts consisting of 78% IBF-NMM (endo/exo = 69/31) and 22% of IBF-MA (only exo detected). In the second experiment, identical treatment of an equimolar mixture of endo IBF-NMM and MA led to a mixture consisting of 80% IBF-NMM (endo/exo = 89/11) and 20% IBF-MA (exo only). These data, coupled with the 5/95 endo/exo equilibrium ratio for the NMM adducts, can be used to calculate upper and lower limits for the energy difference between exo IBF-NMM and exo IBF-MA adducts; the first experiment leads to $\Delta G \geq 3.5$ and the second to $\Delta G \leq 4.2$ kcal·mol⁻¹.

(14) Equilibration of the MA/IBF cycloadducts at 111 °C gave the same endo/exo ratio (5/95) as that observed at the higher temperature.

(10) Koerner, M. Ph.D. Dissertation, UCSB, 1990.

(11) Sauer, J.; Wiest, H.; Mielert, A. *Chem. Ber.* 1964, 97, 3183.

(12) Lee, M. W.; Herndon, W. C. *J. Org. Chem.* 1978, 43, 518. This work has been criticized by Dewar and Pierini (*J. Am. Chem. Soc.* 1984, 106, 203) on two grounds: (a) measurement by D & P of a rate constant for exo retro-DA reaction 5.7 times larger than that of L & H and (b) a comparison of equilibrium constants. We note that the possibility of catalysis by an unknown impurity cannot be ruled out as a cause of the rate differences. The equilibrium concern appears to be due to a compounded error. L & H used the wrong (inverse) units in describing the retro-DA process, and D & P seem to have compared their own DA value with the L & H retro-DA value. Correct comparison shows that the equilibrium constants determined at two different temperatures ($\Delta T = 9.5$ °C) in the two laboratories differ by a factor of 3, in the expected direction, i.e., inversely related to temp for the DA reaction. Neither the rate nor equilibrium difference would affect our conclusions about MA and NMM adduct stability.

(13) The activation energies of first- and second-order reactions may be directly compared if an unchanging 1 M concentration of one of the reagents for the second-order process is assumed.

These approximate 80/20 NMM/MA adduct mixtures are quasiequilibrium points. Although the time (288 h) corresponds to >8 half-lives for the rDA reaction of IBF-MA, it is only a fraction of a half-life for the analogous reaction of IBF-NMM. This is reflected in the endo/exo IBF-NMM ratios, which are far from the ca. 5/95 equilibrium ratio. Thus, longer reaction time would drive the quasiequilibrium toward additional exo IBF-NMM, and away from IBF-MA adduct, and would make the greater stability of NMM (compared with MA) adducts more evident.

The ratio of rate constants for formation of exo/endo adducts was obtained by carrying out reactions under kinetically controlled conditions (short times). This was done at 25, 80, and 132 °C for both MA and NMM. Both dienophiles exhibited preferential formation of endo adduct at all temperatures, with selectivity decreasing with increasing temperature. For MA, the amounts of endo product were 76.5, 67, and 62.5%, and for NMM these amounts were 96, 87, and 81.5%. The higher temperature values for MA and NMM correspond to $\Delta\Delta G^\ddagger$ values of 0.4 and 1.2 kcal·mol⁻¹, respectively. The reactions of IBF parallel those of furan in that endo product is formed more rapidly than exo, although the relative selectivity of the two dienophiles is inverted for the two dienes.

In order to complete an activation energy diagram for IBF similar to that given in Figure 1 for furan, a rate constant for an IBF cycloaddition is needed. Only one such value has appeared in the literature.¹⁵ Moursoundis and Wege determined the rate constant (75.8 M⁻¹s⁻¹; $\Delta G^\ddagger = 14.8$ kcal·mol⁻¹) for the reaction of IBF with MA in benzene at 25 °C. In order to estimate a rate constant at 132 °C in chlorobenzene, some assumptions must be made.¹⁶ Among reasonable possibilities, we chose to assume that the reaction of IBF with MA has the characteristic DA $\Delta S^\ddagger = -35$ cal·mol⁻¹·deg⁻¹.¹⁷ The rate constant calculated using this assumption is ca. 10 times larger than the constant at room temperature, and $\Delta G^\ddagger(132) = 18.6$ kcal·mol⁻¹. The process is partitioned into $\Delta G^\ddagger(\text{endo}) = 19.0$ and $\Delta G^\ddagger(\text{exo}) = 19.4$ kcal·mol⁻¹ by taking into account the kinetically controlled product ratio. These values are used in the construction of Figure 2, left.

The ΔS^\ddagger assumption leads to some uncertainty with respect to the educt energy level depicted.¹⁷ However, the rate constants for both retro-Diels-Alder reactions were independently determined by making use of the scavenging ability of NMM. A 10-fold molar excess of NMM was employed to assure the effective irreversibility of the scission of the MA-IBF adducts, and clean first-

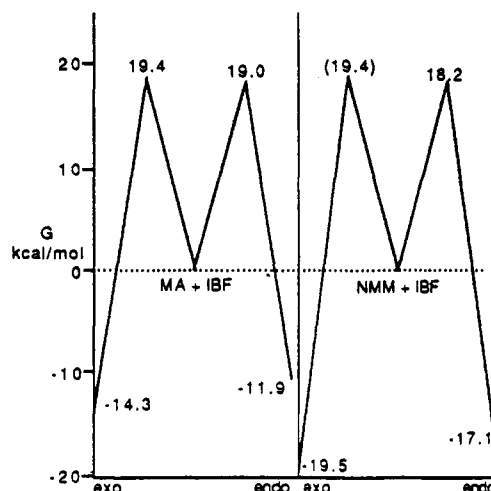


Figure 2. Free energy comparisons for the systems MA + IBF (left) and NMM + IBF (right) in PhCl at 132 °C.

order rate plots were obtained. Note that this method gives the rate constants for the dissociation (rather than interconversion) of both stereoisomers and does not require knowledge of the kinetically controlled product ratio or of the equilibrium constant.

The NMM + IBF system is more difficult to characterize. Again, the ground-state energies of MA and NMM were taken as equal, and the further assumption was made that the rates of formation of exo cycloadducts are the same for both dienophiles. The NMM-IBF rDA reaction k_{endo} was determined by measuring the rate of approach to the endo/exo = ca. 5/95 equilibrium ratio, and the corresponding k_{exo} was calculated by taking into account the kinetically controlled product ratio. The complete energy diagram derived in this way (Figure 2, right) requires a number of assumptions and leads to a somewhat larger difference in MA/NMM adduct energy (5 kcal·mol⁻¹) than the range (3.4–4.2 kcal·mol⁻¹) established by direct equilibration. The smaller value is considered the more accurate, and the apparent difference between the furan and isobenzofuran systems may not be meaningful.

Furan and IBF differ in Diels-Alder reactivity by several orders of magnitude. That NMM cycloadducts are more stable than those of MA for both dienes suggests that this outcome will be general. This conclusion is further supported by *ab initio* calculations described below.

Related Dienophiles. The effects of substituents on r-DA reaction rates have not been extensively studied, and there is no quantitative information on substituent effects on r-DA reactions of IBF adducts. McCormick and Shinmyozu¹⁹ have reported the reaction of dimethylmaleic anhydride (1) with IBF; their qualitative observations suggest that the methyl substituents enhanced the rate of the r-DA step. We have prepared the exo isomer²⁰ of 1 with IBF and determined the rate of the r-DA step at 132 °C. This was done as described above for the unsubstituted MA derivative by carrying out the reaction in the presence of excess (10 equiv) of NMM. Clean first-order behavior was observed, giving the rate

(15) Moursoundis, J.; Wege, D. *Aust. J. Chem.* 1988, 41, 235. The rate of disappearance of IBF was followed, and the rate constant is thus the sum of constants for endo and exo isomer formation.

(16) The Eyring equation is used. It is assumed that there are negligible solvent effect differences between benzene and chlorobenzene and that the reaction of IBF with MA has a characteristic activation entropy, $\Delta S^\ddagger = -35$ cal·M⁻¹·deg⁻¹.

(17) The assumption of a characteristic DA reaction ΔS^\ddagger is open to question, especially in light of the discussion found in a recent paper by Sciano et al.¹⁸ Although IBF is many orders of magnitude less reactive than the diradicals described in this reference, it is nonetheless a very reactive diene in cycloadditions and may deviate from characteristic ΔS^\ddagger behavior. To the extent that the ΔS^\ddagger assumption is in error, a shallower well for starting materials would result (Figure 2). For example, if the assumption of rate doubling for each 10° temperature increase is made ($\Delta S^\ddagger = \text{ca. } 0$), the calculated rate constant for the MA + IBF cycloaddition would increase nearly 1000-fold, and give $\Delta G^\ddagger = 14.4$ kcal·mol⁻¹, in place of the 18.6 kcal·mol⁻¹ described in the text. These values probably define the uncertainty limits on the starting material energy levels in Figure 2.

(18) Sciano, J. C.; Wintgens, V.; Haider, K.; Berson, J. A. *J. Am. Chem. Soc.* 1989, 111, 8732.

(19) McCormick, J. P.; Shinmyozu, T. *J. Org. Chem.* 1982, 47, 4011.

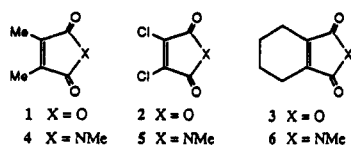
(20) The exo structure of this IBF-1 adduct has been established by X-ray analysis: Schlemper, E. O.; Shinmyozu, T.; McCormick, J. P. *Acta Crystallogr., Sect. B* 1982, 38, 2981. For all examples in the present study, we use exo/endo descriptors to indicate the position of the anhydride (or imide) ring.

Table I. IBF Cycloadducts and Free Energy Factors

dienophile	endo/exo			equilibrium (ΔG°) 132 °C	retro-Diels-Alder $10^6 k$ (s^{-1}) (ΔG^\ddagger), 132 °C	
	kinetic control (ΔG^\ddagger)				endo	exo
	25 °C	80 °C	132 °C			
MA	77/23	67/33	63/37(0.41)	5/95 (2.4)	240 (30.6)	5.9 (33.5)
1				7/93 (1.9) ^a		150 (30.9) ^b
2						190 (30.8)
3						87 (31.4)
NMM	96/4	87/13	82/18 (1.20)	ca. 5/95 (2.4)	0.85 (35.1) ^c	0.0095 (38.7)
5	20/80	23/77	28/72 (-76)	2/98 (3.1)	2.5 (34.2)	0.36 (35.8) ^c
6	25/75	24/76	26/74 (-84)	13/87 (1.5)	0.95 (35.0)	0.40 (35.7) ^c

^a This equilibrium ratio is based on a single point, at 111 °C, given in ref 19. ^b Measured in the present study, at 132 °C. ^c The ΔG^\ddagger determined from the measured rate constant for conversion of this to the other stereoisomer was corrected by subtraction of $\Delta\Delta G^\ddagger$ (kinetic control), and the resultant ΔG^\ddagger was used to calculate the rate constant for the r-DA step.

constant shown in Table I. The methyl substituents enhance the rate 25-fold.



Two additional exo adducts of substituted maleic anhydrides (2 and 3) were prepared and examined in this manner. The exo dichloro adduct (2-IBF) was the only isomer observed from a room-temperature reaction of preformed IBF with 2 (single bridgehead ¹H NMR signal). The exo assignment is based on conversion to the *N*-methylmaleimide analog (5-IBF) by treatment with methylamine, following the general procedure of Mehta et al.²¹ The adduct 2-IBF undergoes r-DA reaction 32 times faster than the unsubstituted analog.

Tetrahydrophthalic anhydride (3) was found to react rather slowly with IBF at room temperature, and a rate constant for this DA step was measured by following the loss of IBF by NMR: $k = 1.2 \times 10^{-2} \text{ M}^{-1}\text{s}^{-1}$. The substituents in this instance reduce the rate of the DA reaction by an estimated factor of 6300, based on comparison with the rate of reaction of IBF with MA ($k = 76 \text{ M}^{-1}\text{s}^{-1}$, in benzene at 25 °C) determined by Wege and Moursoundis.¹⁵

The exo 3-IBF adduct was formed by heating 1-ethoxy-1,3-dihydroisobenzofuran with 3 in toluene containing acetic anhydride for 24 h. This method gave material with only one bridgehead ¹H NMR signal. Attempts to convert this anhydride to the *N*-methylimide derivative were unsuccessful; only starting material was recovered even under forcing conditions. The exo stereochemistry in this instance rests on analogy with other IBF reactions under these conditions, and the behavior of the substituted *N*-methylmaleimides described below. The r-DA reaction of 3-IBF was 15 times faster than that of the unsubstituted MA derivative.

Chloro, methyl, and cyclo-(CH₂)₄ substituents thus enhance the rate of exo r-DA reactions by modest amounts, ranging from 15 to 32. The much larger rate-diminishing effect on the DA reaction of 3 shows that the transition state and cycloadduct are destabilized, relative to unsubstituted MA, by similar amounts.

For all the anhydrides examined, the scavenging power of NMM allowed clean first-order determination of r-DA

rate constants. The rates of r-DA reactions of substituted NMM derivatives are less obviously suited to this approach, although the results with these materials (Table I) show that unsubstituted NMM would still be useful for this purpose. Not aware of this, we approached these reactions by an alternative method that required determination of the rates of stereoisomer interconversion, the relative rates of isomer formation under kinetic control, and the endo/exo equilibrium position. All of these factors were determined at 132 °C, and lower temperature kinetic control values were also obtained (Table I). The rates for interconversion of stereoisomers represent the true rates of r-DA reaction only for the kinetically disfavored adduct (exo for NMM itself, endo for the adducts of 5 and 6). For the other stereoisomer, the measured rate constant was used to calculate ΔG^\ddagger for isomer interconversion, and this was corrected by subtraction of $\Delta\Delta G^\ddagger$ (kinetic control), to give ΔG^\ddagger shown in Table I, which in turn was used to calculate the true rate constant for the r-DA step (Table I).

Several conclusions emerge: (1) all of the maleimide analogues are more stable toward r-DA reactions than their MA counterparts; (2) the dichloro- and -(CH₂)₄- substituents increase the rates of their r-DA reactions of exo isomers by factors of 38 and 42, respectively; these effects are thus quite similar in the anhydride and imide derivatives; (3) substituent effects on r-DA reactions of the endo isomers are small (dichloro) to negligible (-(CH₂)₄-); (4) the substituents have an appreciable effect on kinetically controlled product distribution, such that the exo isomer predominates for the substituted maleimides, in contrast to NMM itself; (5) although rates for DA reactions for the substituted maleimides have not been determined, these are likely slower than for NMM itself, at least for the alkylated derivatives; coupled with the r-DA rate information, we conclude that NMM cycloadducts enjoy the highest overall stability of this series, mainly due to the exo isomer.

In conclusion, "avidity"²¹ is a useful combined kinetic and thermodynamic property of dienophiles that can be applied to the determination of rate constants, or to the exchange of dienophiles for synthetic purposes. NMM is the best of the various maleimides and anhydrides studied experimentally to date, but other dienophiles may also exhibit this unusual combination of reactivity and product stability.²²

(21) Mehta, N. B.; Phillips, A. P.; Fu, F.; Brooks, R. E. *J. Org. Chem.* 1960, 25, 1012.

(22) Bis-arylsulfonyl ethylenes are interesting candidates for exploration of avidity, based on the reported irreversibility of a reaction with cyclopentadiene; see: De Lucchi, O.; Fabbri, D.; Cossu, S.; Valle, G. *J. Org. Chem.* 1991, 56, 1888.

Table II. Calculated Energies^a

compd	HF/6-31G*	MP2/6-31G*	ZPE
hydrogen	-1.126 83	-1.144 10	5.9
maleic anhydride	-377.230 17	-378.239 27	34.2
succinic anhydride	-378.421 15	-379.442 10	48.0
maleimide	-357.407 63	-358.402 49	41.5
succinimide	-358.603 31	-359.609 78	55.3

^a Total energies are given in hartrees. ZPE are in kcal·mol⁻¹.

Table III. Calculated HF/6-31G* Geometries

parameter	maleic anhydride	succinic anhydride	maleimide	succinimide
r(C=O)	1.172	1.173	1.185	1.187
r(CO-C)	1.491	1.515	1.500	1.519
r(CO-X)	1.360	1.357	1.381	1.376
r(C-C)	1.317	1.527	1.319	1.535
r(N-H)			0.996	0.998
∠(OC-X-CO)	110.0	113.0	112.0	115.4
∠(X-CO-C)	107.2	109.4	105.1	107.2
∠(OC-C-C)	107.8	104.1	108.9	105.1
∠(X-C=O)	123.3	122.2	126.7	125.2
∠(C-C=O)	129.5	128.4	128.2	127.5

Calculated Heats of Hydrogenation of MA and Maleimide. Calculations²³ were performed on MA and succinic anhydride, and (unsubstituted) maleimide and succinimide, in order to see if the experimental effects described above arise in these simplified models, which use hydrogenation as an approximation to DA cycloaddition.²⁴

The calculations support the experimental observations in predicting larger heats of hydrogenation of maleimide than MA. At the HF/6-31G* level, the heat of hydrogenation of maleimide is 2.6 kcal·mol⁻¹ more exothermic than that of MA, while at the MP2/6-31G**/HF/6-31G* level, the difference is 2.5 kcal·mol⁻¹.²⁵ The origin of this phenomenon is unclear. Comparison of MA and maleimide shows their carbon-carbon double bonds to be virtually the same length, revealing none of the greater antiaromatic character one might assume to be present in maleimide relative to MA.²⁶ Further analysis of the molecular orbitals involved and the changes in geometries associated with hydrogenation show no dramatic differences. Apparently the differing heats of hydrogenation are the sum total of many small differences between the two reactant/product pairs.

The greater stability of NMM cycloadducts could thus be viewed as an expected result, leaving the very similar rates of NMM and MA DA reactions as the unusual feature. The transition state for a DA reaction can be considered as highly ordered (ΔS^\ddagger is usually very similar to ΔS_0) but otherwise more closely resembling starting materials than product (little bond formation); this view provides a rationale for the similarities in rates and differences in product stability, although it falls short of predicting that

the rates of MA and NMM should be nearly identical with a wide range of dienes.

Experimental Section

NMM and substituted NMMs 4-6 were prepared by treatment of the corresponding anhydrides with methylamine, following the general procedure of Mehta et al.²¹ The reaction of 3,4,5,6-tetrahydrophthalic anhydride (3) was relatively slow, but separation of 6 from unreacted 3 was easily accomplished by silica gel chromatography.

The cycloadducts of furan with NMM have been previously reported.²⁷ The rate constants for this system in CD₃CN (sealed NMR tube, immersed in a refluxing CH₂Cl₂ bath, 40 °C) were determined by following the disappearance of absorptions at 6.74 (vinyl H of NMM) and 6.43 ppm (2 H of furan), and the appearance of absorptions at 6.50 (vinyl H of exo adduct) and 6.35 ppm (vinyl H of endo adduct). Over a period of 63 h, 21 spectra were recorded. The kinetically controlled ratio (63% endo, 37% exo) was constant over the first 6 h, allowing determination of rate constants by treatment as irreversible second-order reactions; at longer times, the endo/exo ratio slowly decreased, reflecting partial equilibration. The r-DA reactions are too slow for convenient determination of the equilibrium position at 40 °C; this was calculated from equilibria established at 62, 69, and 80 °C and extrapolating the results to 40 °C. Equilibration was confirmed at each temperature by NMR examination over time of sealed tubes, starting with pure exo adduct and ca. 1:1 endo/exo mixtures in each instance. Heating was continued until the ratios of adducts and educts were identical from each starting material. The 40 °C extrapolated values for 0.49 M starting material are as follows: furan = NMM = 0.03 ± 0.01 M, endo adduct = 0.023 M, and exo adduct = 0.44 M. The adducts of IBF with NMM are known.²⁸ The kinetically controlled ratio at 25 °C was obtained by treatment of IBF, formed by base-induced elimination of 1-ethoxy-1,3-dihydroisobenzofuran, with NMM. Kinetically controlled ratios at 80 and 132 °C were obtained by mesitoic acid catalyzed reaction of the same IBF precursor with NMM in refluxing benzene (45 h) and chlorobenzene (2 h), respectively.

The known adducts of IBF with MA were isolated in pure form. Endo adduct was obtained by recrystallization (hexanes/CH₂Cl₂) of the mixture (endo/exo = 80/20) formed by treatment of preformed IBF with MA (-70 °C to ambient), mp 173.5-174.5 °C (lit.²⁹ mp 172 °C). The exo isomer was isolated by recrystallization (CH₂Cl₂) of the mixture formed by heating MA and the IBF precursor with acetic anhydride in chlorobenzene for 38 h (endo/exo = 5/95), mp 218-220 °C (lit.²⁹ mp ca. 212 °C).

exo-3a,9a-Dichloro-4,9-epoxynaphtho[2,3-c]furan-1,3-dione. A mixture of 200 mg (1.22 mmol) of 1-ethoxy-1,3-dihydroisobenzofuran, 203 mg (1.22 mmol) of 2,3-dichloromaleic anhydride (2), and 0.18 mL of acetic anhydride in 2 mL of toluene was refluxed for 18 h. The crude discolored product (333 mg) showed a single bridgehead proton absorption by NMR. Recrystallization from hexanes/CH₂Cl₂ afforded 95 mg (27%) of presumed exo adduct, mp 150-151 °C: ¹H NMR δ 5.80 (s, 2 H) 7.42-7.47 (m, 2 H), and 7.52-7.58 (m, 2 H); ¹³C NMR δ 47.7, 86.7, 123.7, 129.2, 139.0, 165.9; IR (CDCl₃) 1745, 1810, 1885 cm⁻¹. Anal. Calcd for C₁₂H₆Cl₂O₄: C, 50.56; H, 2.12. Found: C, 50.44; H, 2.05.

exo-3a,9a-Butano-4,9-epoxynaphtho[2,3-c]furan-1,3-dione. A similar reaction (24 h reflux) of 204 mg of the IBF precursor and 202 mg of 3 gave 383 mg of crude product that appeared to be a single isomer by ¹H NMR. Recrystallization (hexanes/CH₂Cl₂) gave 169 mg of pure presumed exo isomer, mp 150-152 °C: ¹H NMR δ 0.75-0.85 (m, 2 H), 1.05-1.30 (m, 4H), 2.05-2.15 (m, 2 H), 5.54 (s, 2 H), 7.29-7.35 (m, 2H), and 7.37-7.43 (m, 2 H); ¹³C NMR δ 17.8, 24.7, 56.5, 86.2, 122.2, 128.0, 141.7, 175.4; IR (CDCl₃) 1775, 1845 cm⁻¹. Anal. Calcd for C₁₆H₁₄O₄: C, 71.10; H, 5.22. Found: C, 71.06; H, 5.23.

(23) Gaussian 92, Revision B: Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. *Gaussian 90*, Inc. Pittsburgh, PA 1992.

(24) Ab initio calculations at the levels used often correlate well with experimental heats of hydrogenation; for a recent example, see: Wiberg, K. B.; Nakaji, D. Y.; Morgan, K. M. *J. Am. Chem. Soc.* 1993, 115, 3527.

(25) The effect of electron correlation on hydrogenation calculations is generally small; see: Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; John Wiley & Sons: New York, 1986, pp 285-288.

(26) The difference in C=C bond lengths observed between MA and maleimide corresponds to 0.04 kcal·mol⁻¹ when ethylene is distorted similarly at the HF/6-31G* level of theory.

(27) Anderson, W. K.; Milowski, A. S. *J. Org. Chem.* 1985, 50, 5423.

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When the reaction of **3** with preformed IBF was carried out at rt in ether, aliquots examined by ^1H NMR (60-MHz cw instrument, ether solvent) showed that the reaction was essentially complete within 4 h. Three points determined at 0.2, 1.0, 2.5, and 4 h exhibited unreacted IBF absorptions (δ at 8.0 ppm for the furan protons), in the relative amounts of 77, 36, 13, and <2%, respectively, which corresponds to a second-order rate constant of $1.2 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$.

exo-3a,9a-Dichloro-4,9-epoxy-2-methyl-3a,4,9,9a-tetrahydro-1H-benz[*f*]isoindole-1,3(2*H*)-dione. A mixture of 1-ethoxy-1,3-dihydroisobenzofuran (157 mg, 0.958 mmol) and 14 μL (0.10 mmol) of diisopropylamine in 2 mL of ether was treated with 0.90 mL (1.44 mmol) of *n*-BuLi (1.6 M in hexane). After 0.25 h, the mixture was poured into brine/ether. The ether layer was dried over K_2CO_3 , and added to a solution of **2** (174 mg, 0.97 mmol) in 2 mL of ether, with stirring for 1 h. The solvent was evaporated to give 276 mg of crude product, endo/exo = 20/80. Silica gel chromatography (20% ether/hexanes) afforded 108 mg of endo/exo mixture and 73 mg (25%) of essentially pure exo adduct. After recrystallization (hexanes/ CH_2Cl_2), analytically pure exo adduct had mp 260–261 $^\circ\text{C}$; ^1H NMR δ 3.20 (s, 3H), 5.65 (s, 2H), 7.38 (m, 2H), 7.50 (m, 2H); ^{13}C NMR δ 26.6, 85.4, 123.5, 128.6, 139.8, 171.3; IR (CDCl_3) 1800, 1730 cm^{-1} . Anal. Calcd for $\text{C}_{13}\text{H}_9\text{Cl}_2\text{NO}_3$: C, 52.38; H, 3.04. Found: C, 52.12; H, 2.84.

Treatment of the MA analogue described earlier with methylamine at rt for 26 h gave the same exo NMM adduct, uncontaminated by endo material, reinforcing the exo assignment of the MA adduct.

A small amount of endo adduct (2-NMM) was obtained by recrystallization of the mixture from chromatography. It had mp 215–218 $^\circ\text{C}$ (^1H NMR δ 2.39 (s, 3H), 5.67 (s, 2 H), 7.29–7.37 (m, 4H)) and was further characterized by combustion analysis. Found: C, 52.38; H, 2.93.

exo-3a,9a-Butano-4,9-epoxy-2-methyl-3a,4,9,9a-tetrahydro-1H-benz[*f*]isoindole-1,3(2*H*)-dione. A solution of IBF was prepared as described above from 161 mg (0.98 mmol) of precursor and added to a solution of *N*-methyl-3,4,5,6-tetrahydrophthalimide (162 mg, 0.98 mmol) in 5 mL of ether. Evaporation after 5 h gave 295 mg of crude product that was chromatographed (silica gel, hexanes to ether) to give 146 mg (52%) of mixed endo/exo = 25/75 product; essentially pure exo adduct was obtained by recrystallization from methanol, mp 166–169 $^\circ\text{C}$: ^1H NMR δ 0.8 (br m, 2 H), 1.05 (m, 4H), 2.05 (m, 2H), 3.08 (s, 3H), 5.37 (s, 2H), 7.28 (m, 2H), 7.34 (m, 2H); ^{13}C NMR δ 18.0, 24.3, 54.7, 85.2, 122.0, 127.4, 142.6, 180.95; IR (CDCl_3) 1765, 1685 cm^{-1} ; MS(CI) calcd for $\text{C}_{17}\text{H}_{18}\text{NO}_3 + \text{H}$ 284.1298, found 284.1292.

The endo product was identified by ^1H NMR absorptions at 2.26 (s, 3H) and 5.17 ppm (s, 2H) in the mixture described above.

Rates of r-DA Reactions of MA and Substituted MA Adducts. The reaction of *exo*-MA-IBF adduct is representative. A mixture of 101 mg (0.467 mmol) of the adduct and 528 mg (4.75 mmol) of NMM in 2.0 mL of chlorobenzene was refluxed, with periodic cooling and removal of the solvent, replacement by CDCl_3 , and ^1H NMR examination. The NMR solvent was evaporated and replaced by chlorobenzene and the reaction restarted. The MA adduct decreased with time, in spectra examined after 1, 8, 26, 40, 60, 85, and 200 h, at which point the reaction was complete within measurement limits. A plot of $\ln[\text{MA-IBF}]$ vs time gave $k = 5.9 \times 10^{-6} \text{ s}^{-1}$.

Calculations

All structures were optimized at the RHF/6-31G* level of theory³⁰ using the Gaussian 92 series of programs.²³ Frequency calculations were performed at the same level and scaled by 0.89 to give zero-point energies. All optimized geometries proved to be minima. Correction for electron correlation was determined with the second-order Møller–Plesset perturbation method.³¹ Maleic anhydride and maleimide were constrained to the C_{2v} point group during geometry optimization. Succinic anhydride and succinimide were not constrained but proved to prefer essentially C_{2v} symmetry. The calculated energies are shown in Table II, while the calculated geometries are shown in Table III.

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Supplementary Material Available: IR and NMR spectra of the novel cycloadducts, final *Z* matrices for the calculated structures, and an explanation of the procedure used for quasiequilibrium calculations (15 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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