# Why Do Catalytic Quantities of Lewis Acid Generally Yield More Product than 1.1 Equiv in the Intramolecular Diels−Alder Reaction with a Furan Diene? 2.[1] AM1 Calculations and Mathematical Simulation of the Equilibria

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The results presented here provide additional support for our hypothesis based on the relative basicity of the reaction controlling functional group to rationalize experimental observations on intramolecular Diels−Alder reactions with a furan diene (IMDAF) regarding the quantity (0.1 or 1.1 equiv) of Lewis acid required to facilitate the reaction most effectively. Heats of formation, $\Delta H_f$, and heats of reaction, $\Delta H_R$, have been obtained using AM1 calculations for 26 IMDAF reactions. These $\Delta H_R$ are generally exothermic (indicating that these IMDAF reactions are favorable) and can be qualitatively correlated with experimental yields of adduct, thereby providing a means of predicting the feasibility of the IMDAF promoted by 0.1 equiv of Lewis acid. The equilibria involved in the Lewis acid-promoted IMDAF reaction have been qualitatively interpreted using reaction coordinate diagrams and quantitatively investigated by generating a mathematical simulation of the reaction scheme. This demonstrates that the experimental behavior of the IMDAF reaction is well represented by the relative basicity hypothesis and that the LA concentration-dependent behavior should also be observed for other Lewis acid-promoted organic reactions.

The Diels−Alder reaction (DA)[2] is a valuable tool for the organic chemist by virtue of the high stereo- and regiocontrol possible in the construction of highly functionalized cyclic systems.[3] However, the reaction is not always facile, and often Lewis acids (LA) are employed to promote the reaction. We have been particularly interested[4] in the intramolecular DA reaction with a furan diene (IMDAF) for application to the synthesis of natural products. As part of these studies, we discovered[4d,h,i,j] that for reactions **1 → 2**, 0.1 equiv of methylaluminum dichloride (MAC) gave better conversion of starting materials (SM) to products (P) than 1.1 equiv of MAC (Scheme 1 and Table 1). In contrast, we have found that the related systems with acetylenic dienophiles **3** (Scheme 2) give higher conversion to P in the presence of 1.1 rather than 0.1 equiv of LA (Table 1). A similar dependence on LA equivalents has also been reported by Snider[5] for an ene reaction. The literature shows that, for the most part, LA-promoted

**Scheme 1**
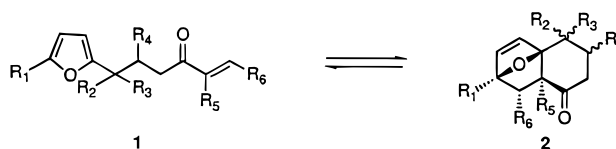


| | R₁ | R₂ | R₃ | R₄ | R₅ | R₆ |
|---|----|----|----|----|----|----|
| **a** | H | H | H | H | H | H |
| **b** | H | H | H | H | Me | H |
| **c** | H | H | H | H | H | Me |
| **d** | H | H | H | H | Me | Me |
| **e** | Me | H | H | H | H | H |
| **f** | Me | H | H | H | Me | H |
| **g** | Me | H | H | H | H | Me |
| **h** | H | Me | Me | H | H | H |
| **i** | H | Me | Me | H | Me | H |
| **j** | H | Me | Me | H | H | Me |
| **k** | H | Me | Me | H | Me | Me |
| **l** | Me | Me | Me | H | H | H |
| **m** | Me | Me | Me | H | Me | H |
| **n** | Me | Me | Me | H | H | Me |
| **o** | Me | Me | H | H | H | H |
| **p** | Me | Me | H | H | Me | H |
| **q** | Me | Me | H | H | H | Me |
| **r** | Me | H | H | Me | H | H |
| **s** | Me | H | H | Me | Me | H |
| **t** | Me | H | H | Me | H | Me |

IMDA reactions have generally used at least 0.95 equiv of the LA when the dienophile is activated by an ester or an aldehyde,[6] though there are a few examples of "catalytic" IMDA reactions using unsaturated aldehydes.[7] This suggests that the type of activating group can be critical in determining the amount of LA required for

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**Table 1. Enthalpies of Formation, $\Delta H_f$, and Reaction, $\Delta H_R$, from AM1 Level Calculations and Experimentally Observed SM:P Ratios**

| SM | SM $\Delta H_f{}^a$ | P $\Delta H_f$ | $\Delta H_R$ | 0.1 equiv of LA[b,c] | 1.1 equiv of LA[b,c] |
|---|---|---|---|---|---|
| 1a | −115.5 | −159.4 | −43.9 | 0:100 | 0:100 |
| 1b | −145.2 | −164.8 | −19.6 | 11:89 | 35:65 |
| 1c | −158.6 | −177.8 | −19.2 | 31:69 | 78:22 |
| 1d | −183.3 | −176.1 | 7.2 | 95:5 | 100:0 |
| 1e | −144.8 | −176.1 | −31.3 | 0:100 | 0:100 |
| 1f | −174.5 | −181.6 | −7.1 | 0:100 | 19:81 |
| 1g | −187.3 | −193.4 | −6.1 | 24:76 | 82:18 |
| 1h | −132.2 | −178.7 | −46.5 | (Florisil 0:100)[d] | |
| 1i | −161.1 | −181.2 | −20.1 | 40:60 | 68:32 |
| 1j | −176.1 | −196.6 | −20.5 | 27:73 | 73:27 |
| 1k | −200.8 | −191.6 | 9.2 | 100:0 | 100:0 |
| 1l | −161.9 | −195.4 | −33.5 | (Florisil 0:100)[d] | |
| 1m | −192.0 | −197.5 | −5.5 | 23:77 | 78:22 |
| 1n | −208.4 | −212.1 | −3.7 | 69:31 | 78:22 |
| 3a | −20.5 | −40.9 | −20.4 | | 0:100[e] |
| 3b | −206.9 | −181.4 | 25.5 | | 12:88[e] |
| 3c | −202.8 | −185.2 | 17.6 | 99:1 | 13:87[e] |
| 5a | −128.4 | −130.5 | −2.1 | 80:20 | |
| 5b | −81.2 | −86.8 | −5.5 | 7:93 | |
| 5c | −53.1 | −58.0 | −4.9 | 5:95 | |
| 7a | −474.9 | −654.8 | −179.9 | | |
| 7b | −699.1 | −868.6 | −169.5 | | |
| 8a | −20.2 | −205.5 | −185.3 | | |
| | | | | | (SM:Peq.:Pax) |
| 1o | −157.3 | eq −191.6 | −34.3 | | 0:90:10 |
| | | ax −188.3 | −31.0 | | |
| 1p | −185.4 | eq −197.1 | −11.7 | | 9:88:3 |
| | | ax −192.0 | −6.6 | | |
| 1q | −203.3 | eq −208.8 | −5.5 | 17:75:4 | 79:16:5 |
| | | ax −205.4 | −2.1 | | |
| 1r | −159.4 | eq −197.5 | −38.1 | (Florisil 0:100:0)[d] | |
| | | ax −191.2 | −31.8 | | |
| 1s | −187.4 | eq −202.9 | −15.5 | | 11:89:0 |
| | | ax −196.2 | −8.8 | | |
| 1t | −202.5 | eq −215.1 | −12.6 | 11:87:2 | 61:31:8 |
| | | ax −208.4 | −5.9 | | |

[a] $\Delta H_f$ and $\Delta H_R$ in kJ mol$^{-1}$. [b] Unless indicated otherwise, reaction conditions are 1.1 equiv of MAC, CH$_2$Cl$_2$, 8 h, −78 °C and 0.1 MAC, CH$_2$Cl$_2$, 2 h, −65 °C.[4d,h−k] [c] Isolated yields are generally very close to these figures, indicating that there is no significant decomposition of either SM or P; hence, these ratios can be regarded as yields. [d] We have found that reactions generally give better yields of product with 0.1 equiv of MAC than with Florisil;[4d,h−k] therefore, it is reasonable to assume that these reactions will go to completion with 0.1 equiv MAC. [e] 1.1 or 0.1 equiv of DMAC, −50 °C, 2.5 h. Note that DMAC was used to reduce aromatization of adducts that was seen with MAC.

**Scheme 2**



**3**                                          **4**
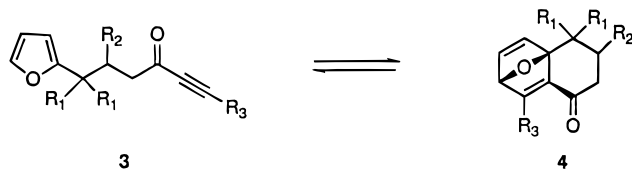
**a** R$_1$ = R$_3$ = Me, R$_2$ = H

**b** R$_1$ = Me, R$_2$ = H, R$_3$ = TMS

**c** R$_1$ = H, R$_2$ = Me, R$_3$ = TMS

successful reaction. In this regard, we have previously defined the higher conversion to P with 0.1 equiv of LA as "type A" reactions and the higher conversion to P with 1.1 equiv of LA as "type B" reactions.[1]

These observations indicate that the relative amount of LA employed influences the position of the IMDAF equilibrium. Therefore, in a strict chemical sense, the LA *cannot* be described as a "catalyst". However, since the LA increases the rate of reaction, is not consumed during the reaction, and can be employed in low relative

**Scheme 3**
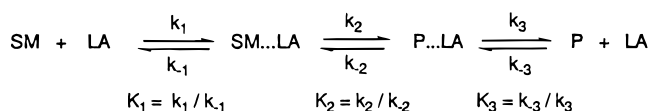


concentration, at least in a language sense, the term "catalyst" seems most appropriate. Herein therefore, we have chosen to describe the use of 0.1 equiv of LA as "catalytic quantities" and 1.1 equiv of LA as "stoichiometric quantities".

In order to rationalize these observations for the type A and B IMDAF reactions, we have previously offered an explanation based on the general equilibria involved (Scheme 3) and the relative basicity of the ketone group in SM and P.[1,4d,h,i] The hypothesis requires that for type A reactions (like **1 → 2**), with catalytic quantities of LA, the LA preferentially coordinates with the enone of SM and promotes the DA reaction; *i.e.*, the SM carbonyl is more basic than the P carbonyl group. Once the P⋅⋅⋅LA complex is formed, the LA dissociates from P and is then able to recoordinate with SM. This ultimately shifts the equilibrium toward P. With an excess of LA the observed equilibrium tends to reflect SM⋅⋅⋅LA ⇌ P⋅⋅⋅LA, which for the IMDAF reactions **1 → 2** tends to lie toward SM. For type B reactions (like **3 → 4**), with catalytic quantities of LA, the LA coordinates with the ynone of SM and promotes the DA reaction and the P⋅⋅⋅LA complex is formed. The LA is now complexed to the more basic site and does not dissociate. This ultimately prevents the conversion to P by failing to regenerate the reactive complex SM⋅⋅⋅LA. With an excess of LA the observed equilibrium SM⋅⋅⋅LA ⇌ P⋅⋅⋅LA tends to lie toward P. This hypothesis has been supported by low-temperature NMR complexation studies[1] and *ab initio* calculations of Lewis acid complexes.[8]

The often poor yields of cycloadducts obtained from even simple IMDAF reactions under a variety of experimental conditions[4] has led us to state previously[4a] that these IMDAF reactions have an unfavorable equilibrium toward SM. However, on the basis of our observations of reasonable to excellent adduct yields in the presence of catalytic quantities of LA, we realized that this was *not* generally true[1] and that a high activation energy (due to the loss of aromaticity and high product strain) must make the equilibrium *unobtainable* rather than unfavorable. This realization prompted us to consider the energetics and reaction scheme of the IMDAF reactions. Analogous studies have recently been reported by Dolata and Harwood[9] using WIZARD and MM2 programs to calculate the transition states of IMDAF reactions under partial kinetic control at high pressure. Houk *et al.*[10] have carried out transition state modeling using a wide range of IMDA reactions to generate an empirical force

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field based on MM2 to calculate diastereoselectivity; however, they did not extend their studies to furan diene systems.

The IMDAF reactions are very amenable to study. Since we have previously shown that the LA-promoted IMDAF reactions (with either catalytic or stoichiometric quantities of LA) are under thermodynamic control,[1,4i] only relative ground state energies of SM and P are required, and the number of reactive conformations are limited by the stereochemistry of both SM (*i.e.*, s-cis diene) and P (*i.e.*, *exo* only). In order to improve the knowledge of the factors controlling these reactions, we have carried out semiempirical calculations at the AM1 level on the IMDAF systems. A more qualitative understanding of the intricacies of the effect of LA on the IMDAF reactions is also possible via reaction coordinate diagrams. The AM1 calculations help us to position SM and P relative to each other in these diagrams. We have not calculated the energies of the complexes SM···LA or P···LA here since experimentally we observe better P yields with catalytic quantities of LA than with stoichiometric LA in most cases. Hence, these calculations are most useful for the IMDAF reactions with catalytic quantities of LA. Further studies on SM···LA and P···LA are in progress.

In order to gain further support for the hypothesis, we have used a computer simulation of the general reaction pathway (Scheme 3) to investigate the trends due to changing (i) the relative basicities of SM and P and (ii) the energetics of the reaction. This approach allows us to determine if the general pathway (Scheme 3) can reproduce the experimental observations. This has been accomplished by generating an expression for the experimentally observed P:SM in terms of the equilibrium constants for each step and the experimental variables for the initial concentration of SM and LA.

This paper presents our results on the use of AM1 level calculations to describe the energetics of the IMDAF reaction and a qualitative discussion on the effects of LA using reaction coordinate diagrams. The use of a computer simulation of the general reaction pathway as a means of verifying the behavior trends is described. The results of these considerations and the general implications to LA-promoted reactions are described herein.

## Results and Discussion

**1. Energetics of the IMDAF Reaction.** In order to probe the energetics of IMDAF reactions for which we already know their experimental characteristics, we have calculated[11] using SPARTAN[12] $\Delta H_f$ values for the IMDAF addends and adducts in Schemes 1, 2 and 4, and, hence, calculated $\Delta H_R$. Correlation of experimental SM:P ratios with $\Delta H_R$ is a reasonable expectation given that the yields of these reactions with catalytic quantities of LA tend to reflect the thermodynamic equilibrium between SM and P. We found that in order to reproduce "favorable" reactions, AM1 semiempirical[13] calculations were required. The $\Delta H_f$ and $\Delta H_R$ of the closely related IMDA systems **7**–**8**[7b] and **9**–**10** (Schemes 5 and 6) have been

(11) Calculations were performed using the AM1 semiempirical method within the SPARTAN program package. $\Delta H_R$ values were evaluated from the calculated $\Delta H_f$ of the geometry-optimized structures for **1**–**2** (**a**–**t**), **3**–**4** (**a**–**c**), **5**–**6** (**a**–**c**), and **7**–**10**.

(12) SPARTAN 2.0, Wavefunction, Inc., Irvine, CA. Carpenter, J. E.; Baker, J.; Hehre, W. J.; Kahn, S. D. SPARTAN User's Guide, 1991.
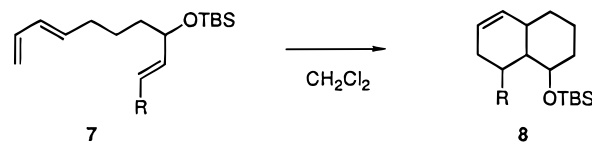
(13) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. J. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
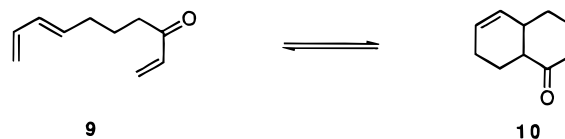
**Scheme 4**
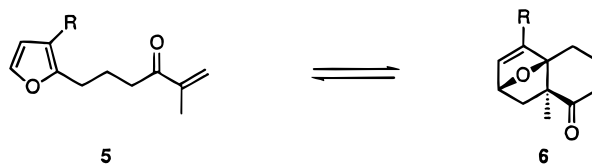


a   R = CO$_2$*i*Pr

b   R = CH$_2$OMe

c   R = CH$_2$OBn

**Scheme 5**



a. R = CHO,  0.2 EtAlCl$_2$, -78°C,  1 min., 62%

b. R = CO$_2$*i*Pr,  1.0 EtAlCl$_2$, 8°C, 18 h., 60%

**Scheme 6**



calculated for comparison (Table 1). The $\Delta H_R$ values indicate that the IMDAF reactions (Table 1) are indeed generally favorable enthalpically (except reactions of **1d**, **1k**, **3b**, and **3c**). A comparison of **1a** → **2a** ($\Delta H_R = -43.9$ kJ mol$^{-1}$) with related IMDA reaction **9** → **10** ($\Delta H_R = -185.3$ kJ mol$^{-1}$) indicates that the IMDAF reaction is significantly less favorable than its nonfuran analogue. A significant contribution to this difference is the aromaticity of furan (67 kJ mol$^{-1}$).[14]

The AM1 $\Delta H_f$ calculations also correlate well with other observed features of the LA-promoted IMDAF. $\Delta H_f$ for **2a** with an *endo* orientation is $-138.9$ kJ mol$^{-1}$; hence, there is approximately a 20 kJ mol$^{-1}$ preference for the **2a**-*exo* ($\Delta H_f = -159.4$ kJ mol$^{-1}$). Experimentally, we do not observe the formation of the *endo* adduct in any of the LA-promoted reactions of **1a**–**t** or **5a**–**c**. The calculations also predict that the equatorial methyl groups in adducts of **2o**–**t** are preferred by 3.3–6.7 kJ mol$^{-1}$ over the axial adduct, with the greatest preference seen with the methyl $\beta$ to the furan (R$_4$ = Me, Scheme 1). Experimentally, we have seen that both adducts form initially and gradually equilibrate to give predominantly the equatorial system.[1] General trends in $\Delta H_R$ can be analyzed by comparing analogous reactions (*e.g.*, for the effect of a methyl group on furan, compare **1a** → **2a** with **1e** → **2e**, *etc.*). The major trends are that alkyl substitution on the diene or dienophile makes the IMDAF $\Delta H_R$ less favorable. The effects on $\Delta H_R$ due to substituents are: On the furan, a 5-Me substituent contributes about $+14$ kJ mol$^{-1}$, and the 3-substituents contribute $+15$ kJ mol$^{-1}$. A single $\alpha$- or $\beta$-Me substituent on the dienophile moiety contributes about $+26$ kJ mol$^{-1}$. In comparison, the effect of alkyl substitution on the tether on the enthalpy of the reactions is only slight, but generally makes the reaction more favorable (in nine of 13 cases,
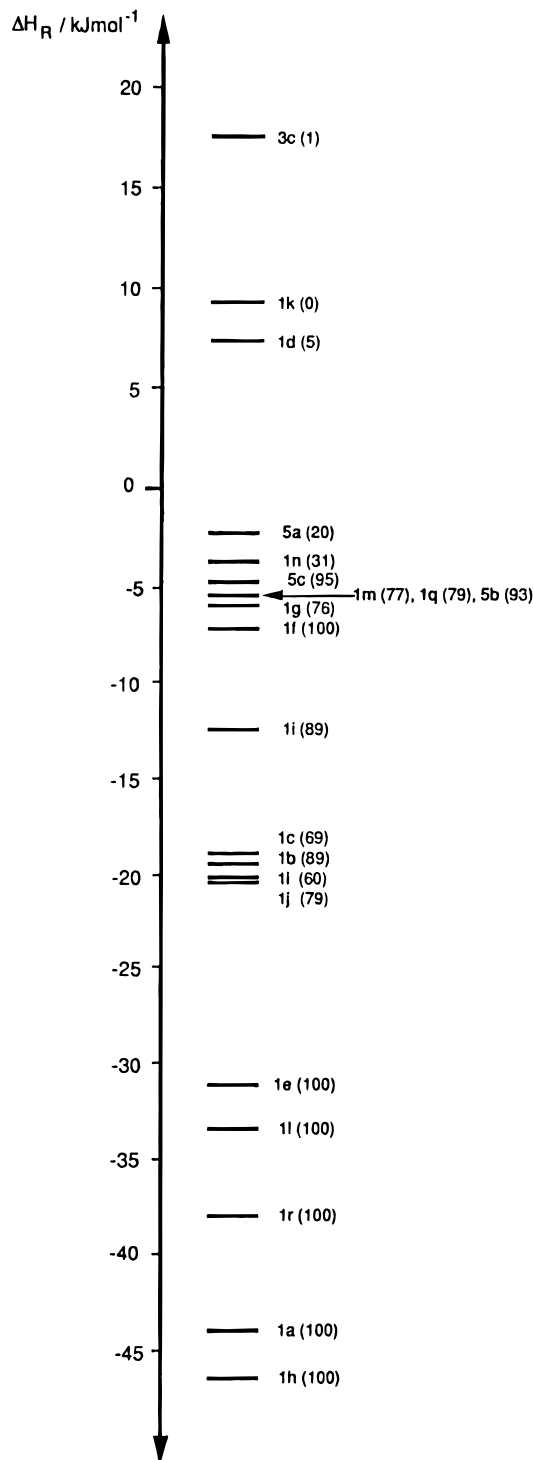
(14) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, NY, 1985.

value +2.2 to −8.4 kJ mol⁻¹) with a Me $\beta$ to the furan having a greater effect than $\alpha$. The effect of $\alpha,\alpha$-Me$_2$ is not significantly different from that of a single $\alpha$-Me. This observation is interesting in terms of the *gem*-dialkyl effect,[15] as it suggests that it is not an enthalpic effect. The most useful observation in these trends is that the effects seem to be additive.

For the IMDAF reactions with acetylenic dienophiles **3** → **4** (Scheme 2), the reaction is predicted to be unfavorable when the terminal group is trimethylsilyl (TMS). This is reflected by the poor conversion observed for **3c** with catalytic quantities of LA. The improved yields with 1.1 equiv of LA reflects the relative stability of the P···LA complex compared to the SM···LA complex[8] which have not been evaluated in these studies. This result shows how the yield of these IMDAF reactions can be dramatically influenced by the relative catalyst concentration. Note also that the reaction of acetylenic system **3a** is calculated to be as favorable as the equivalently substituted olefin **1j**.

Although it is the change in free energy, $\Delta G_R$, which governs the outcome of reactions, we have tried to use $\Delta H_R$ to investigate the differences between these IMDAF systems and thereby provide a tool for predicting the feasibility of IMDAF reaction with catalytic quantities of LA (Figure 1). It is expected that the entropy of IMDAF reactions will be negative (*i.e.*, $\Delta S_R < 0$),[16] resulting in an unfavorable contribution to $\Delta G_R$. The entropy contributions to the IMDAF systems are not amenable to calculation, and since the computational time required was not justified by a significant improvement in insight, we feel that it is more advantageous to consider $\Delta H_R$ alone.[17] It is important to remember that since $\Delta S_R \neq 0$, and that other factors (such as solvation) have been neglected, an SM:P of 50:50 does not corresond to $\Delta H_R = 0$. The *general* trend (Figure 1) is that increasingly negative $\Delta H_R$ does correspond to increased experimental yield; *i.e.*, reactions which were poor yielding experimentally are calculated to be unfavorable. Hence, for the IMDAF reaction in the presence of *catalytic quantities* of LA, AM1 is a useful method of assessing, in a *qualitative manner*, the feasibility of a particular system prior to synthesis. Kinetically controlled reactions (*e.g.*, high-pressure IMDAF) are more problematic and require a different approach.[9]

For the IMDA reactions **7a** → **8a** and **7b** → **8b** (Scheme 5),[7b] the reactions are calculated to be so favorable (−179.9 and −169.5 kJ mol⁻¹, respectively) that the energetics of LA complexation is minor compared to the overall energetics of the DA reaction, and the changes in $K_{obs}$ caused by changing from stoichiometric to catalytic quantities of LA are experimentally unobservable. This indicates, therefore, that there should not be a significant difference in the thermodynamic SM:P ratio when an aldehyde or an ester is used to activate the IMDA

(15) (a) Eliel, E. L.; Wilen, S. H. In *Stereochemistry of Organic Compounds*; Wiley: New York, NY, 1994; pp 682−4. (b) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 22 and references cited therein. (c) See ref 9b.

(16) See ref 14, pp 182−3.

(17) Although entropies of activation of similar IMDAF reactions are known (ref 15b), we have not found any entropies of reaction in the literature. It is tempting to assume that the change in $\Delta S_R$ for the series of IMDAF reactions is small (*i.e.*, $\Delta\Delta S_R \sim 0$); however, there is no literature precedent for this. Indeed, in an investigation of the *gem* dialkyl effect for the formation of alkylcyclohexanes, it has been stated that the entropy and enthalpy effects are of comparable importance and neither can be neglected (ref 18).

(18) Allinger, N. L.; Zalkow, V. *J. Org. Chem.* **1960**, *25*, 701.



**Figure 1.** Calculated AM1 $\Delta H_R$ (kJ mol⁻¹) for each of the IMDAF reactions (Schemes 1, 2, and 4) displayed on an "energy ladder".[9] The value in brackets is the experimentally observed yields of P (%). Note that there is a reasonable correlation with reactivity.

reactions **7** → **8**. The use of >0.95 equiv of LA for the ester systems is, therefore, probably a kinetic effect (*i.e.*, it is used to decrease the time required to reach equilibrium). Indeed, it has been reported that aldehydes are better activating groups than esters.[6a,7b,8]
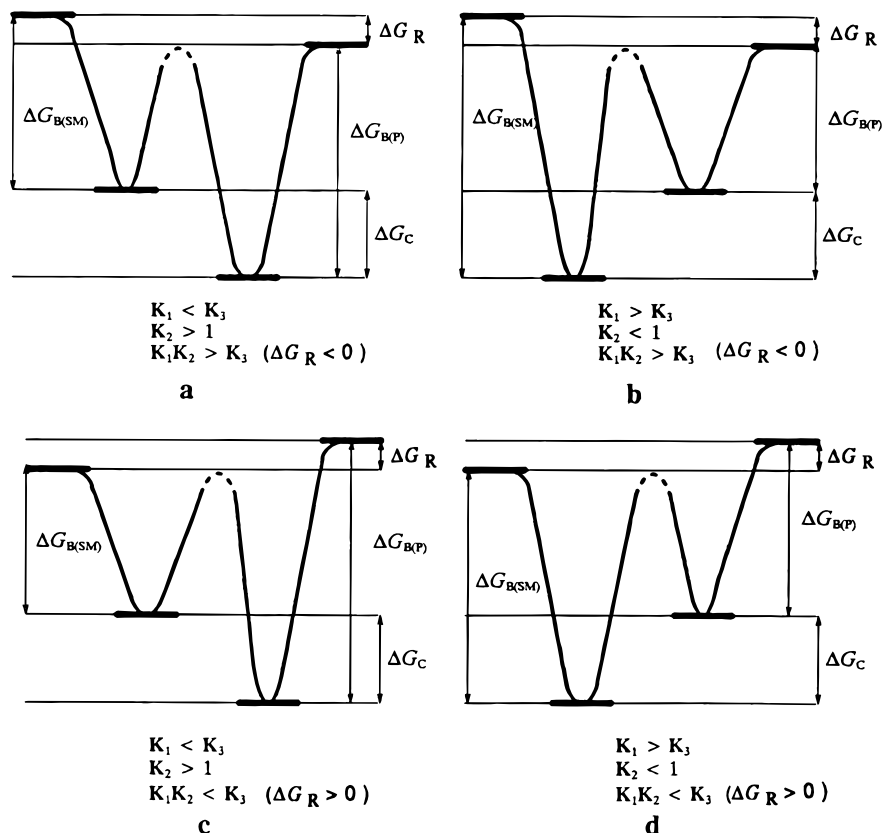
**2. Reaction Coordinate Diagrams.** The AM1 $\Delta H_R$ calculations indicate that although IMDAF reactions are exothermic, they are less exothermic than analogous IMDA (or DA) reactions. In the usual case for DA (or some IMDA) reactions, the free energy change for the

**Figure 2.** Reaction coordinate diagrams for different scenarios in the LA-promoted IMDAF reaction.

reaction, $\Delta G_R$, is large and negative, being dominated by the enthalpy change associated with the formation of two $\sigma$ bonds from two $\pi$ bonds. If stoichiometric quantities of LA are used in a solvent of low basicity, SM and/or P may exist almost entirely in the complexed forms, SM··· LA and P···LA, respectively. Energy changes associated with differences in the basicity of SM and P are usually small compared to $\Delta G_R$, and consequently, the free energy change for SM···LA $\rightleftharpoons$ P···LA is also negative. The presence of the LA, whether in catalytic or stoichiometric quantities, serves only to increase the rate at which the reaction approaches equilibrium but does not significantly alter the position of the equilibrium. IMDAF reactions are unusual in the sense that they are not strongly exogonic and may even be endogonic (*i.e.*, $\Delta G_R \cong 0$), due in part to the extra stability of SM (aromatic furan nucleus) and in part to the lower stability of P (strain inherent in the bridged tricyclic ring system). The LA dependence of total isolated P may be qualitatively understood in terms of free energy diagrams for the reaction coordinates (Figure 2) and the associated equilibria given in Scheme 3. The circumstances depicted in the four subcases are selected for discussion and related to specific examples. Other scenarios maybe possible but are not discussed here. With IMDAF reactions, the energy changes associated with the differences in basicity of SM and P are not small compared to $\Delta G_R$, and the free energy difference of the complexed forms, $\Delta G_c$ (which relates to $K_2$), may be larger or smaller, or even of opposite sign compared to $\Delta G_R$. The presence or absence of the catalyst may, therefore, significantly alter the outcome of the reaction. For the cases depicted (Figure 2), $|\Delta G_c| > |\Delta G_R|$ in all cases, but the thermodynamic stabilities and relative basicities of SM and P are altered to create four situations. Note that the yields with

catalytic quantities are reflected by the outer levels (*i.e.*, is SM or P more stable?) and the yields with stoichiometric quantities are reflected by the inner levels (*i.e.*, is SM···LA or P···LA more stable?).

In Figure 2a, with a favorable overall reaction ($\Delta G_R < 0$) and P more basic than SM, stoichiometric quantities of LA will improve the yield of the reaction compared to that with catalytic quantities of LA. IMDAF **3a** → **4a** is an example of this case. However, if SM is more basic than P (*e.g.*, the enone/ketone systems), case 2b is observed where catalytic quantities of LA provide P formation, *i.e.*, $K_{obs} > 1$, whereas stoichiometric quantities of LA decrease the yield, *i.e.*, $K_{obs} < 1$. IMDAF reactions which we have labeled type A[1] fall in this category, for example, reaction **1c** → **2c**. If the reaction is endogonic ($\Delta G_R > 0$), or only weakly exogonic, the yield with catalytic quantities of LA will be small, but will be improved with stoichiometric quantities of LA if the basicity of P is greater than that of SM (*e.g.*, the ynone/enone systems), then Figure 2c applies. Type B reactions, such as reaction **3c** → **4c**, follow this scenario. If the basicities of SM and P are similar, or SM is more basic than P, as in Figure 2d, then neither catalytic nor stoichiometric quantities of LA will lead to efficient product formation, for exampl, **1d** → **2d**.

**3. Simulation of Reaction Scheme.** The reaction coordinate diagrams provide a qualitative picture of the influence of LA and the equilibria involved in Scheme 3 on the outcome of IMDAF reactions. A more quantitative analysis is possible using a mathematical approach to the equilibria of Scheme 3. This has been done by using a computer to calculate SM:P ratios based on input "experimental conditions". This has allowed us to probe the effects of changing the amount of catalyst and the relative basicities of SM and P.

In order to do this, an expression for the observed SM:P in terms of experimental variables (LA and SM concentrations) is required. The equilibrium constants in Scheme 3 are defined as:

$$K_1 = [SM\cdots LA]/[SM] \, [LA] \qquad (1a)$$

$$K_2 = [P\cdots LA]/[SM\cdots LA] \qquad (1b)$$

$$K_3 = [P\cdots LA]/[P] \, [LA] \qquad (1c)$$

Equilibrium constants $K_1$ and $K_3$ measure the basicity, *relative to solvent*, of SM and P, respectively, toward the LA. The effective values of $K_1$ and $K_3$ may therefore be less than or greater than unity. The former situation applies with the solvent competes favorably for the LA. In our studies with MAC in methylene chloride, $K_1$ and $K_3$ are expected to be greater than unity, but this would not be the case in THF. Equilibrium constant $K_2$ directly measures the relative stability of complexed SM and P and is greater than unity if the complex $P\cdots LA$ is more stable than the complex $SM\cdots LA$. The equilibrium constant for the uncatalyzed DA reaction in terms of SM and P is $K_{DA}$:

$$K_{DA} = [P]/[SM] = K_1 K_2/K_3 \qquad (2)$$

Note that the reaction is favorable in the absence of LA if $K_1 K_2 > K_3$. In our experiments, the reaction mixture, including any added LA, has been quenched and the product is isolated from the combined amounts of P and $P\cdots LA$. Likewise, recovered SM originates both from SM and $SM\cdots LA$. Hence, the operationally useful quantity is, therefore, $K_{obs}$:

$$K_{obs} = [P]_{tot}/[SM]_{tot} \qquad (3a)$$

$$= ([P] + [P\cdots LA])/([SM] + [SM\cdots LA]) \qquad (3b)$$

By substituting for [P], [P$\cdots$LA], [SM], and [SM$\cdots$LA] in terms of the three equilibrium constants, $K_1$, $K_2$, and $K_3$, and the free catalyst, [LA], $K_{obs}$ can be expressed as:

$$K_{obs} = K_1 K_2(1 + K_3[LA])/K_3(1 + K_1[LA]) \qquad (4)$$

The experimentally known quantities are the initial amounts of addend, $[SM]_0$, and catalyst $[LA]_0$; hence, an expression for [LA] is required:

$$[LA]_{tot} = [LA]_0 = [LA] + [SM\cdot LA] + [P\cdots LA] \qquad (5)$$

By similar substitutions to those used above, the following expressions can be obtained

$$[LA] = 1/2((B^2 + 4D[LA]_0)^{0.5} - B) \qquad (6)$$

where

$$B = [SM]_0 - [LA]_0 + D$$

and

$$D = (K_3 + K_1 K_2)/K_1 K_3(1 + K_2)$$

Equation 6 can be substituted into eq 4 to generate the full expression for $K_{obs}$ in terms of $K_1$, $K_2$, $K_3$, $[SM]_0$, and $[LA]_0$; however, the expression is very cumbersome and is not reproduced here. Note that under equilibrium conditions and if the relative basicities of SM and P are the same, *i.e.*, $K_1 = K_3$, then from eq 4, $K_{obs} = K_2 = K_{DA}$, and that in the absence of added LA that eq 4 collapses to $K_{obs} = K_1 K_2/K_3 = K_{DA}$ as required by eq 2. The complex, nonlinear equation for $K_{obs}$ may be readily solved and visualized using Mathematica[19] to generate graphical representations of the expression to illustrate the features under investigation.

Figure 3a−d are 3-D surface representations of $K_{obs}$ (*i.e.*, yield) dependence on $K_1$ and $K_3$ (*i.e.*, SM and P basicity) for reactions with catalytic and stoichiometric quantities of LA with $K_2 = 0.25$ and 4. These values of $K_2$ were chosen because we felt that they were representative of the IMDAF reactions of interest to us. To aid in the interpretation of these figures, note that (i) if $K_{obs} > 1$ then it implies that the reaction yields $[P]_{tot} > [SM]_{tot}$ and (ii) that the plane defined by the rear corner through the forward corner (see Figure 3a) corresponds to $K_1 = K_3$, and hence, points to the right of that plane have $K_3 > K_1$, implying that P is more basic than SM. This would correspond to the reactions of the acetylenic IMDAF systems (Scheme 2).[1] Similarly, points to the left of that plane have $K_1 > K_3$ (SM is more basic than) corresponding to the reactions of the enone IMDAF systems. These 3-D surfaces are related to the coordinate diagrams in Figure 2 via the relationships between the terms in eq 2 with $\Delta G_R$ and $\Delta G_C$.

In Figure 3a,b, $K_2 = 0.25$ (*i.e.*, $[SM\cdots LA] > [P\cdots LA]$). Figure 3a shows that with 1 equiv of LA, the reaction will only generate P efficiently when $K_1 \gg K_3$ (*i.e.*, SM much more basic than P). With 0.1 equiv of LA, Figure 3b, P is generated over a wider range of relative basicities. However, little P formed when $K_3 > K_1$.

For Figure 3c, d, $K_2 = 4$. (*i.e.*, $[P\cdots LA] > [SM\cdots LA]$). Figure 3c, for stoichiometric LA, clearly shows that, in most scenarios, efficient conversion to P is obtained, but particularly when $K_1 \gg K_3$. However, if $K_1$ is small, the equilibrium is shifted toward SM. In contrast, Figure 3d strikingly shows how with just 1 mol % of LA the *same* equilibrium is dramatically shifted in favor of P, particularly when SM is more basic than P (*i.e.*, $K_1 > K_3$).

The $K_2$ values selected for the simulation were chosen to mimic the IMDAF reactions. In general, IMDA reactions (and other LA-promoted organic reactions) will be characterized by much more favorable energetics which implies that $K_2$ will be much larger. The behavior of such reactions (*e.g.*, $9 \rightarrow 10$) has been investigated using a simple numerical evaluation of the expression for $K_{obs}$[20] using values of $[SM]_0 = 0.1$ M and $[LA]_0 = 0.1$ and 0.01 M. This has shown that even if $K_2$ is made larger provided $K_1 > K_3$, then catalytic quantities of LA will give higher conversion to P than stoichiometric LA (*e.g.*, with $K_1 = 10$, $K_2 = 10\,000$, $K_3 = 1$, then $K_{obs} \cong 57\,000$ for stoichiometric and $K_{obs} \cong 92\,000$ with catalytic quantities of LA). If, however, $K_3 > K_1$, then stoichiometric LA gives higher conversion to P (*e.g.*, with $K_1 = 10$, $K_2 = 10\,000$, $K_3 = 20$, then $K_{obs} \cong 6700$ for stoichiometric and $K_{obs} \cong 5200$ with catalytic quantities of LA). These observations indicate the importance of the relative basicity hypothesis for determining the amount of LA required for promoting organic reactions most profitably. In these cases though, where the reactions are very favorable, the yields are already so high that the changes

(19) Mathematica is a trademark of Wolfram Research Inc., Champaign, IL.

(20) Evaluation of $K_{obs}$ was carried out using a simple Fortran program for the full version of eq 4 in terms of eqs 5 and 6.
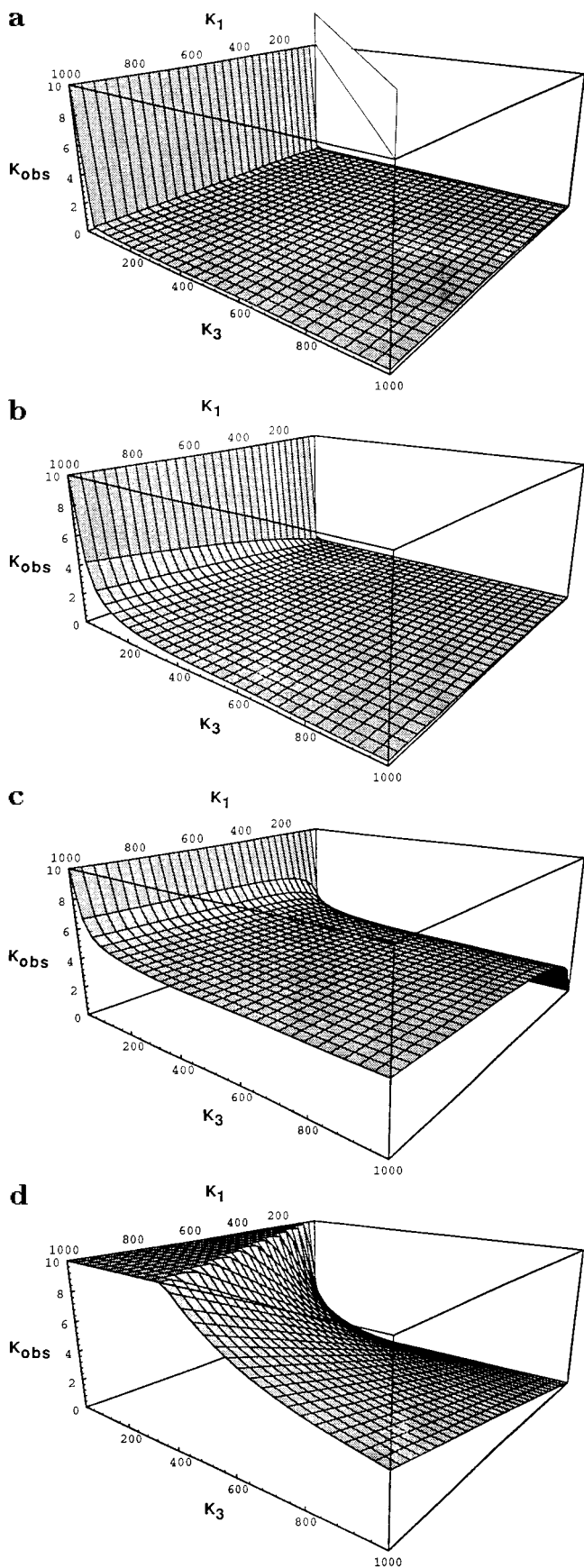
**Figure 3.** 3-D plots of eq 4 obtained using Mathematica to show the general characteristics of the kinetic Scheme 3. The following conditions were used: (a) $[SM]_0$, $[LA]_0 = 0.1$ M; $K_1$, $K_3 = 0.1-1000$; $K_2 = 0.25$; (b) $[SM]_0 = 0.1$ M; $[LA]_0 = 0.01$ M; $K_1$, $K_3 = 0.1-1000$; $K_2 = 0.25$; (c) $[SM]_0$, $[LA]_0 = 0.1$ M; $K_1$, $K_3 = 0.1-1000$; $K_2 = 4$; (d) $[SM]_0 = 0.1$ M; $[LA]_0 = 0.001$ M; $K_1$, $K_3 = 0.1-1000$; $K_2 = 4$.

will not be observable experimentally. However, in a practical sense, the use of catalytic quantities of LA may be preferred due to cost, easier workup, and reduced side reactions. Hence, we encourage chemists to consider the Lewis basicity of the functional groups in their systems as they decide how much LA to employ.

These 3-D figures reproduce the experimental charactersitics of both the type A reactions (*i.e.*, increasing P with reduced catalyst) when SM is more basic than P and type B reactions (*i.e.*, increasing P with stoichiometric catalyst) when P is more basic than SM. It is important to note that this occurs *regardless of whether of $K_2$ is favorable or not*. This accord with the experimental evidence implies that the LA-promoted IMDAF reaction is well described by the general Scheme 3. The figures also serve to demonstrate how the outcome of a reaction can be dramatically effected by the relative concentration of SM and LA. Since the surfaces are derived for a general scheme, the results should be applicable to other organic reactions that follow the same scenario.

## Conclusions

The reasonable qualitative agreement observed between the experimentally observed yields and the AM1 calculated $\Delta H_R$ for the *catalytic quantities* of LA-promoted IMDAF reactions indicates that AM1 provides a reasonable tool for assessing the feasibility of executing a desired IMDAF reaction prior to synthesis. This is a valuable method due to the potential synthetic utility of the IMDAF reaction which we have shown can occur readily in the presence of catalytic quantities of LA. We are currently using such methods to aid in the development of an asymmetric IMDAF reaction.

The mathematical formulation and simulation (as depicted by Figure 3a−d) of the simplified general reaction scheme for the LA-promoted IMDA (Scheme 3) reproduces in a quantitative manner the experimentally observed dependence of total isolated P yields on the relative LA concentration. This result demonstrates the validity of the general Scheme 3 and provides further support for the hypothesis for the LA promotion of IMDAF reactions and, indeed, for other organic reactions with similar reaction profiles. The 3-D figures also demonstrate the potential utility of programs like Mathematica for evaluating mechanistic schemes. We hope in the future to use the model scheme to aid in the evaluation of $K_1$, $K_2$, and $K_3$ from experimental data.

The results from these studies provide further support for the hypothesis made previously to explain our experimental observations that catalytic quantities of MAC gives higher yields of P than with 1.1 equiv of MAC for the reactions in Scheme 1. With these results and the previously reported results of NMR complexation studies,[1] we feel that our hypothesis has been verified.