3130 *J. Org. Chem.* **1993**, *58*, 3130–3133

A Chemical, Spectroscopic, and Theoretical Assessment of the Lewis Acidity of $LiClO_4$ in Diethyl Ether

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Received January 25, 1993

Moderate diastereoselectivity is observed in the reaction of cyclopentadiene with dimethyl maleate and optically active dimenthyl fumarate in $LiClO_4$/diethyl ether. Moderate regioselectivity is also seen in the reaction of isoprene and methyl acrylate in the same medium. NMR experiments and MNDO calculations, in conjunction with published work on Li^+ in the gas phase, demonstrate that the strong, intrinsic Lewis acidity of Li^+ is moderated in ether by complexation to the solvent and the counterion.

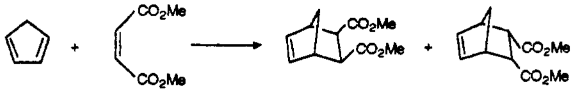
Introduction

$LiClO_4$ in diethyl ether (LP/DE) is an excellent medium to perform Diels-Alder reactions which are sluggish in other solvents.[1] Because many of these sluggish reactions are accelerated under high pressure, the effect of LP/DE on the Diels–Alder reaction was attributed by Grieco and co-workers to the large "internal" pressure of the solvent.[2] This correlation is in line with similar effects observed in water,[3] a solvent with a very large cohesive pressure.[4] Braun and Sauer also attributed the effect that LP/DE had on the stereoselectivity of the Diels–Alder reaction of cyclopentadiene (CP) and methyl acrylate (MA) to a polar solvent effect.[5] Forman and Dailey[6] and, more recently, Righetti and co-workers[7] have shown, however, that these results are not due to a solvent effect but to catalysis by the lithium ion.

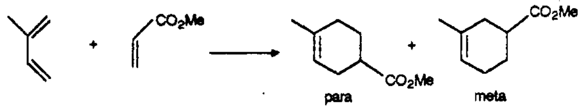
Because LP/DE is an important catalyst in the Diels–Alder and other reactions,[1,8] it is important to assess the Lewis acidity of the medium. This presents a problem because there are a variety of ways in which this can be done. Lewis acidity may be defined thermodynamically by the ability of an acid to complex reversibly to a model compound. In principle, one can define a Lewis acidity scale in a manner similar to the more familiar pH and H_0 scales which are, of course, appropriate for Brønsted acids, but this approach has proven to be elusive.[9] A Lewis acidity scale could also be defined by the ability of an acid to catalyze a reaction and alter its regiochemistry and stereochemistry, and it is in the latter sense of the term that we will describe the acidity of LP in DE. By comparing the behavior of LP/DE in several ways to more familiar Lewis acids such as $AlCl_3$ and BF_3, one can arrive at a consistent picture of the acidity of the ionic medium. The lithium cation is in fact a superior Lewis acid—in the gas phase—but its acidity is moderated in DE by the presence of the perchlorate counterion and complexation to DE.

Results and Discussion

Although one usually associates Lewis acid catalyzed Diels–Alder reactions with a kinetic effect, regio- and diastereoselectivity are also enhanced.[10] This is certainly the case for LP/DE, as first noted by Braun and Sauer for the reaction of CP with MA[5] and later by Grieco and co-workers for the reaction of CP with ethyl acrylate.[2] The endo/exo selectivities for these reactions [7.3:1 (38.1 wt % LP) and 8:1 (5.0 M LP), respectively] are modest compared to the selectivity observed for the $AlCl_3$-catalyzed reaction of CP with MA (99:1), for example.[16] Similarly, we have found the endo to exo product ratio in the reaction of CP with dimethyl maleate (DMM) (eq 1) at ambient temperature to change from an initial value of 3:1 in DE to a limiting value of 8:1 in the presence of 6 M LP in DE. Contrast this to a value of 20:1 obtained for the same



(1)



(2)

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(10) The endo selectivity in the Diels–Alder reaction is often attributed to a favorable secondary orbital interaction of the LUMO of the dienophile with the HOMO of the diene in the endo transition state. The enhanced endo selectivity in the Lewis acid catalyzed reaction may be due to an even more favorable secondary orbital interaction.[11] This is consistent with the fact that when acrolein forms complexes with H^+ [11] and with Na^+ and Li^+ [12] the coefficient at the carbonyl carbon in the LUMO increases in magnitude. Other effects have been proposed to explain the enhanced selectivity.[13] It is a reasonable, but as yet largely untested, hypothesis that the endo selectivity will correlate with the Lewis acidity[14,15] of the catalyst. This is borne out in at least one case.[16] Similar arguments can be made for the enhanced regioselectivity of Lewis acid catalyzed Diels–Alder reactions.[11,17]

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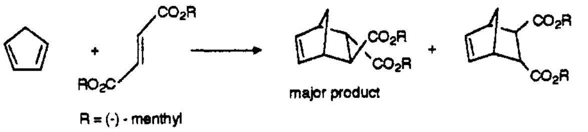
Table I. Percent Diastereomeric Excess (% DX) for the Reaction of CP with (−)-Dimenthyl Fumarate

reactn condns	% DX[a]	reactn condns	% DX[a]
neat	−3.8	10 mmol $AlCl_3$/DE[b]	38.3
1.0 M LP/DE	14.7	unactivated Al_2O_3[b]	13.8
3.0 M LP/DE	20.6	activated (200 °C) Al_2O_3[b]	16.8
5.0 M LP/DE	16.8	Et_2AlCl in toluene (−20 °C)[c]	91

[a] Major diastereomer indicated in eq 3, except for reaction run in the absence of solvent which produced a slight excess of the other diastereomer. [b] Reference 21. [c] Reference 22.

reaction in the presence of $AlCl_3$.[18] Furthermore, we have detected a modest increase in regioselectivity for the reaction of isoprene and MA in LP/DE, going from a "para" to "meta" ratio of 2.5:1 for the reaction run in the absence of solvent to a value of 3.4:1 obtained for the reaction in 6 M LP in DE. By contrast, the $AlCl_3$-catalyzed reaction gives a selectivity of 19:1.[19]

Diastereoselectivity is also enhanced in LP/DE when an optically activity dienophile is used. When CP was treated with (−)-dimenthyl fumarate (DMnF) in LP/DE at ambient temperature, two optically active diastereomers were produced (eq 3). As expected, the percent diastereomeric excess (% DX) increased as the concentration of LP increased (Table I), but the effect was moderate.[20] By comparison with the modest % DXs in LP/DE, the % DXs obtained when the strong Lewis acids, $AlCl_3$ and $(CH_3CH_2)_2AlCl$,[14,15] were used as catalyst are much larger. Even when the reaction was run on unactivated alumina,[21] a medium not ordinarily thought of as having any Lewis acidity, the % DX is comparable to the best values in LP/DE. These data also suggest that the lithium ion in LP/DE is a modest Lewis acid.



(3)

When a Lewis acid complexes to the electron-withdrawing group of the dienophile, it removes electron density from the carbon–carbon double bond and lowers the energy of the lowest unoccupied molecular orbital (LUMO) of the resulting complex, whose interaction with the highest occupied molecular orbital (HOMO) of the diene, which is the most significant MO interaction, becomes more favorable. This has the net effect of lowering the energy of the transition state of the bimolecular reaction. Because induced changes in chemical shift reflect changes in electron density about the carbon–carbon bond of the dienophile–Lewis acid complex and changes in the LUMO of the same complex are available from MO theory, one can develop empirical Lewis acidity scales based on NMR spectroscopy and MO calculations.

Childs and co-workers examined the effect that Lewis acids have on the ^1H and ^{13}C chemical shifts of α,β-unsaturated aldehydes and ketones such as crotonaldehyde (CA) in methylene chloride at −20 °C.[14] From the magnitude of the induced shifts an empirical Lewis acidity scale was developed. Laszlo and Teston, on the other hand, developed a scale based on MNDO calculations of 1:1 complexes derived from CA and the Lewis acid.[15] Their calculated LUMO (π^*) energies are a measure of Lewis acidity and correlate nicely with the previously mentioned NMR results and the rates of Lewis acid-catalyzed ene reactions.[23] On both the NMR and MO scales BBr_3 is a strong Lewis acid, $AlCl_3$ a more moderate one, and $(CH_3CH_2)_3Al$ a weak acid.

Table II. Induced Chemical Shifts of Crotonaldehyde (H_3) and Diethyl Ether in Solutions of CA in LP/DE at −20 °C

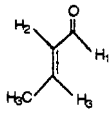
			induced shifts			
	initial concn		CA		diethyl ether	
entry	$[LP]_0$	$[CA]_0$	$\Delta\delta_{exp}$[a]	$\Delta\delta_{the}$[b]	$\Delta\delta(CH_2)$[c]	$\Delta\delta(CH_3)$[c]
1	0.30	0.24	0.25	0.27	0.01	0.03
2	0.45	0.36	0.33	0.32		
3	0.60	0.48	0.38[d]	0.36	0.05	0.03
4	1.0	0.80	0.44[d]	0.44	0.07	0.04
5	2.0	1.6	0.54	0.53	0.12	0.07
6	5.0	4.0	0.61	0.62	0.28	0.13

[a] Relative to $CA(H_3)$ in DE at −20 °C. [b] Values obtained assuming $K_{eq} = 3.20$ and $\Delta\delta_\infty = 0.764$. [c] Chemical shifts relative to those for DE at −20 °C. [d] See ref 24.

Table III. Induced Chemical Shifts of $CA(H_3)$ in CH_2Cl_2 and DE Solutions Containing Lewis Acids[a]

	Lewis acid (concn)			
solvent	BBr_3	BF_3	LP	$AlCl_3$
CH_2Cl_2[b]	1.49	1.17		1.23
DE	0.94 (1 M) 1.02 (2 M)	0.26 (2 M) 0.91 (neat)[c]	0.53 (1 M) 0.76 (limiting)	1.61 (1 M)[d]

[a] 25% excess Lewis acid relative to CA unless stated otherwise. [b] Data from ref 14. [c] $BF_3 \cdot Et_2O$ plus CA in a 4:3 ratio. [d] See text for explanation.



CA

The Lewis acidity of LP was determined using the methodology of Childs by measuring the induced downfield shift of H-3 of CA in DE at −20 °C. CH_2Cl_2 could not be used because LP is insoluble in this solvent. Besides, it is the acidity of LP/DE which is at issue here. Unlike the examples cited by Childs where complexation between the Lewis acids and CA is essentially irreversible (large equilibrium constants), LP reversibly complexes not only to CA but also to DE, which also shows induced downfield shifts (Table II). To obtain the induced shift of the CA–LP complex, it was thus necessary to extrapolate the data to infinite LP concentration. To accomplish this goal, the data were fit to a model in which it was assumed that LP reversibly forms a 1:1 complex with CA and the observed chemical shift is a weighted average of the shifts due to uncomplexed and complexed CA (see Appendix). Two parameters of the model, K_{eq}, the equilibrium for formation of the complex, and $\Delta\delta_\infty$, the induced chemical shift of the LP–CA complex, were adjusted to fit the

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(24) When the data were originally obtained, the $\Delta\delta_{exp}$ values for entries 3 and 4 were 0.51 and 0.53, respectively. These values could not be made to fit to any scheme including the one with $K_{eq} = 3.20$ and $\Delta\delta_\infty = 0.764$. Repeating the experiment for entries 3 and 4 gave the values reported in Table II, which clearly fit the theoretical model very well. We can offer no explanation for the discrepancy in our original data.

experimental data. When $K_{eq} = 3.20$ and $\Delta\delta_\infty = 0.76$ are used, a good fit is obtained (Table II). Because the measured induced shifts are accurate to ±0.02, the true $\Delta\delta_\infty$ value likely is 0.76 ± 0.02.

According to Childs the magnitude of the induced shift is a direct reflection of Lewis acidity. As can be seen in Table III, the induced shifts for BBr_3, BF_3, and $AlCl_3$ in CH_2Cl_2 are considerably larger than that due to LP in DE and are thus more acidic. $SnCl_4$ and $(CH_3CH_2)_3Al$, with induced shifts of 0.87 and 0.63, respectively, have comparable Lewis acidities to LP, if one neglects the influence of solvent. To make the comparisons fairer, however, experiments with the three Lewis acids shown in Table III were repeated with CA in DE at −20 °C. Both BBr_3 and BF_3 reversibly complex to CA and DE. Although limiting induced shifts for H_3 in CA were not obtained in these cases, induced shifts were obtained for two concentrations of BBr_3 and BF_3. It is clear from the data (Table III) that the induced shifts with 2 M BBr_3 and neat $BF_3{\cdot}Et_2O$ (approximately 8 M BF_3), 1.02 and 0.91, respectively, are larger than the limiting shift for LP. The limiting shifts for BBr_3 and BF_3 are undoubtedly larger than these values. BBr_3 and BF_3 in DE are thus more acidic than LP in the same solvent.

$AlCl_3$ (1 M) in DE at −20 °C yielded a two-phase system in which CA only resided in the lower phase. The proton resonances in the lower phase were considerably broadened compared to the other cases examined. The induced shift for H_3 of CA, 1.61, did not change when the excess $AlCl_3$—relative to CA—was increased from 25% to 75%. The induced shifts for the CH_2 and CH_3 groups of DE at 0.48 and 0.36, respectively, also did not change.[25] The lower phase apparently is already saturated in $AlCl_3$ when 25% excess Lewis acid was used. The induced shifts for the CH_2 and CH_3 groups of DE in the upper phase did change, however, going from values of 0.08 and 0.10 with 25% excess $AlCl_3$ to 0.19 and 0.15 with 75% excess $AlCl_3$.[26] The extra $AlCl_3$ in the experiment with 75% excess $AlCl_3$ clearly went into the top layer. Whatever the explanation for this intriguing behavior[27] the induced shift for H_3 of CA with $AlCl_3$ is significantly larger than that for LP. $AlCl_3$ is also more acidic in ether than lithium perchlorate.

The NMR results clearly show that LP/DE is a weaker Lewis acid than BBr_3, BF_3 and $AlCl_3$ in the same medium. This conclusion is in contradistinction to that predicted from MO calculations on the CA–Li^+ complex. Laszlo and Teston have developed a Lewis acidity scale based on the LUMO energies of a series of CA–Lewis acid complexes as determined by MNDO calculations.[15] Their scale is based on the reasonable premise that the lower the LUMO energy of the complex is the more acidic is the Lewis acid component of that complex. This suggestion has now been successfully subjected to an experimental test.[23] The theoretical Lewis acid scale is similar in fact to the Childs scale and provides a theoretical justification to that scale.

We have performed a MNDO calculation on the CA–Li^+ complex in a manner identical to that used by Laszlo and Teston (CA, cisoid, planar; Li^+, in plane, anti to the C_1–C_2 bond of CA).[28] The calculated LUMO energy of −4.57 eV is far more negative than that for BCl_3 (−2.52 eV), the most acidic Lewis acid on the Laszlo–Teston scale, suggesting that the Li^+ is a very powerful Lewis acid. The calculated enthalpy of interaction (ΔH_{int}) of −47.92 kcal/mol for the CA + Li^+ → complex reaction is also far more exothermic than for the corresponding reaction of any Lewis acid on the Laszlo–Teston scale. The calculated ΔH_{int}, however, is in line with Li^+ affinities in the gas phase obtained by Beauchamp and his group,[29] which the calculation is in fact mimicking. The NMR results and MO calculation differ so radically because the NMR experiments were performed in solution and the calculation reflects behavior in the gas phase.

There are three reasons why the solution- and gas-phase results differ so markedly. First, the Li^+ in solution is complexed to the ether oxygen of DE. Transfer of Li^+ from this complex to CA will be far less exothermic than that derived from the MNDO calculations. Enthalpies derived from gas-phase reactions bear this out (eqs 4 and 5).[29] Secondly, solvation of the CA–Li^+ complex will raise the energy of the LUMO, thus reducing the apparent Lewis acidity of LP in DE. Ab initio calculations on a series of Li^+–acrolein complexes in which the number of solvating water molecules around the complex was varied bear this out convincingly.[12] Third, the MO calculations ignore the perchlorate anion. Because of cation–anion interactions via electrostatic attraction, ion pairing, etc., the electrophilicity of the Li^+ will be further reduced. That the anion can influence the Lewis acidity of Li^+ has been documented in the work of Pushin et al. who showed that catalytic activity of a series of lithium salts decreased in the order: $ClO_4^- > Br^- > Cl^-$.[30]

	ΔH_{int} (kcal/mol)	
$Li + CH_2O \rightarrow CH_2OLi^+$	-36	(4)
$Me_2O{\cdot}Li^+ + CH_2O \rightarrow CH_2OLi^+ + Me_2O$	+3.5	(5)

Conclusion

MO calculations and gas-phase experiments show that Li^+ is an intrinsically strong Lewis acid. This Lewis acidity is considerably moderated in DE by solvation effects and interaction with the perchlorate anion.

Experimental Section

NMR Experiments. To a flame-dried, 50-mL round-bottomed flask (with septum) under Ar at −78 °C was added first the Lewis acid, then by injection the ether, and last the crotonaldehyde also by injection. After being stirred for 15 min the mixture was transferred under Ar to an NMR tube and the spectrum recorded at −20 °C.

Diels–Alder Reactions. The Diels–Alder reactions were run in LP/DE at ambient temperature. Product ratios were determined by gas chromatography except for those deriving from dimenthyl fumarate which were analyzed by a literature procedure.[21]

Appendix

Mathematical Model for the Reaction of Crotonaldehyde with Lithium Perchlorate in Diethyl Ether. Assume that CA and LP react according to

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[25] A meaningful integration of the resonances in the lower phase has been impossible to obtain because the peaks are broad.

[26] It is stiking how much larger the induced shifts of DE in the lower layer are compared to those for the top layer.

[27] One explanation for the observations is that the lower layer consists of an ether insoluble complex of CA, DE, and $AlCl_3$.

[28] The geometry of the cisoid form of CA was first deduced by a molecular mechanics calculation, and this was used as input for the MNDO calculation.

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$$CA + LP \rightleftarrows CA\text{–}LP \qquad (6)$$

where CA–LP is the complex formed between the two species. The equilibrium constant for this system is given by

$$K_{eq} = \frac{[CA\text{–}LP]}{[CA][LP]} \qquad (7)$$

Because $[LP]_o = [LP] + [CA\text{–}LP]$ and $[CA]_o = [CA] + [CA\text{–}LP]$, where $[LP]_o$ and $[CA]_o$ are the initial concentrations of the substrates, one can express K_{eq} in terms of one variable ([CA]) only:

$$K_{eq} = \frac{([CA]_o - [CA])}{[CA]([LP]_o - [CA]_o + [CA])} \qquad (8)$$

This equation can be solved for [CA] by use of the quadratic formula. Only the positive root has any physical significance. The observed chemical shift for H_3 (δ) is described as a weighted average of the shifts of CA (δ_A) and CA–LP ($\delta_{CP\text{-}LA}$):

$$\delta = \frac{[CA]}{[CA] + [CA\text{–}LP]}\delta_A + \frac{[CA\text{–}LP]}{[CA] + [CA\text{–}LP]}\delta_{CA\text{–}LP} \qquad (9)$$

The induced shift, $\Delta\delta$, is then given by

$$\Delta\delta = \delta - \delta_A = -\frac{[CA\text{–}LP]}{[CA] + [CA\text{–}LP]}\delta_A + \frac{[CA\text{–}LP]}{[CA] + [CA\text{–}LP]}\delta_{CA\text{–}LP} \qquad (10)$$

Rearranging eq 10 and using the equality $[CA]_o = [CA] + [CA\text{–}LP]$ affords

$$\Delta\delta = \frac{[CA]_o - [CA]}{[CA]_o}\Delta\delta_\infty \qquad (11)$$

where $\Delta\delta_\infty = \delta_{CA\text{-}LP} - \delta_A$ is the induced shift of the complex. One can combine the solution for [CA] from eq 8 with equation 11 and obtain, after considerable manipulation,

$$([CA]_o\Delta\delta - [LP]_o\Delta\delta_\infty)(\Delta\delta - \Delta\delta_\infty)K_{eq} = \Delta\delta\Delta\delta_\infty \qquad (12)$$

Acknowledgment. The authors thank the Research Corporation, Department of Energy, and National Science Foundation for support of this work.