

## Lithium Perchlorate Catalysis of the Hetero Diels-Alder Reaction: a Specific Lithium Cation Effect.

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(Received in UK 15 July 1991)

*Key words:* lithium perchlorate - solvents - catalysis - Diels-Alder reaction.

**Abstract** - The lithium perchlorate catalysis of the hetero Diels-Alder reaction between 1-phenyl-4-benzylidene-5-pyrazolone and ethyl vinyl ether was kinetically investigated in five solvents.

The rate increases as the salt concentration increases and a linear relationship between the relative rate and the molar fraction of the salt can be obtained.

All correlations converge on a single value and this strongly supports the presence of a catalysis promoted by the lithium cation acting as a Lewis acid. The nature of the interaction between the catalyst and the solvent was also investigated.

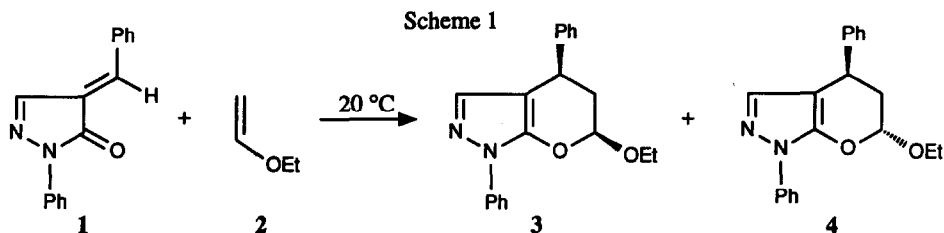
Breslow and Guo<sup>(1)</sup> reported the effect of several salts [among them lithium perchlorate (LP)] in water and "water-like" solvents on the rate of the Diels-Alder (D.A.) reaction.

The rate acceleration dramatically increases when the reaction is performed in 5 M LP-diethyl ether. Grieco and co-workers<sup>(2)</sup> suggested that the source of the effect, usefully applied to the synthesis of cantharidin, may be due to the inherent cohesive pressure of the medium.

A careful choice of the solvent seems crucial since no effect was observed in the intramolecular D.A.<sup>(3)</sup> reaction of 1,8,10-undecatrien-3-one when the reaction is carried out in benzene, in the presence of 1.1 equivalents of LP added as 1 M solution in acetonitrile.

A recent kinetic investigation of the D.A. reaction between acrylonitrile and 9,10-dimethylanthracene in the presence of various concentrations of LP in diethylether, was interpreted by Forman and Daile,<sup>(4)</sup> as clear evidence that the rate acceleration is due to Lewis acid catalysis with the lithium cation behaving as the acid.

Our interest in the solvent effect<sup>(5-10)</sup> and the acid catalysis<sup>(8,11)</sup> of the D.A. and hetero D.A. (H.D.A.) reactions had already led us to study the effect of LP, in differing solvents, on the H.D.A. reaction between 1-phenyl-4-benzylidene-5-pyrazolone (**1**) and ethyl vinyl ether (**2**) (Scheme 1), and we wish to report our own results on this topic.



#### The LP effect on the H.D.A. reaction.

The kinetic runs were studied by u.v.-vis. spectroscopic analysis of the disappearing pyrazolone **1** at 20 °C. The second order rate constants were then calculated from the pseudo-first order values determined in the presence of 100-300 fold excess of **2** (see experimental section for details).

The first solvent tested was diethyl ether (*dee*) and the rate significantly increases with the increase of the LP added to the solution. The rate constants reported in table 1 are the average of at least three kinetic runs.

The effect was significant since a 2.16 M LP solution gives a rate that is 300 times faster than the rate in the pure solvent ( $k_{dee}$ ). Following a procedure already adopted to determine the proton catalytic effect on H.D.A.,<sup>(8)</sup>  $\log(k_{catal}/k_{dee})$  was plotted against  $(-\log \chi)$ , where  $\chi$  represents the molar fraction of the salt, and the graph reported in figure 1 was obtained. This is a curve at very low salt concentrations, but becomes a linear relationship for medium to high concentrations of LP. By extrapolating the linear sector of values, the relative rate for  $(-\log \chi)=0$  was found to be  $870 \pm 80$ .

With this result in hand, the catalytic effect of LP solutions in the differing range of the salt solubility, was tested in acetonitrile (*an*), acetone (*ac*), methanol (*m*), and i.propanol (*i*).

Differing concentrations of salt are required in each solvent to develop the catalytic effect, and, when the rate constants reported in table 2 were treated as previously described, the graphs reported in figure 2 were obtained. Not only at high concentrations of salt four linear relationships were obtained, but the extrapolated values for  $(-\log \chi)=0$  all converged on the same  $k_{rel}$  value:  $850 \pm 80$ .<sup>(12)</sup>

Table 1. Rate constants for the H.D.A. reaction of 1 and 2 at 20 °C in LiClO<sub>4</sub>/*dee* solutions.

No.	M(LiClO <sub>4</sub> )	$\chi$	$10^4 \times k$ (l mol <sup>-1</sup> sec <sup>-1</sup> )
1	0	0	0.35 ± 0.1 <sup>a</sup>
2	3.43 10 <sup>-5</sup>	3.61 10 <sup>-6</sup>	0.45 ± 0.05
3	1.51 10 <sup>-5</sup>	1.59 10 <sup>-6</sup>	0.76 ± 0.04
4	9.96 10 <sup>-4</sup>	1.04 10 <sup>-4</sup>	1.85 ± 0.05
5	0.0028	2.90 10 <sup>-4</sup>	3.55 ± 0.05
6	0.0033	3.46 10 <sup>-4</sup>	4.43 ± 0.07
7	0.0055	5.75 10 <sup>-4</sup>	3.85 ± 0.15
8	0.010	1.04 10 <sup>-3</sup>	8.9 ± 0.15
9	0.011	1.07 10 <sup>-3</sup>	6.2 ± 0.6
10	0.027	2.80 10 <sup>-3</sup>	19.5 ± 0.4
11	0.055	5.78 10 <sup>-3</sup>	24.6 ± 0.5
12	0.10	0.0110	28.5 ± 0.4
13	0.25	0.0256	48.5 ± 0.8
14	0.50	0.0500	61.5 ± 0.3
15	0.75	0.0733	68.5 ± 0.5
16	1.00	0.0966	79.0 ± 0.8
17	1.33	0.1254	87 ± 1
18	2.16	0.1920	108 ± 1
1			2.94 ± 0.04 <sup>b</sup>

<sup>a</sup>) $k_{dee}$ ; <sup>b</sup>) $\log k_{rel}$  is the intercept of the linear relation reported in fig. 1 between the log of the data 4-18:  $\rho = -0.54$ ;  $r = 0.996$ .

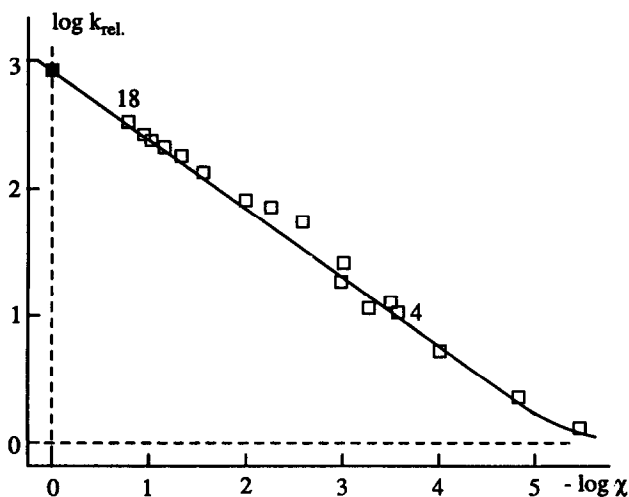


Figure 1. Plot of  $\log(k_{catal}/k_{dee})$  vs  $(-\log \chi)$  for the H.D.A. reaction of 1 and 2 at 20 °C in LP-*dee* solutions (Table 1)

Table 2. Rate constants for the H.D.A. reaction of 1 and 2 at 20 °C in LP-*an* (1a solutions), LP-*ac* (1b solutions), LP-*m* (1c solutions), and LP-*i* (1d solution).

1a solutions	$\chi$	$10^4 \times k$	1b solutions	$\chi$	$10^4 \times k$
1	0	0.71 ± 0.02	1	0	0.59 ± 0.02
2	1.97 × 10 <sup>-4</sup>	0.91 ± 0.02	2	1.13 × 10 <sup>-3</sup>	0.73 ± 0.03
3	1.63 × 10 <sup>-3</sup>	1.80 ± 0.04	3	6.39 × 10 <sup>-3</sup>	1.43 ± 0.02
4	3.45 × 10 <sup>-3</sup>	2.58 ± 0.04	4	0.0112	2.12 ± 0.02
5	4.64 × 10 <sup>-3</sup>	4.0 ± 0.1	5	0.0280	5.60 ± 0.05
6	8.71 × 10 <sup>-3</sup>	6.96 ± 0.05	6	0.0337	6.10 ± 0.05
7	0.0162	10.9 ± 0.1	7	0.0503	9.6 ± 0.3
8	0.0290	17.5 ± 0.1	8	0.0667	12.2 ± 0.2
9	0.0414	31.1 ± 0.4	9	0.104	24.3 ± 0.3
10	0.0530	35.9 ± 0.2	10	0.147	50.3 ± 0.3
	1	2.88 <sup>a</sup> ± 0.04		1	2.93 <sup>b</sup> ± 0.07
1c solutions	$\chi$	$10^4 \times k$	1d solutions	$\chi$	$10^4 \times k$
1	0	8.0 ± 0.2	1	0	7.55 ± 0.05
2	8.10 × 10 <sup>-4</sup>	8.5 ± 0.1	2	7.59 × 10 <sup>-4</sup>	7.6 ± 0.1
3	4.07 × 10 <sup>-3</sup>	8.6 ± 0.1	3	2.04 × 10 <sup>-3</sup>	9.8 ± 0.1
4	0.020	12.6 ± 0.15	4	7.60 × 10 <sup>-3</sup>	10.7 ± 0.2
5	0.043	25.6 ± 0.6	5	0.022	15.7 ± 0.5
6	0.074	36.5 ± 1.5	6	0.048	23.5 ± 0.5
7	0.081	56 ± 1	7	0.073	25.9 ± 0.3
8	0.101	101 ± 3	8	0.089	30.5 ± 0.5
9	0.122	139 ± 2	9	0.097	39.0 ± 0.5
10	0.176	290 ± 15	10	0.104	46.5 ± 0.5
11	0.259	640 ± 20	11	0.118	55.8 ± 0.5
	1	2.98 <sup>c</sup> ± 0.08		1	2.86 <sup>d</sup> ± 0.07

<sup>a</sup>)  $\log k_{\text{rel}}$  is the intercept of the linear correlation between the log of data 4-10;  $\rho$ , -0.93;  $r$ , 0.995.

<sup>b</sup>)  $\log k_{\text{rel}}$  is the intercept of the linear correlation between the log of data 5-10;  $\rho$ , -1.30;  $r$ , 0.984.

<sup>c</sup>)  $\log k_{\text{rel}}$  is the intercept of the linear correlation between the log of data 5-11;  $\rho$ , -1.91;  $r$ , 0.983.

<sup>d</sup>)  $\log k_{\text{rel}}$  is the intercept of the linear correlation between the log of data 8-11;  $\rho$ , -2.43;  $r$ , 0.998.

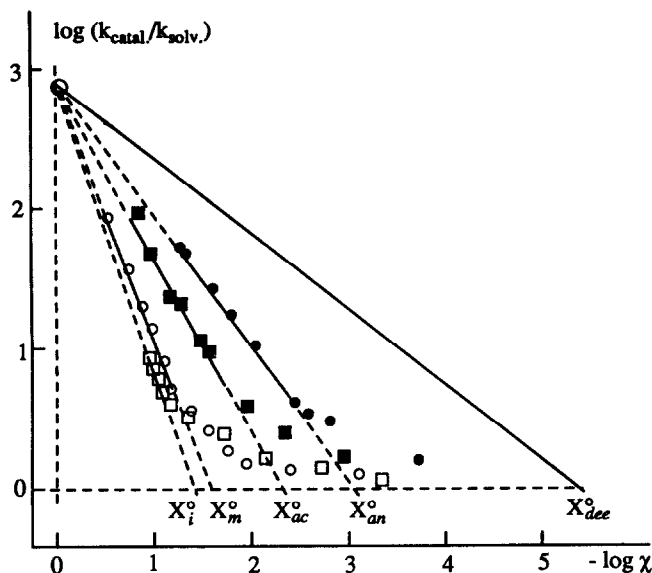


Figure 2. Plot of  $\log(k_{\text{catal}}/k_{\text{pure solvent}})$  vs  $(-\log \chi)$  for the H.D.A. reaction of 1 and 2 at 20 °C in LP-an (●), LP-ac (■), LP-m (○), and LP-i (□) (table 2). The linear relationship for LP-dee solutions reported in fig. 1 is shown schematically.

This result can be rationalized if the differing solutions contain a common catalytic species. Moreover it will be demonstrated that the catalytic species is the lithium cation whose active concentration depends upon the solvating power of each solvent.

Few simple kinetic determinations support this assumption. The rate in acetone and methanol of the H.D.A. reaction between 1 and 2 was determined in the presence of [12]crown-4, a crown ether specific for  $\text{Li}^+$  complexation<sup>(13)</sup> (table 3). The effect is significant if compared to blank experiments, the rate is lowered and this is strong evidence that the catalyst is the lithium cation.

Further important information can be derived from figure 2. If the linear relationships for the five solvents are extrapolated for  $\log(k_{\text{catal}}/k_{\text{solvent}}) = 0$ , five  $X^{\circ}$  data are obtained ( $X^{\circ}_{\text{dee}}=5.44$ ,  $X^{\circ}_{\text{an}}=3.10$ ,  $X^{\circ}_{\text{ac}}=2.25$ ,  $X^{\circ}_{\text{m}}=1.56$ , and  $X^{\circ}_{\text{i}}=1.34$ ) that can be taken as the values of  $(-\log \chi)$  required to develop the catalytic effect. Hence, to understand the type of interaction involved between the solvent and the catalytic species, these  $X^{\circ}$  data are treated using the Kamlet-Taft approach<sup>(14)</sup> which takes into account the different contributions of the solvent: the polarity-polarizability term, basicity and acidity contributions, and the cohesive pressure of the solvent.

Table 3. Rate constants for the H.D.A. reaction of 1 and 2 at 20 °C in the presence of [12] crown-4.

solvent	M (LiClO <sub>4</sub> )	M [12] crown-4	k <sub>rel</sub>
acetone	----	----	1
	----	0.0124	1.1
	0.0118	----	3.8
	0.0118	0.0124	1.3
methanol	----	----	1
	----	0.0674	1.6
	0.0642	----	5.1
	0.0642	0.0674	2.7

If the lithium cation is the catalytic species, the acidity parameters of the solvents are not expected to be involved. Only two terms result significant:  $\pi^*$ , which is the polarity-polarizability term, and  $\beta$ , which is the basicity term of the solvent. The Kamlet-Taft treatment of the  $X^\circ$  data gives equation 1.

$$X^\circ = 10.1 - 7.22 \times \pi^* - 5.85 \times \beta \quad (1)$$

This two-parameters correlation is good ( $r = 0.979$ ) and both parameters contribute about 50% each.

## CONCLUSION.

The LP-catalysis of D.A. and H.D.A. reactions cannot be interpreted as the result of an "internal pressure" effect of the solutions. When the cohesive pressure of the medium is involved in D.A. reactions, the rate acceleration is always very small as shown by the literature data.<sup>(9)</sup>

Furthermore the kinetic data in tables 1 and 2 do not correlate with the  $E_T$  values of LP solutions, values which were taken from the literature<sup>(15,16)</sup> and were confirmed by our own experiments using the Reichardt betaine<sup>(17)</sup> as indicator.

In conclusion the kinetic effect of LP on D.A. and H.D.A., when it occurs,<sup>(4)</sup> can only be due to a specific interaction between one of the cycloaddends and the lithium cation acting as a Lewis acid. In the H.D.A. reaction between 1 and 2 the LP-catalysis is the result of the interaction between the  $\alpha,\beta$ -unsaturated carbonyl system and  $\text{Li}^+$ . This  $\text{Li}^+$  effect on the LUMO energy and coefficients of an  $\alpha,\beta$ -unsaturated carbonyl system was illustrated on acrolein by Lefour and Laupy<sup>(18)</sup> through STO-3G calculations.

Further work is progress to test the effect on the D.A. reaction of lithium salts with differing anions and of salts with differing cations.

## EXPERIMENTAL SECTION.

**Materials** - Ethyl vinyl ether (2) was commercial freshly distilled product. The lithium perchlorate was reagent grade dried under vacuum at 140 °C for 8 hours. The solvents for the kinetic runs were freshly distilled anhydrous reagent grade (u.v. spectroscopic grade when available). 1-Phenyl-4-arylidene-5-pyrazolone (1), *cis*- and *trans*-[2,4]2-ethoxy-4,7-diphenyl-2,3-dihydro pyrano[2,3-*c*] pyrazoles 3 and 4 were prepared in accordance with the literature method.<sup>(19,20)</sup>

**Kinetics** - The overall reaction rates were measured by following the disappearance of 1 on a Perkin Elmer Lambda 5 spectrophotometer provided with a thermostatted-cell transport assembly and an automatic multicell programmer. The solutions were measured in 1.00 cm OS Hellma cuvettes with 3 cm<sup>3</sup> capacity. Measurements were taken at the wavelengths of 410, 420, 425, and 430 nm (the maximum absorptions of the solutions) depending on the salt concentration.

In a 25 cm<sup>3</sup> volumetric flask the solvent-salt solution was prepared by weighing the needed amount of lithium perchlorate. The flask was filled with the required solvent and then again weighed in order to determine the salt concentration. A sample of 1 (2-5 mg) was weighed and dissolved in this solution. Ethyl vinyl ether (*ca.* 0.5-1 cm<sup>3</sup>) was poured into an accurately weighed 10 cm<sup>3</sup> volumetric flask containing *ca.* 5 cm<sup>3</sup> of the required solvent. The flask was again weighed to accurately determine the amount of 2 and then filled with solvent. Three samples of the salt solution of 1 (2.00 cm<sup>3</sup> measured using a pipette) were placed in three cuvettes thermostatted at 20 °C and constant amounts (from 0.25 to 0.75 cm<sup>3</sup>, accurately measured with a microsyringe) of the ethyl vinyl ether solution were added. After vigorous mixing, the kinetic determinations were initiated.

**Determination of the [3]:[4] ratios** - These were performed by h.p.l.c. on a Waters Associated ALC/CPC 244 liquid chromatograph with a Waters mod. 490E detector operating at 254 nm. The chromatographic separations were performed on a stainless column (25 cm length x 4 mm internal diameter) pre-packed with Lichrosorb Si 60 (10 µm) Merck; eluant: cyclohexane-ethyl acetate 90:10; flow: 0.8 cm<sup>3</sup> min<sup>-1</sup>; retention times: 3, 9.2 min; 4, 7.3 min.

Three solutions of known compositions of 3 and 4 were prepared with the ratio [3]/[4] in the range 85/15 - 97/3, each composition being tested on two independent samples at least four times each. The determination of the correction factor by an appropriate programme of the integrator enables the determination of the relative concentration of the two cycloadducts.

Solutions of 1 (0.005 M) and 2 (0.5 M) in each solvent for a selected number of salt concentrations were thermostatted at 20 °C. At different degrees of completion of the reaction, a portion of the reaction mixture was quenched in water and extracted with dichloromethane. After drying and evaporation of the solvent the residue, dissolved in a small amount of eluant, was analyzed. Each solution was tested on two independent samples at least three times each and the data obtained are reported in table 4. These values are constant under kinetic conditions, but for higher salt concentrations and longer reaction times an equilibration of the product distributions toward the thermodynamic *trans* adduct occurs.

Table 4. Product distribution of the H.D.A. adducts 3 and 4 in differing solvent-salt solutions at 20 °C.

M Solvent	[3]:[4] <sup>(a)</sup>					
	0	0.01	0.05	0.1	0.5	1.0
Diethyl ether	88:12	91:9	-----	-----	-----	95:5
Acetone	92:8	93:7	-----	94:6	-----	95:5
Acetonitrile	94:6	-----	-----	-----	92:8	93:7
i.Propanol	96:4	-----	96:4	-----	96:4	-----
Methanol	96:4	-----	-----	96:4	-----	96:4

<sup>a)</sup>The error was in the limit ± 1.0%

## ACKNOWLEDGEMENT

The National Research Council (C.N.R.) and the M.U.R.S.T. offered financial support to this research.

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