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SOLVENT EFFECT AS THE RESULT OF FRONTIER MOLECULAR ORBITAL INTERACTION. IV.[1] A PARALLEL BETWEEN SOLVENT EFFECT AND ACID CATALYSIS IN THE INTRAMOLECULAR HETERO-DIELS-ALDER REACTION [2]

ANDREINA CORSICO CODA, GIOVANNI DESIMONI,* GIUSEPPE FAITA, PIERPAOLO RIGHETTI and GIANFRANCO TACCONI

Dipartimento di Chimica Organica, Università di Pavia,
Viale Taramelli, 10, 27100 Pavia, (Italy)

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Abstract - The solvent effect of the intramolecular hetero-Diels-Alder (I.H.D.A.) reaction of 1-phenyl-4-[2-(3-methyl-2-butenyloxy)benzylidene]-5-pyrazolone (3) was measured in several solvents. The rate increased with increases in the Acceptor Number of the solvent, following a hyperbolic relationship. This was rationalized as being the result of a coordination of the solvent, acting as an electrophile, with the α,ß-unsaturated heterodienic fragmentation, whose LUMO was lowered.

The thermodynamic parameters of the intramolecular reaction were compared to those of a closely similar intermolecular reaction and the differences discussed.

The rate constants of the I.H.D.A reaction of (3) were further determined at 20°C in benzene solutions, in the presence of varying amounts of monochloro-, dichloro-, trichloro-, trifluoroacetic acid and acetic acid. In the high acid concentration region, a linear relationship between rate and the molar fraction of the catalyst was observed and the rates of the reaction in the above acid were extrapolated.

When the kinetic data in differing solvents and acids were plotted vs the Acceptor Number of the reaction medium, all data lay on a single hyperbolic curve. Thus, solvent effect and acid catalysis have the same mechanism: both acids and solvents (with the strength of each represented by its respective Acceptor Number) behave as electrophiles, which coordinate the carbonyl of the pyrazolone, lower energy separation between HOMO dienophile and LUMO heterodiene and increase the rate of the reaction.

The solvent effect of intermolecular Diels-Alder (D.A.)[3,4] and hetero-D.A. (H.D.A.)[1] reactions was investigated in previous papers of this series.

A correlation was found between the kinetic data and the Acceptor Number (AN)[5] of the solvent and this was interpreted in terms of a coordination of the solvent, acting as an electrophile, with the reagents.

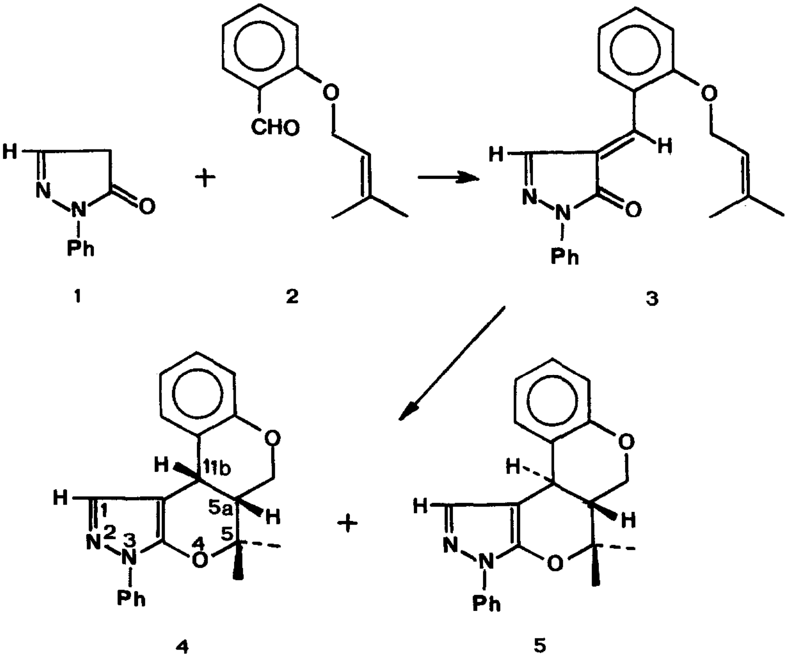
The interaction between the LUMO of the solvent (directly related to AN[6]) with FMOs of dienophiles in D.A. reactions with direct electron demand,[7] gave a stabilization of the LUMO dienophile and a lower energy separation between this and the HOMO diene; consequently, the reaction rate increased with increases in the AN of the solvent.

The interaction between FMOs of solvents and heterodienes in H.D.A. reactions with inverse electron demand,[7] gave a stabilization of the LUMO heterodiene, a lower energy separation between this and HOMO dienophile and the reaction rate again increased with increases in the AN of the solvent. When strongly hydrogen-bonding alcohols coordinated both heterodiene and dienophile (a vinyl ether), the latter interaction had a negative effect on rate and reduced the positive effect of the former.

To test the range of application of this model we considered the solvent effect of intramolecular [4+2] cycloadditions where diene and dienophile belonged to the same molecule.

We turned our attention to the intramolecular H.D.A. (I.H.D.A.) reaction, this involving an α,β-unsaturated carbonyl group that acts as heterodiene, and an alkyl-substituted olefinic double bond that acts as dienophile. This reaction was studied in detail by Tietze and coworkers[8] and was found to be a clean high-yield reaction: exactly what we need for a kinetic investigation.

In general, the conditions required to obtain the precursor of the cycloadducts are sufficient to induce cycloaddition. *E.g.*: 1-phenyl-4-[2-(3-methyl-2-butenyloxy)benzylidene]-5-pyrazolone (3) was obtained *in situ* by Tietze and coworkers[9] by Knowenagel condensation of 1-phenyl-5-pyrazolone



(1) and 2(3-methyl-2-butenyloxy)benzaldehyde (2) in the presence of ethylendiammoniumacetate and, without isolation, it was converted to the I.H.D.A. adducts 4 and 5 by refluxing in several solvents. These conditions do not enable kinetic investigation of the cycloaddition.

To avoid this, 1 was allowed to react <u>at room temperature</u> with 2 in the presence of N,N-dicyclohexylcarbodiimide. After 8 hrs, the orange solution was evaporated to dryness at room temperature and column chromatography allowed us to isolate pure 3.

When 3 was refluxed in benzene for about 15 hrs, the colour of the solution disappeared and a mixture of <u>cis</u> and <u>trans</u> [5a,11b]5,5-dimethyl-3- phenylchroman[4',3':4,5]pyran[3,2-d]pyrazoles (4 and 5 respectively) was obtained in a nearly quantitative yield. These I.H.D.A. adducts were separated by column chromatography and their physical parameters and NMR spectra were identical to those reported by Tietze.[9]

Table 1. Rate constants for the I.H.D.A. reaction of 3 at 50°C in different solvents and AN of the solvent

N	Solvents	AN	$10^5 \times k$ (s^{-1})
1	Cyclohexane	0	1.3 ± 0.1
2	Benzene	8.2	1.7 ± 0.1
3	Ethyl Acetate	9.3	1.5 ± 0.1
4	1,4-Dioxan	10.8	1.80 ± 0.05
5	Nitrobenzene	14.8	1.6 ± 0.1
6	Benzonitrile	15.5	1.70 ± 0.05
7	N,N-Dimethylformamide	16.0	3.1 ± 0.1
8	Acetonitrile	18.9	2.85 ± 0.05
9	Dimethylsulfoxide	19.3	5.2 ± 0.1
10	Nitromethane	20.5	4.0 ± 0.1
11	Chloroform	23.1	1.50 ± 0.04
12	ter. Amyl Alcohol	(27)[a]	2.85 ± 0.03
13	ter. Butanol	27.1	4.00 ± 0.05
14	sec. Butanol	(32.5)[a]	4.60 ± 0.05
15	iso Propanol	33.8	4.7 ± 0.15
16	n. Propanol	37.3	8.2 ± 0.3
17	Ethanol	37.9	7.0 ± 0.1
18	Methanol	41.3	13.4 ± 0.5
19	Benzyl Alcohol	(50)[a]	33 ± 2
20	Acetic acid	52.9	54 ± 3
21	2-Chloroethanol	(61)[a]	(458)[b]

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[a] values derived from the linear relationship between ANs and Taft's σ^* parameters of alkyl group of alcohols ROH (R = Me, Et, n. Prop, n. But, i.Prop., t. But.) (ρ = 47.8; intercept = 42.4; r = 0.99)

[b] value extrapolated from rates determined at 20°, 25° and 30°C (Table 2).

The Solvent Effect

The kinetic runs were studied in differing solvents at 50°C and followed to about 80% completion by UV-Vis spectroscopic analysis of the disappearing chromophore.

The reaction was found to follow a first-order kinetic, and the rate constants (reported in Table 1) were the average of at least four kinetic runs.

The solvent effect was found to be about 50 in the cyclohexane-acetic acid range.

The rate increased with increases in the AN of the solvent and when log k was plotted vs AN, a good hyperbolic relationship was obtained (Fig. 1).

The main difference between the solvent effect of this I.H.D.A. and that found for the intermolecular H.D.A. reaction between 4-arylidene-5-pyrazolones and isobutylvinyl ether,[1] was the regular increase of the rate even in strongly hydrogen-bonding solvents.

To confirm this trend, we determined the rate in 2-chloroethanol, where the reaction was too fast to be measured at 50°C. Thus, the rate was measured at 20°, 25° and 30°C (Table 2) and the Arrhenius plot gave an extrapolated value at 50°C of $458 \times 10^{-5}\ s^{-1}$ (Table 1). The AN of 2-chloroethanol was not available but it was derived (AN = 61) from the linear relationship between the ANs and Taft's σ^* parameters of the alkyl group of R-OH alcohols.[1]

When this new point was placed on the hyperbola in Fig. 1, it fitted nicely on the previous curve.

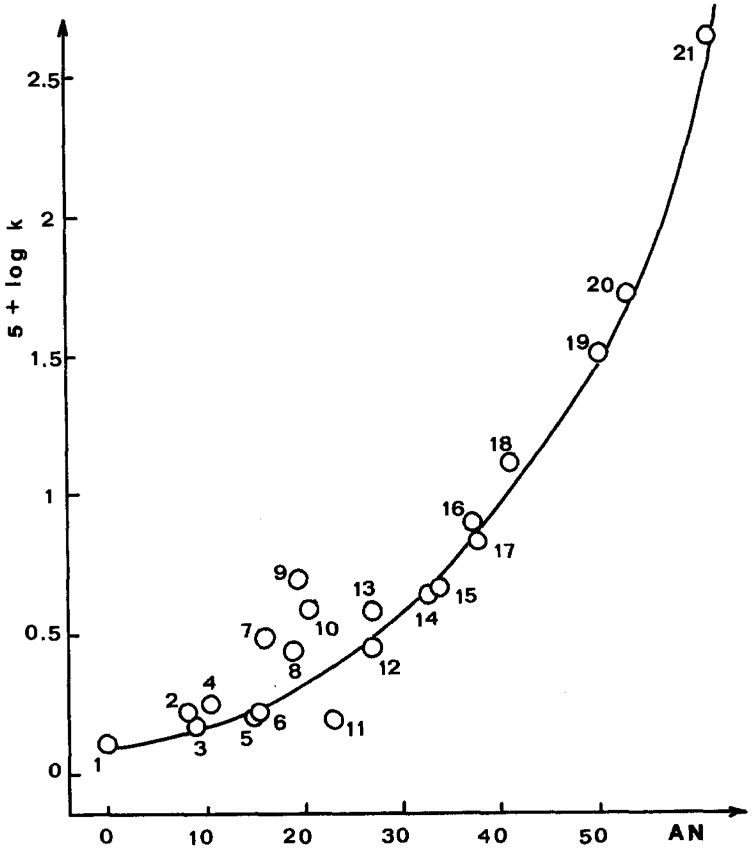

Figure 1. Rate constants of the I.H.D.A. reaction of 3 at 50°C in differing solvents (see Table 1 for numbering) plotted vs the AN of the solvent.

As we have previously seen, the I.H.D.A. reaction of 3 gave two products: 4 and 5. From the (E) configuration of 3 it is evident that 4, the main product, derived from a favoured endo-(E)-syn transition state and 5 from an exo-(E)-anti one.[9]

Tietze[9] determined the [4]/[5] ratio in several solvents and found it to be a function of both solvent and temperature. We tested, by HPLC, the isomer distribution at 50°C in a significant selection of solvents (11 solvents), eventhough the nature of the dienophile fragment cannot allow secondary non-bonding interactions, which are influenced by solvents, as vinylether does.[1] The results are reported (see Experimental) in Table 6 and, from both these and Tietze's results,[9] it can only be deduced that polar solvents (2-chloroethanol excluded) strongly favour the endo transition state.

The most significant result of the kinetic investigation of the solvent effect in I.H.D.A. reaction is the hyperbolic shape of the correlation between the rate and AN of the solvent. Assuming that ΔE is a linear function of log k, a relation[3] between the stabilization energy of the reaction and AN, given by equation (1) (a, b, c and d being constants), explains the observed hyperbolic shape.

$$\Delta E = \frac{a - b\,AN}{c - d\,AN} \qquad (1)$$

This relation is the result of a coordination of the solvent, acting as an electrophile, with the pyrazolone fragment. The olefinic fragment of 3 cannot be coordinated, as vinyl ether can, by strong hydrogen-bonding solvents; hence, scattering of these solvents from the correlation was not observed.

The Activation Parameters

To assume that ΔE is a linear function of log k, presupposes the activation entropy to be a constant within the series of solvents. This was tested in several solvents (Table 2).

Not only was $-\Delta S^{\neq}$ found to be nearly constant with the except of nitrobenzene, but its range (21.5 + 1.2 e.u.) was about half the entropy of the intermolecular H.D.A. reaction of 4-o-methoxybenzyliden-1-phenyl-5-pyrazolone and isobutylvinyl ether (39-40 e.u.).[1]

Whereas a large number of data is known from the literature for the thermodynamic parameters of intermolecular D.A. reaction,[10] those for intramulecular D.A. are rare,[11] and no data are available to compare two closely parallel systems. The present paper enables such a comparison and the results are not limited to the observation, largely expected, that activation entropy is reduced to about one half.

Activation entalpy was found to be larger in I.H.D.A. (18.7, 19.3 and 18.0 kcal/mol in benzene, 1,4-dioxan and methanol respectively - Table 2) than in intermolecular H.D.A. (12.1, 12.5 and 9.9 kcal/mol for the same solvents respectively).[1]

This significant difference (about 7 kcal/mol) is not due to the orbitalic term (ΔE). The heterodiene fragment (pyrazolone) is so similar in both cycloadditions that the energy and coefficients of its LUMO can be considered equal. The HOMO energies of both vinyl ether and the olefinic fragment are very similar if the I.P. of n. butylvinyl ether is 9.10 eV[12] and that of 2-methyl-2-butene is 8.67 eV.[13] Furthermore, the HOMO coefficients cannot induce a large difference in the numerator of the orbitalic term since CNDO/2 calculations gave two large coefficients on the double bond carbon atoms of both 1-methoxyethene (C1 = 0.405, C2 = 0.631)[14] and 2-methyl-2-butene (C2 = 0.529, C3 = 0.591).[15] Hence the orbitalic terms of both inter- and intramolecular H.D.A reactions do not differ significantly.

We believe that the large activation entalpy of I.H.D.A. is due to the strain energy required for its cyclic system to reach the transition state.

Table 2. Rates and activation parameters of I.H.D.A. reaction of **3** in differing solvents

Temp.	$10^5 \times k$ (s^{-1})			
°C	Benzene	1.4-Dioxan	Nitrobenzene	2-Chloroethanol
20	(0.080 ± 0.01)[a]	(0.074 ± 0.005)[a]	(0.114 ± 0.006)[a]	33.3 ± 0.1
25	-	-	-	51.3 ± 0.3
30	-	-	-	85.0 ± 0.3
50	1.7 ± 0.1	1.8 ± 0.1	1.89 ± 0.03	(458 ± 7)[a]
60	4.2 ± 0.2	4.5 ± 0.1	3.96 ± 0.05	-
65	6.1 ± 0.1	-	-	-
70	10.3 ± 0.1	11.1 ± 0.1	9.8 ± 0.1	-
80	-	25.2 ± 0.1	18.3 ± 0.2	-
$\Delta H^{\neq}$ b)	18.7 ± 0.8	19.3 ± 0.5	17.0 ± 0.5	15.9 ± 0.3
$-\Delta S^{\neq}$ c)	22 ± 1.5	20.6 ± 0.5	28 ± 1	20 ± 0.5

Temp.	$10^5 \times k$ (s^{-1})			
°C	ter. Butanol	iso Propanol	Ethanol	Methanol
20	(0.17 ± 0.02)[a]	(0.23 ± 0.02)[a]	(0.32 ± 0.01)[a]	(0.69 ± 0.01)[a]
35			1.55 ± 0.02	3.3 ± 0.1
50		4.59 ± 0.05	7.06 ± 0.05	13.4 ± 0.5
55	5.16 ± 0.05	-	-	-
60	8.1 ± 0.1	11.9 ± 0.1	16.6 ± 0.1	30.9 ± 0.1
65	12.1 ± 0.3	16.7 ± 0.1	-	45.7 ± 0.2
70	18.2 ± 0.3	25.5 ± 0.5	37.1 ± 0.5	-
$\Delta H^{\neq}$ b)	18.0 ± 0.5	18.1 ± 0.4	18.4 ± 0.2	18.0 ± 0.4
$-\Delta S^{\neq}$ c)	23.5 ± 1.5	22.6 ± 1	20.9 ± 0.5	21 ± 1

a) extrapolated rate constants

b) kcal/mol

c) cal K^{-1} mol^{-1}

The Acid Catalysis

The solvent effect was hence rationalized as the result of a coordination of the solvent, behaving as an electrophile, to the heterodiene fragment and the stronger the coordination (represented quantitatively by the AN of the solvent) the faster the reaction resulted.

If we consider that the first step of the D.A. reaction acid catalysis is the coordination of either diene or dienophile with an electrophile,[16] both solvent effect and acid catalysis could be considered as two aspects of the same general phenomenon.

We tried to test this hypotesis on I.H.D.A. of 3.

Preliminary experiments showed that the rate of the reaction of 3 in benzene solution was strongly increased by the presence of acids but that the diastereoisomers ratio (4):(5) did not change significantly (see Experimental).

Thus, we planned a kinetic investigation of this acid-catalyzed reaction at 20°C.

The rate in benzene at 20°C ($k_{benzene}$), which was too slow to be measured, was the extrapolated value obtained from the Arrhenius plot of the rates at 50°, 60°, 65° and 70°C (Table 2) and it was found to be 8.0×10^{-7} sec^{-1}.

The rates in pure acids were too fast to be measured, but it is known that the rate of the D.A. reaction between cyclopentadiene and benzoquinone, catalyzed by trichloroacetic acid in a benzene solution, is a linear function of the stechiometric concentration of the catalyst.[17]

Hence, it could be presumed that the rate of the I.H.D.A. reaction of 3 increases with

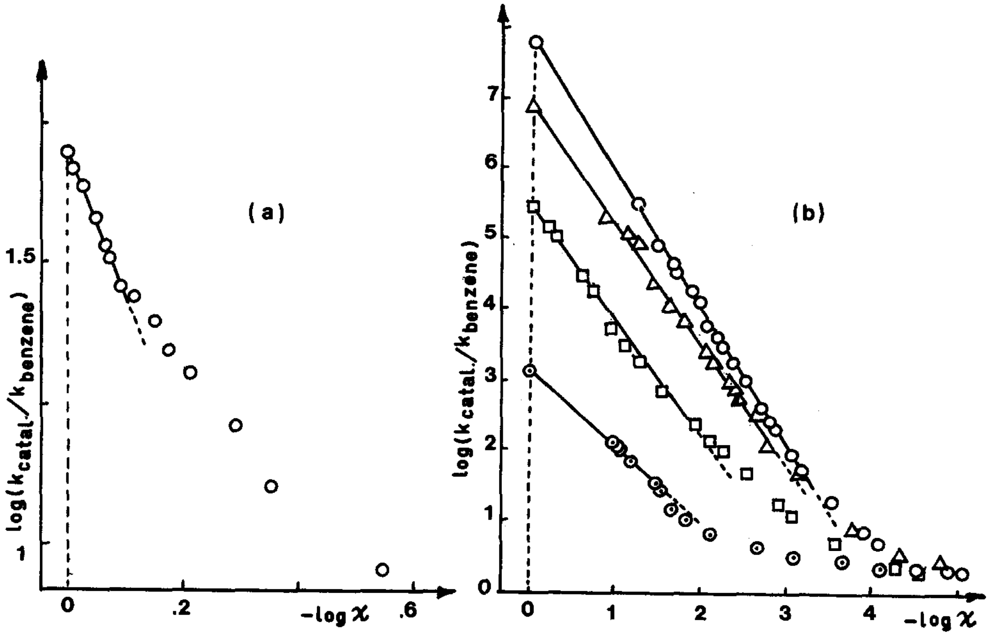

Figure 2. (a) - Plot of log ($k_{catal.}/k_{benzene}$) vs (- log χ) for the I.H.D.A. reaction of 3 at 20°C in benzene - acetic acid solutions (Table 3).

(b) - Plot of log ($k_{catal.}/k_{benzene}$) vs (- log χ) for the I.H.D.A. reaction of 3 at 20°C in benzene - monochloroacetic acid (⊙), - dichloroacetic acid (□), - trichloroacetic acid (△) and - trifluoroacetic acid (○) solutions (Tables 3, 4).

Table 3. Rate constants for the I.H.D.A. reaction of **3** at 20°C in benzene/acetic acid (3a solutions), benzene/monochloroacetic acid (3b solutions), benzene/dichloroacetic acid (3c solutions), and benzene/trichloroacetic acid (3d solution).

3a solutions	χ	$10^6 \times k_{catal.}$	3b solutions	χ	$10^6 \times k_{catal.}$
1	0.189	5.75 ± 0.05	1	7.67×10^{-5}	1.80 ± 0.15
2	0.280	7.10 ± 0.05	2	2.10×10^{-4}	2.20 ± 0.05
3	0.437	10.00 ± 0.05	3	7.67×10^{-4}	2.5 ± 0.1
4	0.555	13.90 ± 0.05	4	2.10×10^{-3}	2.55 ± 0.05
5	0.608	16.15 ± 0.05	5	7.67×10^{-3}	5.35 ± 0.05
6	0.661	17.7 ± 0.1	6	1.49×10^{-2}	8.60 ± 0.05
7	0.700	20.00 ± 0.05	7	2.10×10^{-2}	12.0 ± 0.5
8	0.757	22.25 ± 0.05	8	2.74×10^{-2}	23.0 ± 0.5
9	0.806	23.0 ± 0.1	9	3.20×10^{-2}	27.5 ± 0.5
10	0.839	26.1 ± 0.1	10	6.14×10^{-2}	54 ± 3
11	0.862	27.0 ± 0.1	11	9.24×10^{-2}	80.0 ± 0.5
12	0.886	30.3 ± 0.1	12	9.99×10^{-2}	90.0 ± 0.5
13	0.930	35.2 ± 0.1	13	0.103	91.5 ± 0.5
14	0.975	37.5 ± 0.1	14	0.109	99 ± 1
15	1	40.0[a] ± 0.1	15	0.1106	101 ± 1
	1	40.8[b] ± 0.8		1	1010[c] + 40

3c solutions	χ	$10^6 \times k_{catal.}$	3d solutions	χ	$10^6 \times k_{catal.}$
1	2.62×10^{-5}	1.85 ± 0.01	1	1.64×10^{-5}	2.05 ± 0.05
2	5.00×10^{-5}	1.90 ± 0.01	2	4.49×10^{-5}	2.65 ± 0.05
3	2.62×10^{-4}	3.6 ± 0.2	3	1.64×10^{-4}	6.4 ± 0.1
4	7.17×10^{-4}	8.8 ± 0.1	4	6.88×10^{-4}	40 ± 1
5	1.10×10^{-3}	14.0 ± 0.5	5	1.64×10^{-3}	90 ± 2
6	2.62×10^{-3}	38.0 ± 0.5	6	2.40×10^{-3}	260 ± 20
7	5.00×10^{-3}	78 ± 1	7	3.13×10^{-3}	420 ± 30
8	7.17×10^{-3}	120 ± 1	8	3.82×10^{-3}	580 ± 15
9	1.10×10^{-2}	190 ± 1	9	4.49×10^{-3}	750 ± 30
10	2.62×10^{-2}	560 ± 10	10	6.88×10^{-3}	1390 ± 10
11	5.00×10^{-2}	1260 ± 20	11	8.25×10^{-3}	2000 ± 50
12	7.17×10^{-2}	2400 ± 100	12	1.58×10^{-2}	5400 ± 50
13	0.110	4100 ± 100	13	2.26×10^{-2}	9200 ± 100
14	0.177	13800 ± 200	14	3.47×10^{-2}	17000 ± 500
15	0.212	22400 ± 200	15	5.74×10^{-2}	67500 ± 1000
16	0.520	80000 ± 2000	16	6.88×10^{-2}	94000 ± 1000
17	0.620	105000 ± 2000	17	0.140	164000 ± 2000
	1	220000[d] ± 40000		1	5700000[e] ± 900000

a) experimental rate constant

b) k determined from the linear relation between the log of data 9-14: ρ = -2.59; int. = 1.71; r = 0.994

c) k determined from the linear relation between the log of data 8-15: ρ = -1.05; int. = 3.10; r = 0.999

d) k determined from the linear relation between the log of data 9-17: ρ = -1.64; int. = 5.43; r = 0.994

e) k determined from the linear relation between the log of data 4-17: ρ = -1.66; int. = 6.85; r = 0.997

increases in the amount of catalyst, and that the rate in neat acids may be extrapolated by plotting rate vs the molar fraction of the catalyst.

This approach was tested for acetic acid. The rate constants, at different values ($k_{catal.}$ - at least three runs for these and for all the following values) are reported in Table 3a. and when log ($k_{catal.}/k_{benzene}$) was plotted against (-log χ), the graph reported in Fig. 2a was obtained. This is a curve in low acid concentration region, but becomes a linear relationship in high concentrations of acids. The rate, when extrapolated from this sector of values, (40.8 x 10^{-6}), corresponds fairly well to the experimental value in acetic acid (40.0 x 10^{-6} - Table 3a).

Thus the $k_{catal.}$ values were determined when increasing amount of monochloro-, dichloro-, trichloro- and trifluoroacetic acids were added to the benzene solution of **3** (Tables 3b-d, 4) and when log ($k_{catal.}/k_{benzene}$) was plotted vs (-log χ), the graphs reported in Fig. 2b were obtained.

Table 4. Rate constants for the I.H.D.A. reaction of **3** at 20°C in benzene/trifluoroacetic acid solutions

N	χ	10^6 x $k_{catal.}$
1	8.37 x 10^{-6}	1.6 ± 0.1
2	1.28 x 10^{-5}	1.7 ± 0.1
3	3.05 x 10^{-5}	1.9 ± 0.1
4	8.37 x 10^{-5}	4.1 ± 0.1
5	1.28 x 10^{-4}	5.7 ± 0.05
6	3.05 x 10^{-4}	15.5 ± 0.5
7	5.83 x 10^{-4}	46 ± 1
8	8.37 x 10^{-4}	72.5 ± 0.5
9	1.28 x 10^{-3}	160 ± 5
10	1.56 x 10^{-3}	210 ± 5
11	1.83 x 10^{-3}	305 ± 5
12	3.05 x 10^{-3}	775 ± 5
13	4.18 x 10^{-3}	1.450 ± 50
14	5.34 x 10^{-3}	2.350 ± 50
15	6.41 x 10^{-3}	3.200 + 100
16	8.37 x 10^{-3}	5.950 ± 50
17	1.07 x 10^{-2}	9.650 ± 50
18	1.28 x 10^{-2}	13.500 ± 500
19	1.92 x 10^{-2}	28.000 ± 1.000
20	2.19 x 10^{-2}	35.500 ± 500
21	3.32 x 10^{-2}	59.500 ± 500
22	5.42 x 10^{-2}	245.000 ± 5.000
	1	47.000.000[a] ± 7.000.000

a) rate constant determined from the linear relationship between the logarithms of data 8-22 : slope = -1.89; intercept = 7.77; r = 0.999

At values of about 10^{-2} for monochloro- and dichloroacetic acids, and about 8×10^{-4} for trichloro- and trifluoroacetic acids, all graphs became linear.

Monochloroacetic acid exhibits low solubility in benzene, which prevented the measurement of $k_{catal.}$ values at $\chi > 0.11$. On the contrary, the high solubility of dichloroacetic acid allowed us to measure $k_{catal.}$ values at up to $\chi = 0.62$.

The extrapolation of $k_{catal.}$ at $\chi = 1$ gave the rate constants of the I.H.D.A. reaction of 3 in the above neat acids (Tables 3b-d, 4).

Since the aim of this paper was to consider, in a unified approach, both solvents and acids as electrophiles that catalyze the D.A. reaction, the rate constans of the I.H.D.A. reaction of 3 in differing solvents at 20°C were determined.

From rate constants previously measured at differing temperatures in 1,4-dioxan, nitrobenzene, ter. butanol, isopropanol, ethanol and methanol, the rate constants at 20°C were extrapolated (Table 2).

All the rate constants thus determined (in addition those in acetic acid and 2-chloroethanol) are reported in Table 5 as well as the ANs of both solvents and acids. Some ANs are available in the literature,[5] some derived from the assumed linear relationship between ANs and the ionization constants (pK_a) of acetic acids as measured in nitromethane.[18]

Table 5. Rate constants for the I.H.D.A. reaction of 3 at 20°C in differing solvents and acids and their AN

N	Solvents	AN	$10^6 \times k$ (s^{-1})
1	Benzene	8.2	0.80[a]
2	1,4-Dioxan	10.8	0.74[a]
3	Nitrobenzene	14.8	1.14[a]
4	ter. Butanol	27.1	1.71[a]
5	iso Propanol	33.8	2.37[a]
6	Ethanol	37.9	3.25[a]
7	Methanol	41.3	6.9[a]
8	Acetic acid	52.9	40[b]
9	2-Chloroethanol	(61)	333[b]
10	Chloroacetic acid	(72.8)[c]	1010[d]
11	Dichloroacetic acid	(92.3)[c]	220.000[d]
12	Trichloroacetic acid	(103.7)[c]	5.700.000[d]
13	Trifluoroacetic acid	105.3	47.000.000[d]

a) rate constant extrapolated from values taken from Table 2

b) experimental rate constant

c) value derived from the assumed linear relationship between ANs and the pK_a values of acetic acids in nitromethane

d) rate constant taken from Tables 3 and 4

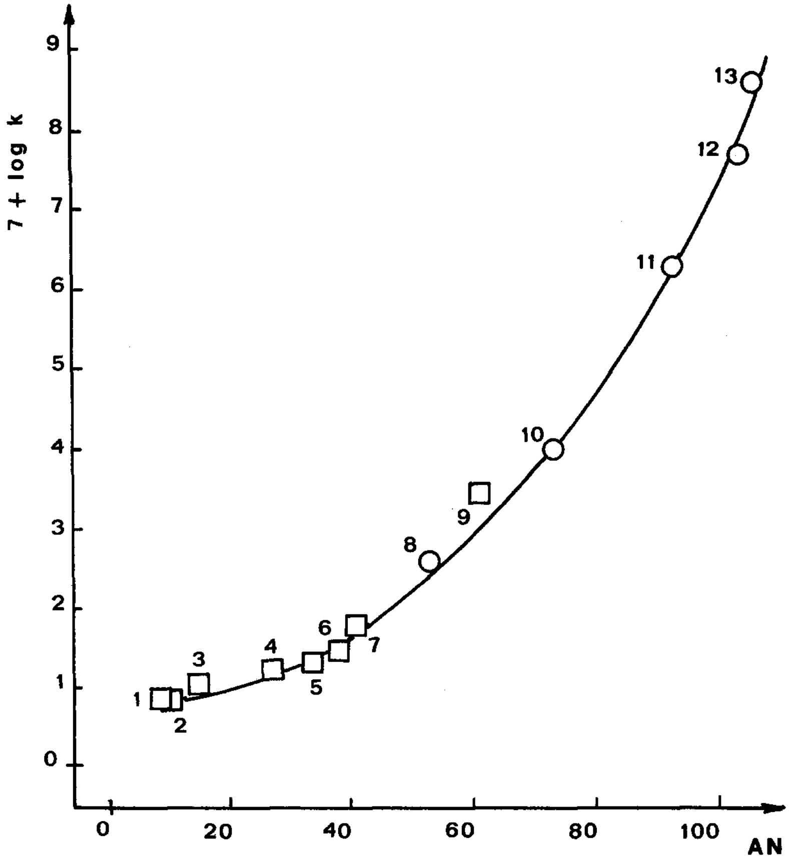

Figure 3. Rate constants of the I.H.D.A. reaction of 3 at 20°C in differing solvents (☐) and acids (○) (Table 5) plotted vs their AN.

Discussion and Conclusion

From the data in Table 5, a clear increase of the rate with increases in the AN of the reaction media can be observed.

When log k was plotted vs the ANs, both of solvents and acids, all data lay on a single hyperbolic curve (Fig. 3).

This curve can be considered the graphic representation of a relationship between the stabilization energy of the reaction and AN, given by equation (1).

From the data of this paper it becomes clear that both solvents and acids act as electrophiles, obviously with differing strength, as measured by their respective ANs, but with the same mechanism.

In conclusion we suggest that, at least in I.H.D.A. reactions, but we believe in most D.A. reactions, solvent effect and acid catalysis act through the same mechanism: an electrophile coordinates either dienophile or diene (in I.H.D.A. the heterodiene), lowers the energy separation of the FMOs involved in the cycloaddition and increases the rate of the reaction.

EXPERIMENTAL

Melting points were determined by the capillary method on a Tottoli apparatus (Büchi). Elemental analyses were carried out with a C. Erba mod. 1106 CHN analyzer. IR spectra were recorded on a Perkin-Elmer 983 infrared spectrophotometer and ^{1}H-NMR spectra on a Bruker WP 80SY spectrometer in $CDCl_3$ solutions.

2(3-Methyl-2-butenyloxy)benzaldehyde (2) was described by Tietze[19] and the sample prepared by us from salicyl aldehyde and 4-bromo-2-methyl-2-butene had b.p. 128°/0.25 mmHg (yield 75%).

1-Phenyl-4-[2-(3-methyl-2-butenyloxy)benzylidene]-5-pyrazolone (3) - To a stirred solution of 1-phenyl-5-pyrazolone (0.94 g. - 5.9 mol) and 2 (1.04 g. - 5.5 mmol) in methylene chloride (30 ml), about 3 g. of N,N'-dicyclohexylcarbodiimide were added. The solution began to become orange and stirring was continued at room temperature untill t.l.c. showed the starting products disappeared (about 8 hrs). The solution was evaporated to dryness at room temperature and the residue was chromatographed on silicagel Merck (70-230 mesh) (eluant cyclohexane-ethyl acetate 9:1). The orange fraction was collected, the solvent was evaporated at room temperature and the residue, dissolved in the minimum volume of benzene, then diluted with light petrol ether, crystallized from the cooled solution as deep orange crystals. The above crystals were dissolved again in benzene, light petrol ether was added, and the cooled solution gave pure 3 m.p. 78-79°C (0.6 g. - 35% yield). Anal. Calcd. for $C_{21}H_{20}N_2O_2$: C, 75.9; H, 6.1; N, 8.4. Found: C, 75.8; H, 5.9; N, 8.4%. ^{1}H-NMR : (3-methyl-2-butenyloxy group) 1.78 (d, 6H), 4.65 (d, 2H), 5.52 (m, 1H); 8.10 (s, 1H, arylidene proton); 8.27 (s, 1H, pyrazolone 3-H). IR : 1709 cm^{-1} (carbonyl).

I.H.D.A. of 3 - G. 0.3 of 3, dissolved in 10 ml benzene were heated at 65°C untill t.l.c. showed the disappearance of the starting product (about 15 hrs). The solution was evaporated and the residue was column chromatographed (silicagel Merck 230-400 mesh, eluant cyclohexane/ethyl acetate 95:5). The first fraction gave 4 as white crystals from petrol ether (0.22 g, 73%) m.p. 129-130°C (lit.[9], m.p. 128.5-130°C). The second fraction gave 5 as white crystals from petrol ether (0.06 g, 20%) m.p. 172-174°C (lit.[9], m.p. 173-175°C). The ^{1}H-NMR spectra of both 4 and 5 were identical to those reported in the literature.[9]

Determination of the (4)/(5) ratio - This was performed, in non-catalyzed reaction, by HPLC on a Waters Associated ALC/CPC 244 liquid chromatograph with a Beckmann mod. 25 spectrophotometer operating at 275 nm as detector. The chromatographic separation was performed on a stainless steel column (25 cm l. x 4.6 mm dia.), packing material Porasil 10 μm, eluant cyclohexane/ethyl acetate 95:5, flow 1.2 ml/min, retention times : (4) 9.6 min., (5) 12.2 min. Five solutions with known composition of pure 4 and 5 were prepared with a ratio (4)/(5) in the range 60/40-90/10, each composition being tested on two independent samples at least four times each. A calibration curve was thus obtained and the unknown compositions were determined by fitting the ratio of the peaks height on it. In a sealed quartz tube 3 (3 mg) and about 2 ml of the solvent were heated at 50°C untill the colour of the solution disappeared. The major part of the solvent was evaporated under vacuum and the residue was dissolved in a small volume of eluant. Each solvent was tested on two independent samples at least four times each and the results are reported in Table 6.

Table 6. Diastereoisomers distribution of the H.D.A. adducts 4 and 5 in different solvents at 50°C.[a]

N	Solvent	4%[b]	5%
1	Cyclohexane	78.9	21.1
2	Benzene	78.5	21.5
3	Ethyl Acetate	78.8	21.2
10	Nitromethane	81.7	18.3
11	Chloroform	79.3	20.7
13	ter. Butanol	79.5	20.5
15	iso Propanol	80.2	19.8
17	Ethanol	82.2	17.8
18	Methanol	84.0	16.0
20	Acetic acid	82.3	17.7
21	2-Chloroethanol	61.3	38.7

a) from the overall rate constants (Table 1) and the products ratio [4] : [5], k_4 and k_5 can be determined for each solvent. Since the products ratio does not change very greatly, two curves can be obtained whose shape does not differ significantly from that in fig. 1.

b) the error was in the limit ± 0.3%

In the acid-catalyzed reactions, the determination of the (4)/(5) ratio was performed by ^{1}H-NMR. G. 0.015 of **3** were allowed to react at 20°C in a 10% solution of the required acid in benzene. Benzene and (when possible) acid were removed under reduced pressure and the residue was dissolved in a 10% solution of deuterated trifluoroacetic acid in C_6D_6. The H-1 protons of **4** and **5** absorbed at about 7.6 and 8.0 δ respectively, in a region that protonation made free from any other signal. The diastereoisomers distribution was always in the range 83 (+3%) vs 17 for **4** and **5** respectively. This ratio did not changed when the reaction was performed in trifluoroacetic acid solution whose χ values were in the range 0.07 - 1.00.

Solvents and Acids - The solvents for the kinetic runs were freshly distilled reagent grade (UV spectroscopic grade when available). The acids were reagent grade.

Kinetics - The first-order rate constants were measured by following the disappearance of **3** on a Perkin-Elmer Lambda 5 UV-Vis spectrophotometer provided of thermostatted cells transport assembly and "automatic multicell programmer". The solutions were measured in 1.00 cm OS Hellma couvettes of 3 ml capacity at 440 nm. A 25 ml solution of **3** in the required solvent was prepared (in the range 0.01 - 0.05 mmol) and ten samples (about 2 ml) were placed into quartz tubes which were sealed. At time zero the samples were placed into an ultrathermostat at 50°C and the absorbance of the solution was determined on a further sample. At appropriate time intervals (from 90 to 3 minutes, depending from the solvent) the reaction was quenched in ice and the residual absorbance of **3** was determined.

To measure both the activation parameters and to determine the extrapolated rate constants reported in Table 2, the determinations at temperatures above 50°C were performed under the previously described conditions. For temperatures below 50°C, six (or less) samples were placed in the spectrophotometer thermostatted couvettes and the automatic program registered the solution absorbance at programmed time intervals.

To determine the acid-catalyzed rate constants a 25 ml solution of **3** in benzene was prepared (about 0.01 mmole) and six samples (in the range 1.00-2.00 ml, accurately measured with a calibrated syringe) were thermostatted in the couvettes. The required amount of acid was weighed in a 10 ml volumetric flask, which was then filled with benzene and again weighed to determine accurately the concentration of the solution. Further dilutions of 1 ml to 10 and 100 ml gave the range of concentrations required for the kinetic determinations. A volume of the thermostatted acid solution (in the range 1.00-2.00 ml, accurately measured with a calibrated syringe) was added to each couvette and, after mixing, the automatic program registered the solution absorbance at programmed time intervals (from 80 minutes to 3 seconds, depending on the type of acid and its concentration).

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