Tetrahedron Vol. 48, No. 9, pp. 1667-1674, 1992
Printed in Great Britain

0040-4020/92 $3.00+.00

Solvent Effect as the Result of Frontier Molecular Orbital Interaction. VII.(1) The Retro-Diels-Alder Reaction.

G. Desimoni,* G. Faita, D. Pasini, P. P. Righetti

Dipartimento di Chimica Organica, Università di Pavia, V.le Taramelli 10, 27100 Pavia, Italy.

(*Received in UK* 31 *December* 1991)

Abstract - The solvent effect on the retro-Diels-Alder (R.D.A.) reaction of 1,4,4a,9a-tetrahydro-4a-methyl-(1α,4α,4aα,9aα)-1,4-methanoanthracene-9,10-dione to 2-methyl-1,4-naphthoquinone and cyclopentadiene was investigated kinetically in 16 solvents. The hyperbolic relationship between the kinetic data and the Acceptor Number of the solvents is strong evidence that the solvent acts as an electrophile which lowers the activation energy of the reaction. Furthermore when these rate constants are plotted *vs* those of the previously investigated Diels-Alder (D.A.) reaction of 1,4-naphthoquinone and 2,3-dimethylbutadiene, a linear relationship is obtained. The linearity of the graph is a good indication that the nature of the solvent effect is the same in both D.A. and R.D.A. reactions.
The above relationships and the thermodynamic parameters strongly suggest that the R.D.A. reaction is a "*late* transition state" pericyclic reaction whose solvent effect derives from a specific interaction between the solvent and the product.

Previous papers in this series(1-6) investigated the solvent effect on Diels-Alder (D.A.) and hetero-D.A. reactions with either heterodienes or heterodienophiles. These results, together with those reported in the literature,(7,8) brought to light significant solvent effects. This intriguing field was rationalized by dividing the solvent effects into three classes:(6)

type a) the solvent acts as an electrophile and the rate increases with the increase of the electrophilic character of the medium;

type b) the solvent acts as a nucleophile and the rate decreases with the increase of the nucleophilic character of the medium;

type c) the solvent effect is the result of non specific solvent-solvent interactions, and a small increase in the rate as the solvent cohesive pressure increases, was observed.

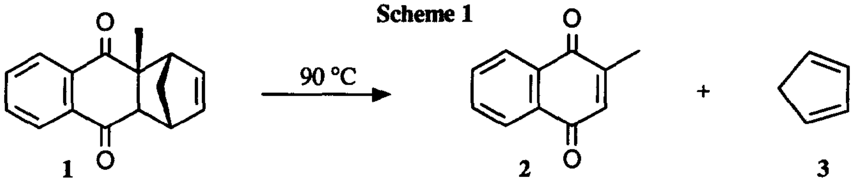
The specific solute-solvent interactions (*types a,b*) depend on the energies of the solute molecular orbitals (MO) that determine which of the $\text{HOMO}_{\text{solute}}$-$\text{LUMO}_{\text{solvent}}$ (*type a*) or $\text{HOMO}_{\text{solvent}}$-$\text{LUMO}_{\text{solute}}$ (*type b*) interactions are involved in the solvent effect.

The obvious extension of this work was to consider the effect of the solvent on the retro-D.A. (R.D.A.) reaction.

Synthetic and mechanistic aspects of this reaction have been reviewed;(9) experimental studies(10) and theoretical calculations(11) of the substituent effect have also been carried out. Till now no study on the solvent effect has been reported in the literature.

In order to compare a R.D.A. with an analogous D.A. reaction, the cycloreversion of 1,4,4a,9a-tetrahydro-4a-methyl-(1α,4α,4aα,9aα)-1,4-methanoanthracene-9,10-dione (**1**), which reacts at 90 °C to give 2-methyl-1,4-naphthoquinone (**2**) and cyclopentadiene (**3**) in a quantitative yield, was investigated (scheme 1).

Scheme 1



RESULTS AND DISCUSSION

The kinetic runs were performed in 16 differing solvents at 90 °C and followed to about 80% completion, using u.v.-vis. spectrophotometric analysis of the appearing chromophore **2**. The reaction was found to follow a first-order kinetic, and the rate constants reported in table 1 are the average of at least four kinetic runs.

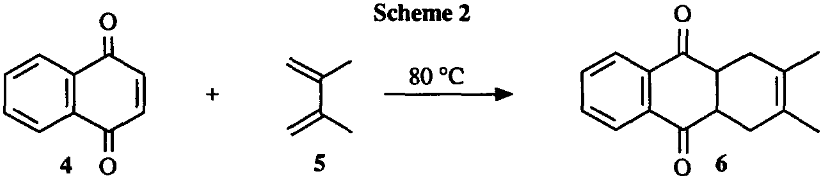
Table 1: Rate Constants for the R.D.A. Reaction of 1 at 90 °C in Differing Solvents and AN of the Solvent.

n	Solvent	AN	10^4 x k (L $mol^{-1}sec^{-1}$)
1	n-Hexane	0	1.94 ± 0.01
2	Cyclohexane	0	2.24 ± 0.01
3	Benzene	8.2	4.68 ± 0.06
4	Ethyl acetate	9.3	4.5 ± 0.2
5	1,4-Dioxane	10.8	6.02 ± 0.08
6	Acetone	12.5	5.71 ± 0.06
7	DMF	16.0	8.6 ± 0.2
8	1,2-Dichloroethane	16.7	7.78 ± 0.06
9	Acetonitrile	18.9	8.23 ± 0.07
10	DMSO	19.3	11.15 ± 0.1
11	Chloroform	23.1	8.51 ± 0.07
12	t-Butanol	27.1	10.0 ± 0.5
13	2-Propanol	33.8	12.2 ± 0.3
14	Ethanol	37.9	13.3 ± 0.3
15	Methanol	41.3	15.9 ± 0.3
16	Acetic acid	50.0	24.9 ± 0.7

The kinetic constants for a selected number of solvents were also determined by h.p.l.c. analysis of the reaction mixture (see experimental section for details) and found to be in accordance with those reported in table 1, within the limit of experimental error.

The solvent effect was found to be about 13 in the n-hexane/acetic acid range. This value is about a half of that found(2) in the D.A. reaction of 1,4-naphthoquinone (4) with 2,3-dimethylbutadiene (DMB-5), reported in scheme 2.

Scheme 2



The activation parameters (table 2) confirmed the nature of the concerted pericyclic process for the R.D.A. reaction of **1**. The $-\Delta S^{\neq}$ values were found to be nearly constant in the solvent series and the values, very close to 0, are in accordance with those reported in the literature.(7,12,13) As expected for a reaction where 2σ bonds are broken and 2π bonds are formed, the activation entalpy of the R.D.A. is far larger than that of the analogous D.A. reaction.

Therefore, if D.A. is an *early* (from an energetic point of view) *transition state* (*t.s.*) pericyclic reaction, a comparison of the activation parameters strongly suggests that R.D.A. is a *late t.s.* pericyclic reaction.

Table 2: Rates and Activation Parameters of the R.D.A. Reaction of 1 Determined in Four Selected Solvents, Compared to the Activation Parameters of the D.A. Reaction between 4 and 5 in the Same Solvents.

T/°C	10^5 x k (l mol^{-1} s^{-1})			
	benzene	DMSO	2-propanol	acetic acid
65	------	------	------	1.46 ± 0.07
70	------	1.11 ± 0.02	1.17 ± 0.02	2.61 ± 0.04
80	1.52 ± 0.01	4.1 ± 0.3	4.14 ± 0.09	8.5 ± 0.3
90	4.68 ± 0.06	11.15 ± 0.1	12.2 ± 0.3	24.9 ± 0.7
100	13.95 ± 0.15	33.4 ± 0.6	34.2 ± 0.5	------
110	40.8 ± 0.5	-----	------	------
R.D.A. $\Delta H^{\neq a}$	28.7 ± 0.2	27.9 ± 0.5	27.8 ± 0.5	27.2 ± 0.8
R.D.A. $-\Delta S^{\neq b}$	0.3 ± 0.6	0 ± 1	0 ± 1	-1 ± 2
D.A. $\Delta H^{\neq a,c}$	12.5 ± 0.8	12.9 ± 0.3	11.7 ± 0.3	11.2 ± 0.3
D.A. $-\Delta S^{\neq b,c}$	41 ± 1	36 ± 1	39 ± 1	38 ± 1

[a] kcal mol^{-1}; [b] cal K^{-1} mol^{-1}; [c] data taken from ref. 2 for the D.A. reaction in scheme 2.

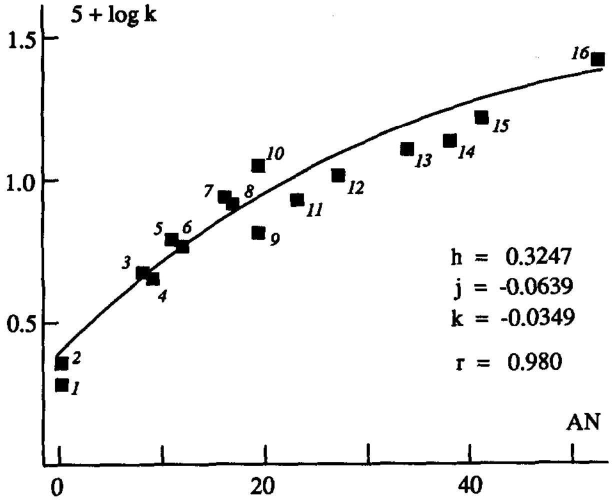


Figure 1: rate constants of the R.D.A. reaction of 1 at 90 °C in differing solvents (see table 1 for numbering) plotted vs the AN of the solvents.

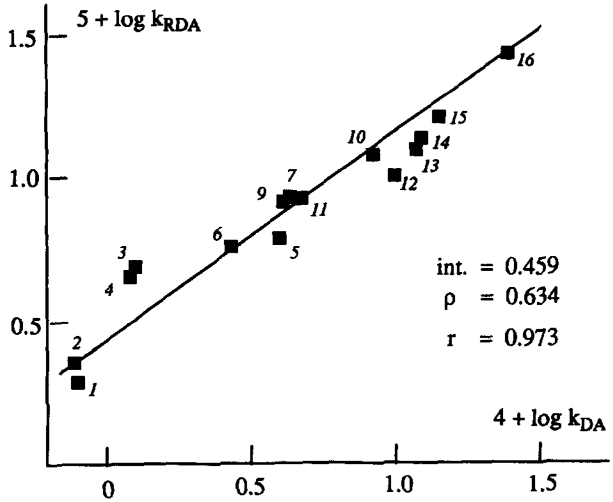


Figure 2: plot of the rate constants of the R.D.A. of 1 (k_{RDA}) vs those of the D.A. reaction of 4 and 5 (k_{DA}).

When the kinetic data in table 1 were plotted *vs* the Acceptor Number(14) (AN) of the solvents, the hyperbolic relationship reported in figure 1 was obtained.

Hyperbolic relationships between kinetic data and ANs were obtained for D.A. reactions,(2-6) in which the solvent acts as an electrophile (*type a* solvent effect). These relationships were derived by applying the perturbation theory to the frontier MO interaction between the solute and the solvent,(2,6) and are represented by equation 1.

$$\log k = \frac{h - j \times AN}{1 - k \times AN} \qquad (1)$$

If the kinetic data of the R.D.A. reaction reported in table 1 are plotted *vs* the kinetic data of the D.A. reaction between naphthoquinone (**4**) and DMB (**5**),(2) the linear relationship in figure 2 is obtained.

The graph in figure 2 gives an important information: its linearity is clear evidence that the solvent acts in both reactions by the same mechanism.

In the D.A. reaction reported in scheme 2, **5** is coordinated by the solvent, and an increase in the solvent's electrophilic character lowers the energy separation between the interacting orbitals of diene and dienophile, decreases perturbation energy, and lowers the slope of the reaction diagram from the reagents to the t.s..

The electrophilic coordination of the solvent with reagent **1**, by slightly lowering its potential energy, is expected to have little effect on the activation energy of the R.D.A. reaction that, indeed, might be increased. Thus the electrophilic interaction of the solvent has to involve a different partner.

The observed effect is rationalized if the electrophilic solvation of the developing product **2** is taken into account. The slope of the reaction diagram of the R.D.A. from the products to the t.s. is decreased as outlined above, hence the activation energy of the R.D.A. is also decreased as the electrophilic character of the solvent increases.(15) A result of the comparison of a similar solvent effect on a reverse endothermic reaction (R.D.A.) *vs* a forward exothermic one (D.A.) is the slope of the linear relationship in figure 2, which is significantly lower than 1.

CONCLUSION.

The hyperbolic relationship in figure 1 shows that the solvent effect on the R.D.A. reaction of **1** is the result of a frontier MO interaction involving the solvent, acting as an electrophile, and the reaction product.

The monoparametric relationship between log k and AN is further confirmed if the Kamlet-Taft multiparametric equation(16) is applied: π^* being the index of solvent dipolarity-polarizability (corrected by a discontinuous polarizability term δ), α the Lewis acidity contribution of the solvent, β its Lewis basicity (integrated by ξ which is the co-ordinate covalency parameter), and $\delta_H{}^2$ the solvent cohesive pressure (equation 2).

$$A = A_o + s \times (\pi^* + d \times \delta) + a \times \alpha + b \times \beta + h \times \delta_H^2/100 + e \times \xi \qquad (2)$$

If equation 2 is applied to the solvent dependent kinetic data in table 1, the regression coefficients s, d, a, b, h, and e, measuring the relative susceptibility of log k to each solvent parameter, show that some parameters do not contribute significantly to the solvent effect. Thus equation 2 can be reduced to a simpler two-term relation (acidity and polarity - equation 3), with the acidity parameter giving the main contribution (56%).

$$\log k = 0.33 + 0.66\,\pi^* + 0.57\,\alpha \qquad (r = 0.985) \qquad (3)$$

The same solvent effect classification derived for D.A.(6) is probably applicable to R.D.A. reactions. Unfortunately all attempts to find a *type-b* solvent effect R.D.A. reaction, suitable for kinetic investigation, were unsuccessful.

EXPERIMENTAL SECTION

Melting points were determined by the capillary method. Elemental analyses were made on Carlo Erba CHN analyzer mod. 1106. ^{1}H-n.m.r. spectra were recorded on Bruker WP80SI spectrometer using $CDCl_3$ as the solvent and tetramethylsilane as the standard, i.r. spectra (nujol mulls) on a Perkin Elmer 983 spectrophotometer.

1,4,4a,9a-tetrahydro-4a-methyl-(1α,4α,4aα,9aα)-1,4-methanoanthracene-9,10-dione **1** - 2.0 g of 2-methyl-1,4-naphthoquinone (11.6 mmol) and 7.63 g of cyclopentadiene (116 mmol) were dissolved in 60 cm^3 of ethanol and refluxed for about six hours. The solvent and the diene excess were evaporated and the residue, crystallized from cyclohexane, gave 1.52 g of **1** (55% yield) as white crystals, m.p. 97-98 °C (lit.,(17) 96 °C). I.r. and ^{1}H-n.m.r. spectra are in accordance with those reported in the literature.(17)

Kinetics.

Spectrophotometric determination of the rate constants - The reaction rates were measured by following the appearance of **2** on a Perkin Elmer Lambda 5 spectrophotometer; solutions were measured in 1.00 cm OS Hellma cuvettes of 3 cm^3 capacity. Measurements were taken at wavelengths of 330 and 350 nm for each solvent.

Table 3. Molar Extinction Coefficient for Each Solvent at 330 (ϵ_{330}) and 350 (ϵ_{350}) nm.

Solvent	ϵ_{330}	ϵ_{350}
n-hexane	2571 ± 40	1187 ± 50
cyclohexane	2506 ± 32	1119 ± 12
benzene	2415 ± 18	1597 ± 12
ethyl acetate	2429 ± 20	1265 ± 8
1,4-dioxane	2312 ± 20	1295 ± 10
acetone	2469 ± 20	1390 ± 10
N,N-dimethylformamide	2575 ± 30	1778 ± 40
1,2-dichloroethane	2486 ± 20	1642 ± 15
acetonitrile	2537 ± 24	1485 ± 38
dimethylsulfoxide	2672 ± 10	1878 ± 20
chloroform	2634 ± 10	2032 ± 10
t-butanol	2522 ± 20	1685 ± 13
2-propanol	2448 ± 20	1597 ± 10
ethanol	2468 ± 20	1571 ± 15
methanol	2719 ± 30	1701 ± 20
acetic acid	2520 ± 20	1708 ± 10

A sample (2-6 mg) of **1** was weighed accurately into a 50 cm^3 volumetric flask that was filled with the required solvent. About 3 cm^3 portions of the homogenous solution were placed into glass vials which were sealed. Ten samples were prepared for each run: seven samples were used for the kinetic run, while the last three ones were used to confirm the calculated absorbance at the infinite time (A_∞). At time zero the initial absorbance was determined and the samples were placed into a thermostat at the required temperature. At appropriate time intervals (from 5 to 100 min. depending on the solvent and the temperature) the reaction was quenched with ice and the absorbance of **2** was measured.

In order to know the absorbance at the infinite time, a calibration curve for each solvent was made. From the molar extinction coefficient (ϵ) and the initial concentration of **1**, A_∞ was obtained for each solvent. Table 3 reports the values of ϵ for each solvent at 330 and 350 nm. Using standard calculations the first-order-rate constants reported in table 1 were then obtained.

H.p.l.c. determination of the rate constants - This was performed on a Waters Associated ALC/CPC 244 liquid chromatograph with a detector operating at 255 nm. The chromatographic separations were performed on a stainless steal column (25 cm x 4 mm internal diameter) pre-packed with Lichrosorb Si 60 (10 µm) Merck; eluant: cyclohexane-ethyl acetate 95:5; flow: 1.0 cm^3 min^{-1}; retention times: **1**, 13.2 min; **2**, 10.4 min.

Five solutions of known compositions of **1** and **2** were prepared with a ratio [**1**]/[**2**] between 90/10 and 20/80. A calibration curve was obtained by fitting the composition of the solutions *vs* $h_1/(h_1+h_2)$; h_1 and h_2 being the peak heights of **1** and **2** respectively.

Solutions of **1** (0.0001-0.001 M) in a selected number of solvents (cyclohexane, benzene, acetone, chloroform, methanol, and acetic acid) were sealed in glass vials and thermostatted at 90 °C. At appropriate time intervals the reaction was quenched, the solvent evaporated under vacuum at room temperature and the residue was dissolved in a small amount of eluant and analyzed. The unknown compositions, determined by fitting the ratio of the peak heights on the calibration curve, allowed us to calculate the first-order-rate constants. These are reported in table 4 and fit those in table 1 within the limit of experimental error.

Table 4. Rate constants for the R.D.A. reaction of 1 at 90 °C determined by h.p.l.c.

solvent	10^4 x k (L mol^{-1} sec^{-1})
cyclohexane	2.6 ± 0.3
benzene	5.1 ± 0.4
acetone	5.9 ± 0.5
chloroform	9.0 ± 0.5
metanol	16.4 ± 0.5
acetic acid	26.0 ± 1.0

AKNOWLEDGEMENT

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

REFERENCES.

1) Part VI. Desimoni, G.; Faita, G.; Righetti, P. P. *Tetrahedron* **1991**, *47*, 5857.
2) Corsico Coda, A.; Desimoni, G.; Ferrari, E.; Righetti, P. P.; Tacconi, G. *Tetrahedron* **1984**, *40*, 1611.
3) Desimoni, G.; Faita, G.; Righetti, P. P.; Tornaletti, N.; Visigalli, M. *J. Chem. Soc., Perkin Trans. II* **1989**, 437.

4) Burdisso, M.; Desimoni, G.; Faita, G.; Righetti, P. P.; Tacconi, G. *J. Chem. Soc., Perkin Trans. II* **1989**, 845.

5) Corsico Coda, A.; Desimoni, G.; Faita, G.; Righetti, P. P.; Tacconi, G. *Tetrahedron* **1989**, *45*, 775.

6) Desimoni, G.; Faita, G.; Righetti, P. P.; Toma, L: *Tetrahedron* **1990**, *46*, 7951.

7) Sauer, J.; Sustmann, R. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 779.

8) The leading reference on the solvent effect is: Reichardt, C. *"Solvents and Solvent Effects in Organic Chemistry"*, VCH, Weinheim, 1988.

9) Fringuelli, F.; Taticchi, A. *"Dienes in the Diels-Alder Reaction"*, J. Wiley, New York, 1990, p. 35-37 and references therein. Ripoll, J. L.; Rouessac, A.; Rouessac, F. *Tetrahedron* **1978**, *34*, 19. Lasne, M. C.; Ripoll, J. L. *Synthesis* **1985**, 121.

10) Nanjappan, P.; Czarnik, A. W. *J. Org. Chem.* **1986**, *51*, 2851.

11) Lehd, M.; Jenson, F. *J. Org. Chem.* **1990**, *55*, 1034.

12) Kwart, H.; King, K. *Chem. Rev.* **1968**, 415.

13) Jenner, J.; Papadopoulos, M.; Rimmelin, J. *J. Org. Chem.* **1983**, *48*, 748.

14) Mayer, V.; Gutmann, V.; Berger, W. *Monatsh. Chem.* **1975**, *106*, 1235.

15) Kamlet, M. J.; Abboud, J. L.; Taft, R. W.; Abraham, M. H. *J. Org. Chem.* **1983**, *43*, 2877.

16) This concept is the result of the application of the principle of microscopic reversibility.

17) Singh, V. K.; Raju, B. N. S.; Deota, P. T. *Synth. Commun.* **1988**, *18*, 567.