JOC Notes

Solvent Effects on the 9-Hydroxymethylanthracene + N-Ethylmaleimide Diels−Alder Reaction. A Theoretical Study

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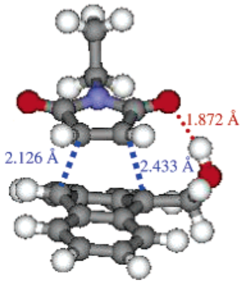
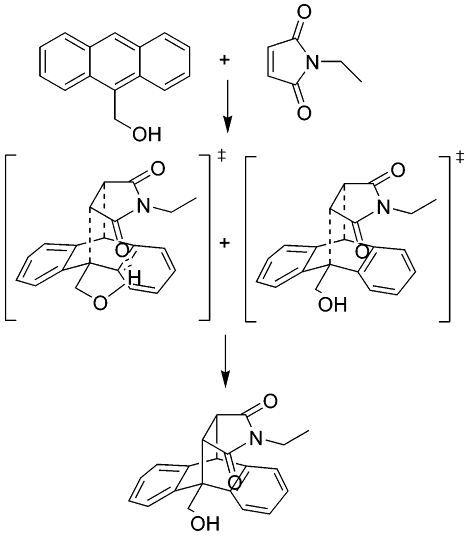


The origin of the high reaction rates of the 9-hydroxymethylanthracene + *N*-ethylmaleimide Diels−Alder reaction in fluorous solvents and supercritical carbon dioxide is analyzed through a combination of regression analyses and theoretical calculations. Both approaches allow the solvent effects on the activation barrier (a decrease by solvophobic interactions, an increase by dipolarity−polarizability) to be attributed to the existence of a hydrogen bond between the two reactants in the transition state, refuting a previous hypothesis based on strong solvophobic interactions.

Since Breslow's discovery in 1980 that aqueous media can induce a significant acceleration of Diels−Alder reactions,[1] a great deal of attention has been paid to the role of solvent effects in this cycloaddition reaction.[2] Presently, such a rate increase is usually explained in terms of a combination of enforced hydrophobic interactions and solute−solvent hydrogen bonds.[3] However, an exception to this rule is found in the case of the cycloaddition between 9-hydroxymethylanthracene and *N*-ethylmaleimide, since a noticeable acceleration is found in isooctane compared with alcohols and acetonitrile (though a very high reaction rate is observed in water).[1] Such anomalous behavior has been attributed by Kumar to large solvophobic interactions[4] (particularly in highly fluorinated−"fluorous"−solvents).[5] This hypothesis has recently been considered as evidence for the solvophobic properties of supercritical CO_2.[6] However, an alternative theory based on the formation of a hydrogen bond between the two reactants in the transition state (TS) can be proposed (Scheme 1)[7] in a similar way to Diels−Alder reactions between chiral dienols and a number of dienophiles (including *N*-phenyl-,[8] *N*-methyl-,[9] and *N*-ethylmaleimide).[10] In the work described here, we analyzed the source of the anomalous behavior in the title reaction by using regression analysis with empirical solvent parameters as well as density-functional theory calculations.

SCHEME 1. 9-Hydroxymethylanthracene + *N*-Ethylmaleimide Reaction



The Kumar hypothesis is supported by a relationship between log *k* and the Hildebrand solubility parameter, δ, in the set of solvents considered. The fit of the U-shaped plot, after the exclusion of trifluoroethanol (TFE) because "*data for the estimation of δ are not readily*

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[1] Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7817−7818.

[2] Cativiela, C.; García, J. I.; Mayoral, J. A.; Salvatella, L. *Chem. Soc. Rev.* **1996**, *25*, 209−218.

[3] Otto, S.; Engberts, J. B. F. N. *Pure Appl. Chem.* **2000**, *72*, 1365−1372.

[4] Solvophobic interactions are a generalization of the concept of hydrophobic interactions with any solvent. See: Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 3rd ed.: Wiley: Weinheim, 2003; pp 27−30.

[5] Myers, K. E.; Kumar, K. *J. Am. Chem. Soc.* **2000**, *122*, 12025−12026.

[6] Qian, J.; Timko, M. T.; Allen, A. J.; Russell, C.; Winnik, B.; Buckley, B.; Steinfeld, J. I.; Tester, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 5465−5474.

[7] This theory was suggested in a footnote in the article by Breslow (ref 1).

[8] (a) Fisher, M. J.; Hehre, W. J.; Kahn, S. D.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4625−4633. (b) Trost, B. M.; Lee, D. C. *J. Org. Chem.* **1989**, *54*, 2271−2274. (c) Datta, S. C.; Franck, R. W.; Tripathy, R.; Quigley, G. J.; Huang, L.; Chen, S.; Sihaed, A. *J. Am. Chem. Soc.* **1990**, *112*, 8472−8478. (d) Hatakeyama, S.; Sugawara, K.; Takano, S. *J. Chem. Soc., Chem. Commun.* **1992**, 953−955.

[9] (a) Sanyal, A.; Snyder, J. K. *Org. Lett.* **2000**, *2*, 2527−2530. (b) Atherton, J. C.; Jones, S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2166−2173.

[10] Tripathy, R.; Carroll, P. J.; Thornton, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 7630−7640.

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available",[5] is fair ($r = 0.90$, 9 solvents), though we have found that the inclusion of the experimental value for TFE leads to a more modest fit ($r = 0.845$). Furthermore, a better description of the results is found through a linear regression if the δ parameter[11] is replaced by its square (called the *cohesive energy density*, which is more suitable for linear energy relationships)[12] and the π^* parameter (representing a blend of dipolarity and polarizability)[13] is also included (eq 1).[14]

$$\log k = 2.484\ (\pm 0.188) - 1.759\ (\pm 0.423)\pi^* + 1.636\ (\pm 0.335) \times 10^{-3}\delta^2 \quad (\text{including TFE}, n = 9, r = 0.895) \quad (1)$$

However, a large deviation is observed for TFE (0.8 log k units),[15] in agreement with the behavior of this solvent as a hydrogen bond donor in a number of Diels−Alder cycloadditions.[16−18] In this case, the increase in the reaction rate can be attributed to the formation of hydrogen bonds with the maleimide carbonyl group, which is not involved in the bond with the diene. The removal of TFE from the solvent set leads to a remarkable improvement in the regression model (eq 2).

$$\log k = 2.294\ (\pm 0.047) - 2.362\ (\pm 0.113)\pi^* + 2.014\ (\pm 0.085) \times 10^{-3}\delta^2 \quad (\text{excluding TFE}, n = 8, r = 0.996) \quad (2)$$

The high r value and the significance of the parameters π^* and δ^2 indicate that such a linear regression is an excellent model for explaining the influence of the solvent properties on the reaction rate. The linear dependence relative to the solvent cohesivity contrasts with the parabolic behavior (using δ instead of δ^2) reported by Kumar.[5] In that case, the high reaction rates found in fluorous solvents are explained in terms of the solubility of the reactants in such media. However, the low solubility of the reactants is not due to the high cohesivity of the solvents (as occurs in water) but is a consequence of the poor solvent−solute interactions. We therefore believe that enforced solvophobic interactions should *not* be expected in fluorous solvents.

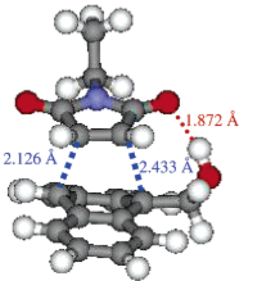

FIGURE 1. Transition state for the 9-hydroxymethylanthracene + *N*-ethylmaleimide reaction, which involves a hydrogen bond according to B3LYP/6-31+G(*d*) calculations.

The coefficient of the π^* parameter indicates that an enhancement of the solvent dipolarity−polarizability leads to a significant decrease in the reaction rate, a situation in contrast with the negligible role that dielectric effects play in common Diels−Alder reactions (e.g., cyclopentadiene + menthyl acrylate[17] or 5-methoxy-1,4-naphthoquinone).[18] This result allows the explanation of the high reactivity induced by perfluorohexane ($\pi^* = -0.48$) or FC-75 ($\pi^* = -0.41$) in comparison with hexane ($\pi^* = -0.11$). Therefore, one can infer a decreasing role of the hydrogen bond as the solvent polarity increases, a situation in agreement with the shift of keto/enol equilibria of 1,3-dicarbonyl compounds toward the carbonylic form in polar media.[18,19]

In an effort to analyze the hydrogen-bond hypothesis, a theoretical study was carried out by using B3LYP/6-31+G(*d*) calculations. Two different transition states have been found depending on the possible occurrence of a hydrogen bond between the two reactants. Despite the fact that this reaction has been studied previously at the AM1[5,20] and B3LYP/6-31G(*d*) levels,[6] the existence of a hydrogen bond in the TS is explicitly reported for the first time (Figure 1). Similar hydrogen bonds have been previously described for theoretical calculations on other Diels−Alder reactions [e.g., furfuryl alcohol + isothiazolone-1,1-dioxide at the MP2/6-31G(*d*) level[21] and 9-(1-hydroxyethyl)anthracene + maleic anhydride using the PM3 method].[22]

The TS that contains a hydrogen bond displays a moderate asynchronicity ($\Delta d = 0.307$ Å), which is greater than that of the counterpart that lacks this feature ($\Delta d = 0.206$ Å).[23] Such a situation is consistent with the increase in asynchronicity reported for the butadiene + acrolein reaction when a water molecule is coordinated to the dienophile.[24]

Furthermore, the hydrogen-bond approach is supported by the calculated activation barriers (17.3 kcal

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[11] δ values (in MPa$^{1/2}$) were taken from the following sources. Non-hydrogen-bonding solvents: (a) Abboud, J.-L. M.; Notario, R. *Pure Appl. Chem.* **1999**, *71*, 645−718. HBD solvents: (b) Marcus, Y. *The Properties of Solvents*; Wiley: Chichester, UK, 1998. FC-75: (c) Ref 4.

[12] Katritzky, A. R.; Fara, D. C.; Yang, H.; Tämm, K. *Chem. Rev.* **2004**, *104*, 175−198.

[13] π^* values (in MPa) of hydrogen-bonding solvents were taken from: (a) Kamlet, M. J.; Abboud, J.-L. M.; Abraham, M. H.; Taft, R. W. *J. Org. Chem.* **1983**, *48*, 2877−2887. For non-hydrogen-bonding solvents, π^* values were taken from: (b) Laurence, C.; Nicolet, P.; Dalati, M. T.; Abboud, J.-L. M.; Notario, R. *J. Phys. Chem.* **1994**, *98*, 5807−5816.

[14] The Kumar parabolic fit indeed consists of a linear regression using both δ and δ^2 parameters. Therefore, no change in the number of independent parameters is introduced in our model through the replacement of δ by the π^* parameter.

[15] Large deviation from a linear regression model has also been found for TFE in a study on the regioselectivity of the isoprene + methyl vinyl ketone Diels−Alder reaction. The corresponding IR spectrum allows this result to be attributed to the double hydrogen-bonding coordination of the solvent to the dienophile. Cativiela, C.; García, J. I.; Mayoral, J. A.; Salvatella, *J. Chem. Soc., Perkin Trans. 2* **1994**, 847−851.

[16] (a) Cativiela, C.; García, J. I.; Mayoral, J. A.; Royo, A. J.; Salvatella, L. *Tetrahedron: Asymm.* **1993**, *4*, 1613−1618. (b) Cativiela, C.; García, J. I.; Gil, J.; Martínez, R. M.; Mayoral, J. A.; Salvatella, L.; Urieta, J. S.; Mainar, A. M.; Abraham, M. H. *J. Chem. Soc., Perkin Trans. 2* **1997**, 653−660.

[17] Cativiela, C.; García, J. I.; Mayoral, J. A.; Royo, A. J.; Salvatella, L. *J. Phys. Org. Chem.* **1992**, *5*, 230−238.

[18] Gajewski, J. J. *J. Org. Chem.* **1992**, *57*, 5500−5506.

[19] Mills, S. G.; Beak, P. *J. Org. Chem.* **1985**, *50*, 1216−1224.

[20] Breslow, R.; Connors, R.; Zhu, Z. *Pure Appl. Chem.* **1996**, *68*, 1527−1533.

[21] Yeung, K.-S.; Meanwell, N. A.; Li, Y.; Gao, Q. *Tetrahedron Lett.* **1998**, *39*, 1483−1486.

[22] Atherton, J. C. C.; Jones, S. *Tetrahedron Lett.* **2001**, *42*, 8239−8241.

[23] This TS (calculated at the B3LYP/6-31G(*d*) level) is shown in ref 5.

[24] Kong, S.; Evanseck, J. D. *J. Am. Chem. Soc.* **2000**, *122*, 10418−10427.

mol^{-1}, in comparison with 20.4 kcal mol^{-1} for the other approach, by using internal energies)[25] and the short O···H distance (1.872 Å). The hydrogen-bond formation in the TS agrees with stereoselectivity data on the closely related 9-(1-hydroxyethyl)anthracene + *N*-methylmaleimide reaction, as well as the reactivity lowering provoked by the replacement of the diene alcohol by the corresponding methyl ether.[9]

The inclusion of electrostatic solvation in water induces a clear increase in the activation barrier, which is larger in the hydrogen-bonding approach (6.1 vs 2.1 kcal mol^{-1}). This is in agreement with the increasing role of the non-hydrogen-bonding approach, as the solvent polarity increases in the closely related reaction.[9] This finding demonstrates the lower strength and efficiency of hydrogen bonds in polar solvents. On the other hand, nonelectrostatic terms lead to a decrease in the activation barrier for both approaches (by 1.1 and 1.5 kcal mol^{-1}, respectively), in agreement with the known role of enforced hydrophobic interactions in Diels−Alder reactions.[3] According to these calculations, the most stable transition state in water corresponds to the non-hydrogen-bonding approach (by 1.4 kcal mol^{-1}).

Good agreement between the results from experimental and computational studies was found in terms of the formation of a hydrogen bond between the reactants. As a consequence, the high experimental reaction rates found in some unusual media (fluorous solvents and supercritical CO_2) should be attributed to their low polarity (rather than solvophobic effects).

In summary, regression analysis on the reaction rates of the 9-hydroxymethylanthracene + *N*-ethylmaleimide cycloaddition indicates that the activation barrier is controlled by both enforced solvophobic interactions and the dipolarity−polarizability of the medium. The formation of a hydrogen bond between the two reactants in the TS explains the decrease in the reaction rate as the solvent polarity increases. B3LYP/6-31+G(*d*) calculations confirmed the presence of such a geometrical feature and support the increase in the activation barrier in polar solvents. These results bring into question the hypothesis suggesting that the rate of the aforementioned reaction in some nonaqueous solvents is controlled by solvophobic interactions.

Computational Details

The reactants and transition states were optimized at the B3LYP/6-31+G(*d*) level by using the Gaussian03 package.[26] The nature of these structures was characterized by means of the correct number of negative eigenvalues in the exact Hessian. Solvent effects were computed for the gas-phase geometries at the same theoretical level by means of the PCM model using the default options.

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Supporting Information Available: Cartesian coordinates (Å), energy values (Hartrees), and solvation terms (kcal mol^{-1}) for the stationary points reported in this work. This material is available free of charge via the Internet at http://pubs.acs.org.

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[25] Free energy calculations (including thermal corrections) show activation barriers of 33.8 and 35.8 kcal mol^{-1}, respectively.

[26] *Gaussian 03*, revision B.05; Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery Jr., J, A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Ivengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, C.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; González, C.; Pople, J. A; Gaussian, Inc.: Pittsburgh, PA, 2003.