

The Influence of Water on the Rates of 1,3-Dipolar Cycloaddition Reactions: Trigger Points for Exponential Rate Increases in Water–Organic Solvent Mixtures. Water-Super versus Water-Normal Dipolarophiles

Richard N. Butler,^{*,†} William J. Cunningham,[†] Anthony G. Coyne,[†] and Luke A. Burke[‡]

Chemistry Department, National University of Ireland, Galway, Ireland, and
Chemistry Department, Rutgers University, Camden, New Jersey 08102

Received April 26, 2004; E-mail: r.debutleir@nuigalway.ie

Abstract: The nature of the rate enhancements caused by gradually increasing the mole fraction of water in the solvent (from 0 to 1) for the cycloaddition reactions of pyridazinium-dicyanomethanide 1,3-dipole, **2**, with the dipolarophiles ethyl vinyl ketone (a water-super dipolarophile) and methyl acrylate (a water-normal dipolarophile) in the organic solvents acetonitrile, acetone, methanol, ethanol, and *tert*-butyl alcohol at 37 °C are explored. In each case as the mole fraction of water surpassed ca. 0.9, exponential rate enhancements were triggered. When methanol replaced water, the rate enhancements were smaller, and no triggering effect was observed. The dramatic rate enhancement triggered for the water-super dipolarophile was significantly reduced as the temperature was raised in the range 29–64 °C. The results suggest that a dominant hydrogen-bonding effect operates in water-induced rate enhancements of 1,3-dipolar cycloaddition reactions with water-super dipolarophiles as well as the hydrophobic effect. The hydrogen-bonding effect involves secondary bridging hydrogen bonding from the primary water-solvation shell of the transition state and the growth of structured water clusters. Theoretical calculations strongly support these conclusions.

Developing an understanding of organic reactions in water has become a field of intense study^{1–7} since Breslow first pointed out the water enhancement of the Diels–Alder reaction. In the area of cycloaddition reactions this work has focused mainly on the Diels–Alder reaction.^{4–6} Extensive kinetic measurements on the rates of Diels–Alder reactions in water relative to organic solvents have been reported, and these have given rise to increasing knowledge of the hydrophobic effect of water in organic reactions.¹ Studies of the *comparative* rates of 1,3-dipolar cycloaddition reactions in water and organic solvents have not attracted the same level of attention. Most studies have focused on reactions of transient nitrile oxides^{8–10}

and nitrilimines¹¹ generated in aqueous environments. In particular there are few reports of rate measurements on 1,3-dipolar cycloadditions in water–organic mixtures. Recently we have noted¹² that introduction of water as cosolvent into cycloaddition reactions of the 1,3-dipoles **1** and **2** in acetonitrile gave small initial rate enhancements followed by remarkable exponential rates increases as the solvent mixture approached pure water. We classified dipolarophiles into water-super and water-normal on the basis of the magnitude of their rate response to water.¹² The experimental difference between water-super and water-normal dipolarophiles is shown in Figure 1. A ketone C=O conjugated to an alkene or alkyne is a water-super dipolarophile. Esters, ethers, sulfones, nitriles, and aryl rings conjugated to an alkene are water-normal dipolarophiles.¹² All show late exponential rate rises, but the effect is much smaller for water-normal cases. Similar exponential rate plots have been reported in the cycloaddition of CN-diphenylnitron with dibutylfumarate.¹³ Herein we explore the factors which influence the shape of these plots, using the 1,3-dipole **2** and the dipolarophiles ethyl vinyl ketone (EVK) and methyl acrylate (MA) as representative examples of water-super and water-

[†] National University of Ireland.

[‡] Rutgers University.

- (1) (a) A review: Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159–164. (b) Biscoe, M. R.; Breslow, R. *J. Am. Chem. Soc.* **2003**, *125*, 12718–12719.
- (2) A review: Engberts, J. B. F. N.; Blandamer, M. J. *Chem. Commun.* **2001**, 1701–1708.
- (3) Breslow, R.; Rideout, D. *J. Am. Chem. Soc.* **1980**, *102*, 7816–7817.
- (4) (a) Otto, S.; Engberts, J. B. F. N. *Pure Appl. Chem.* **2000**, *72*, 1365–1372. (b) Otto, S.; Engberts, J. B. F. N. *Org. Biomol. Chem.* **2003**, *1*, 2809–2820.
- (5) Engberts, J. B. F. N. *Pure Appl. Chem.* **1995**, *67*, 823–828.
- (6) Garner, P. P. In *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic & Professional: London, 1998; pp 1–46.
- (7) Cave, G. W. V.; Raston, C. L.; Scott, J. L. *Chem. Commun.* **2001**, 2159–2169.
- (8) van Mersbergen, D.; Wijnen, J. W.; Engberts, J. B. F. N. *J. Org. Chem.* **1998**, *63*, 8801–8805.
- (9) Inoue, Y.; Araki, K.; Shiraishi, S. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3079–3083.
- (10) Dignam, J. J.; Hegarty, A. F.; Quain, P. L. *J. Org. Chem.* **1978**, *43*, 388–393.

- (11) (a) Molteni, G.; Orlandi, M.; Brogini, G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3742–3745. (b) Ponti, A.; Molteni, G. *New J. Chem.* **2002**, *26*, 1346–1351. (c) Molteni, G.; Ponti, A.; Orlandi, M. *New J. Chem.* **2002**, *26*, 1340–1345.
- (12) Butler, R. N.; Coyne, A. G.; Cunningham, W. J.; Burke, L. A. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1807–1815.
- (13) Gholami, M. R.; Yangjeh, A. H. *J. Chem. Res.(S)* **1999**, 226–227.

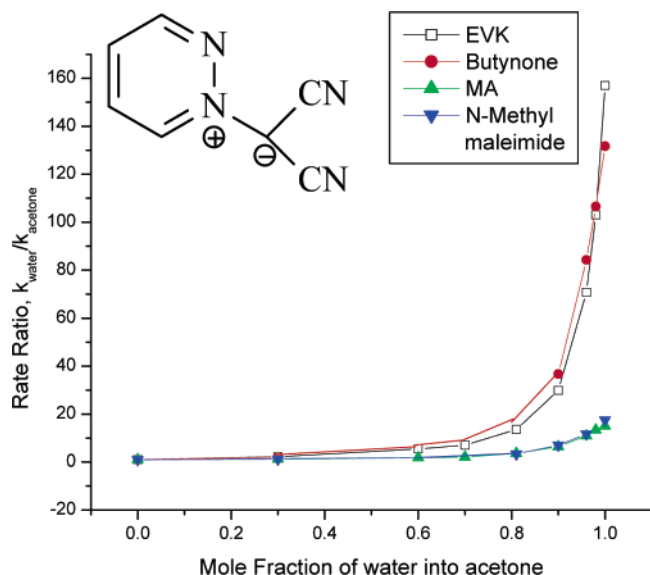
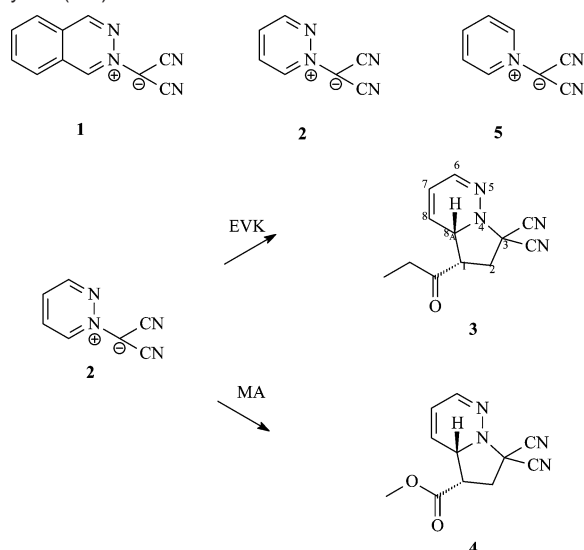


Figure 1. Kinetic distinctions between water-super and water-normal dipolarophiles in cycloadditions with the 1,3-dipole **2** for increasing mole fraction of water in acetone.

Scheme 1. Reagents, (i) Ethyl Vinyl Ketone (EVK), (ii) Methyl Acrylate (MA)



normal dipolarophiles, respectively (see Scheme 1). The results herein have wider implications than for the reactions experimentally investigated.

Results and Discussion

Rate enhancements of cycloaddition reactions in water have been ascribed to three factors:^{1–8} (i) increased polarity of the transition state in water, (ii) the hydrophobic effect which aggregates organic reactants raising the energy of the ground state relative to the transition state, thereby lowering the activation energy, and (iii) special or enhanced hydrogen-bonding effects in the transition state.^{14–16} Our previous results¹²

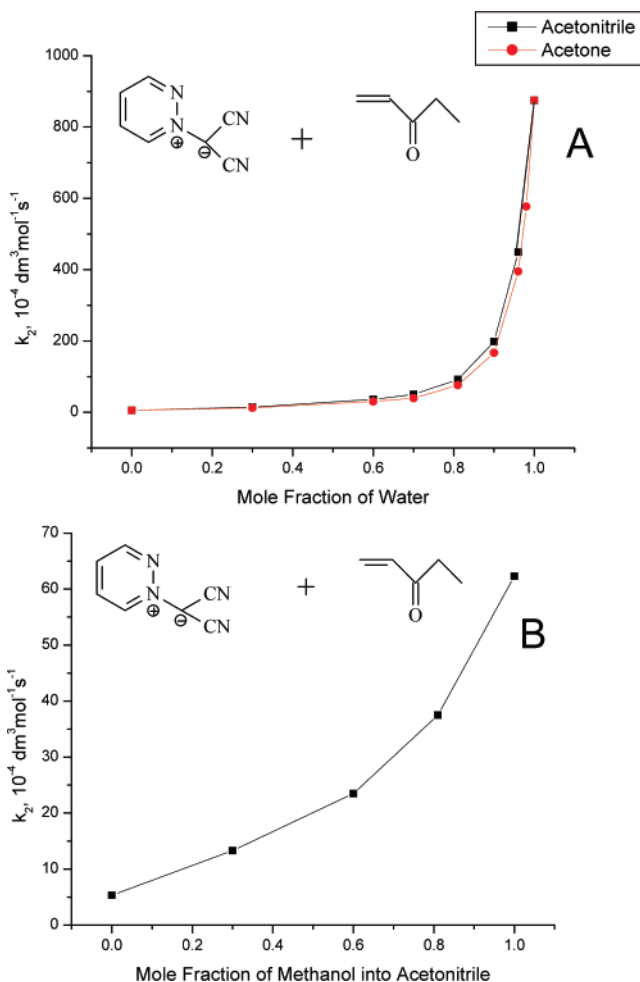


Figure 2. (A) Kinetic effect for the introduction of water to the reaction shown in acetonitrile (■) and acetone (●) at 37 °C; (B) introduction of methanol into acetonitrile at 37 °C.

on substituent and salt effects have indicated that the hydrophobic effect and special hydrogen-bonding effect are the main contributors to rate enhancements in water for the dipoles **1** and **2**. We have raised¹² the questions “why should such a rapid rate enhancement occur so late in the water addition?” and conversely “why should the presence of 0.1mol fraction of MeCN cause such a dramatic drop in the rate of a cycloaddition reaction?” The molecule **1** is not soluble in pure water, and we have now focused these questions on the 1,3-dipole **2** which is soluble.

Trigger Points. On plots such as Figure 1 and A in Figures 2 and 3 there are two significant points, (i) the trigger-point, where the exponential rate increase takes off, and (ii) the terminal point, i.e., the rate in pure water relative to the rate in the pure organic cosolvent (Table 1). The former has not been alluded to previously in the literature. The plots B in Figures 2 and 3 show the comparative influence of introducing MeOH instead of water into the reactions of the 1,3-dipole **2** with the dipolarophiles in the dipolar aprotic solvents acetone and acetonitrile at 37 °C. The rate increase is more gradual, and there is no trigger point. The terminal rate ratios at 37 °C for $k_{\text{MeOH}}/k_{\text{MeCN}}$ for the dipolarophile EVK, is 11.7 as against 164 for water. For the hydrogen-bonding (H-bonding) contribution to the rate enhancements these results suggest that primary H-bonding of solvent O–H groups to the transition state is rate

(14) (a) Blake, J. F.; Lim, D.; Jorgensen, W. L. *J. Org. Chem.* **1994**, *59*, 803–805. (b) Chandrasekhar, J.; Shariffskul, S.; Jorgensen, W. L. *J. Phys. Chem B* **2002**, *106*, 8078–8085.

(15) Furlani, T. R.; Gao, J. *J. Org. Chem.* **1996**, *61*, 5492–5497.

(16) Otto, S.; Blokzijl, W.; Engberts, J. B. F. *N. J. Org. Chem.* **1994**, *59*, 5372–5376.

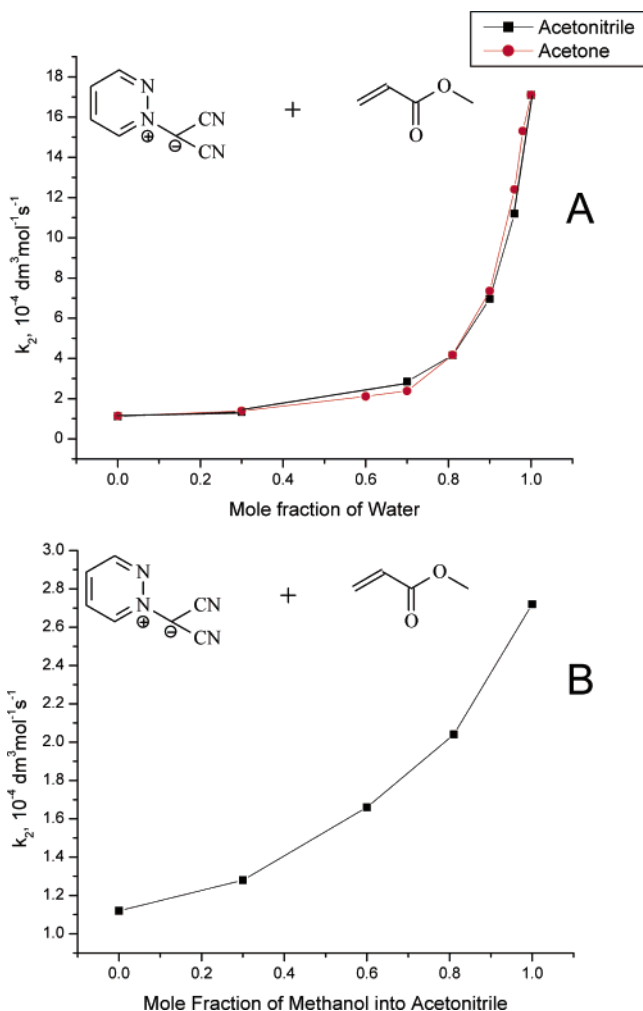


Figure 3. (A) Kinetic effect for the introduction of water to the reaction shown in acetonitrile (■) and acetone (●) at 37 °C; (B) introduction of methanol into acetonitrile at 37 °C.

Table 1. Rates in Pure Solvents for Cycloadditions of **2** with Ethyl Vinyl Ketone (EVK) and Methyl Acrylate (MA) at 37 °C

entry	solvent	EVK ^a k_2 $10^4 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	$k_{\text{water}}/k_{\text{solvent}}$	MA ^a k_2 $10^4 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	$k_{\text{water}}/k_{\text{solvent}}$
1	H ₂ O	875	-	17.1	-
2	MeCN	5.34	164 ^b	1.12	15.3 ^c
3	MeCOMe	5.58	157	1.14	14.9
4	MeOH	62.3	14.0	2.71	6.3
5	EtOH	55.0	15.9	3.07	5.6
6	^t BuOH	42.8	20.4	3.2	5.5

^a Rate constants are reproducible to $\pm 1.5\%$. ^b $k_{\text{water}}/k_{\text{MeCN}}$, (T °C), 207, (29); 118, (50); 82 (64) (Figure 6, line A). ^c $k_{\text{water}}/k_{\text{MeCN}}$ (T °C), 17.6 (29); 15.2 (50); 14.0 (64) (Figure 6, line B).

enhancing, but secondary bridging H-bonding from the first water molecules is necessary for the exponential rate increases. The influence of the alcoholic cosolvents on these curves is shown in Figures 4 and 5. Here water is progressively introduced into cycloaddition reactions of the dipole **2** carried out in methanol, ethanol, and *tert*-butyl alcohol. The terminal k values and solvent rate ratios are in Table 1. The influence of the structural features of the alcoholic solvents on the trigger points is highly significant. For the water-structure breaking molecule, *tert*-butyl alcohol, the trigger point for the exponential rate rise into pure water is pushed to the region of 0.95–0.97 mol fraction of water, much closer to pure water than for the more water-compatible

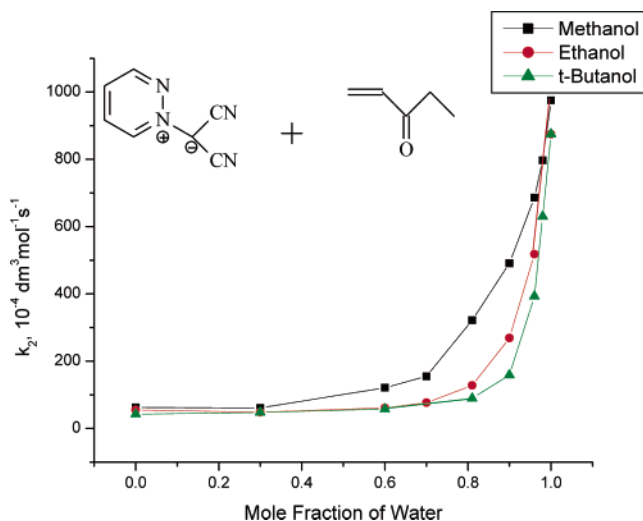


Figure 4. Kinetic effect for the introduction of water to the reaction in methanol (■), ethanol (●) and *tert*-butanol (▲) (EVK, water-super).

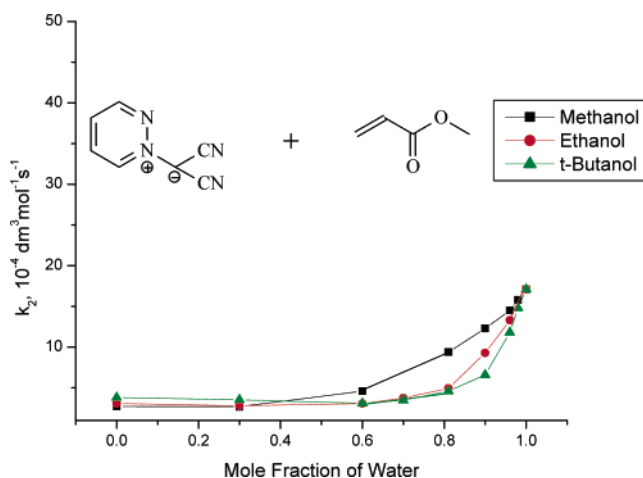


Figure 5. Kinetic effect for the introduction of water to the reaction in methanol (■), ethanol (●) and *tert*-butanol (▲) (MA, water-normal).

molecule MeOH. Conversely, a very small mole fraction of *t*-BuOH when introduced into water causes a dramatic reduction in the rate of the cycloaddition reaction. Like methanol, *tert*-butyl alcohol can participate in primary H-bonding to the transition state, but the steric size of the tertiary alcohol prevents the growth of water structure. The trigger point for the water-promoted exponential rate rise is then pushed toward pure water. These results suggest that the “special H-bonding effect” of water on these cycloaddition reactions includes an important component arising from the growth of water-structured clusters around the hydrophobic transition state. *tert*-Butanol among the alcohols is thus behaving like the dipolar aprotic solvents acetonitrile and acetone but possibly for different reasons. These highly structured dipolar aprotic solvents are H-bond acceptors and may compete with the transition state for water as well as exhibit structure-breaking effects, again pushing the trigger point toward pure water. The effects observed with both the hydroxylic and dipolar aprotic solvents emphasize the importance of water-structure growth around the transition state.

Temperature: Water-Super versus Water-Normal Dipolarophile Behavior. If, as indicated, the growth of structured water clusters around the transition state makes a major contribution to the water-induced exponential rate enhancement

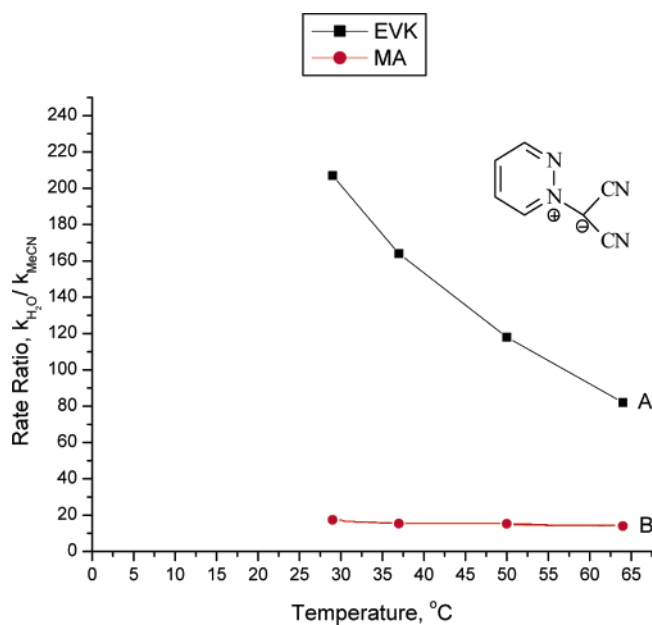


Figure 6. Comparative influence of temperature on the rate ratio k_{H_2O}/k_{MeCN} for EVK and MA.

of the cycloaddition reactions, then raising the temperature of the cycloaddition reaction should reduce the effect. In Figure 6 line A, we show the effect of temperature, in the range 29–64 °C, on the rate ratio k_{water}/k_{MeCN} for the cycloaddition reaction of the dipole **2** with EVK. The rate enhancement in pure water falls off dramatically as the temperature is raised because the rate-enhancing contribution of water-structure growth is considerably diminished. The effect of rising temperature is then to change EVK from a water-super dipolarophile toward water-normal behavior. The behavior of the water-normal dipolarophile methyl acrylate is effectively insensitive to temperature (Figure 6, line B), and k_{water}/k_{MeCN} is 15.3 at 37 °C and 14.0 at 64 °C. This illustrates a significant difference between water-super and water-normal dipolarophiles. For the former the formation of the primary hydrogen bonds at ambient temperatures begins a process where substantial water-structure growth develops around the transition state. Water-normal dipolarophiles do not allow this H-bonding network to develop, and the rate enhancements are much more modest. Extrapolation of the temperature effects shown in Figure 6 imply that the water-super dipolarophilic behavior of EVK would be significantly increased even further on cooling toward 0 °C. However, because of the falling rates of both reactions on such cooling, we could not measure accurate rate ratios at lower temperatures particularly since the reaction rate in acetonitrile became unmeasurable below 25 °C. The increased order of the transition state for the cycloaddition of the water-super dipolarophile relative to the water normal is also illustrated by the comparative Arrhenius data (Table 2). For EVK the ΔS_a value is $-181 \text{ J mol}^{-1} \text{ K}^{-1}$ in water as against -150 in MeCN.

Hydrophobic Rate Acceleration and Antihydrophobic Cosolvent Effects. Rate enhancements of Diels–Alder reactions and alkylation reactions in water have been explained in terms of the hydrophobic effect.^{1,2,17–19,20} Antihydrophobic cosolvent effects^{17,21–23} are viewed as the cause of the falls in rate as

(17) Breslow, R.; Groves, K.; Mayer, M. U. *J. Am. Chem. Soc.* **2002**, *124*, 3622–3635.

(18) Breslow, R.; Maitra, U. *Tetrahedron Lett.* **1984**, *25*, 1239–1240.

Table 2. Measured Arrhenius Data for Reactions of Dipole **2**

dipolarophile	solvent	$10^{-3} \frac{k_f}{\text{dm}^3 \text{mol}^{-1} \text{s}^{-1}} \frac{kJ}{(T/K)}$	$E_f / \text{kJ mol}^{-1}$	$\Delta H_f / \text{kJ mol}^{-1}$	$\Delta S_f / \text{J mol}^{-1} \text{K}^{-1}$
EVK	H ₂ O	177(337), 122(323), 87.5(310), 50.2(302)	28.9	26.2	−181
	CH ₃ CN	2.15(337), 1.03(323), 0.534(310), 0.242(302)	51.7	49.1	−150
MA	H ₂ O	7.99(337), 3.72(323), 1.71(310), 0.807(302)	55.1	52.4	−152
	CH ₃ CN	0.568(337), 0.244(323), 0.112(310), 0.0459(302)	59.8	57.2	−138

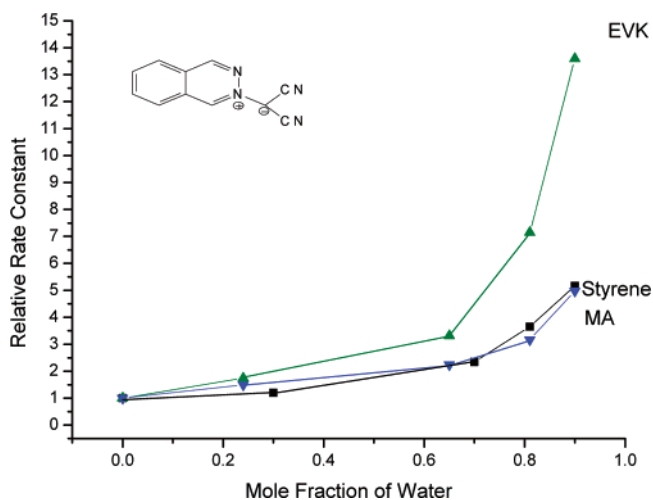


Figure 7. Comparative kinetic effect for the introduction of water, up to 0.9 mol fraction, for the cycloadditions of dipole **1** with EVK (▲), MA (▼), and styrene (■).

small quantities of organic cosolvents are introduced into water. Breslow^{1,24} has established the utility of added salts in diagnosing the presence of hydrophobic effects in organic reactions in water. We have previously shown¹² that added LiCl (a hydrophobic effect-enhancing salt) and guanidinium chloride (an antihydrophobic salt) displayed very similar effects on the rates of the reaction of the dipole **2** with methyl vinyl ketone and methyl acrylate in water. These dipolarophiles differ by only one oxygen atom. The salt effects suggest similar hydrophobic contributions to the water rate enhancements.¹² These cycloadditions have similar mechanisms with the same regiochemistry and endo stereochemistry, but the water rate enhancement, relative to MeCN, is 10 times greater for the vinyl ketone. Since both substrates have strong H-bonding acceptor sites, it is unlikely that the hydrophobic effect alone is producing such different responses. In such situations H-bonding contributions must participate as well as hydrophobic effects.¹⁵ A dipolarophile such as styrene has no strong H-bond acceptor sites (other than possible weak π interactions with water OH). Styrene is therefore a dipolarophile where the hydrophobic effect should be dominant. In Figure 7 we compare the influence of water up to 0.9 mol fraction on the reactions of the phthalazinium 1,3-dipole **1** with EVK, MA, and styrene. Styrene displays water-normal behavior, and it does not show a large exponential rate enhancement. For these reasons we believe the H-bonding

(19) Breslow, R.; Zhu, Z. *J. Am. Chem. Soc.* **1995**, *117*, 9923–9924.

(20) Blokzigi, W.; Blandamer, M. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1991**, *113*, 4241–4246.

(21) Breslow, R.; Zhu, Z. *J. Am. Chem. Soc.* **1995**, *117*, 9923–9924.

(22) Breslow, R.; Connors, R. V. *J. Am. Chem. Soc.* **1995**, *117*, 6601–6602.

(23) Breslow, R.; Connors, R. V. *J. Am. Chem. Soc.* **1996**, *118*, 6323–6324.

(24) Breslow, R.; Rizzo, C. J. *J. Am. Chem. Soc.* **1991**, *113*, 4340–4341.

structural contribution is the main cause for the difference between the water-super dipolarophile, such as alkyl vinyl ketones, and the water-normal cases.

Theoretical Calculations

The theoretical calculations lend support for water-structure development about the carbonyl group in EVK and MA in the cycloaddition transition state. We concentrated on the interactions of water clusters with the carbonyl group.

Calculations were carried out on the reactants and TS structures, each with 0, 4, or 6 water molecules in a cage-like cluster. The Gaussian03 suite of programs²⁵ was used with the B3LYP²⁶ DFT method and the 6-31G(d) basis set,²⁷ supplemented with frequency calculations to ascertain the correct number of imaginary frequencies for a given structure. All optimizations used analytical gradients with force constants calculated at every step (*calcall* option). Significant points were then reoptimized with the 6-311++G(d,p) basis set.

The results provide indications that activation energies are lowered with the presence of water clusters about the carbonyl O atoms and that they are significantly lowered for a ketone compared to those for an ester in the presence of a water cluster. Calculations were also performed for a carbonyl group with a MeCN molecule on one side and a 4-water cluster on the other.

In keeping with the practice of using shorter alkyl branch analogues, EVK is replaced in the calculations by methyl vinyl ketone, MVK. The computational study was expanded to include the 1,3 dipole, pyridinium-dicyanomethanide, **5**, as well as the pyridazinium-dicyanomethanide, **2**, used in the experiments. This is to detect if the ring nitrogen atom in **2**, which is located near the carbonyl in the TS structure, has a significant interaction with the water cluster. In the case of 0- and 4-waters, the TS structures for MVK and MA correspond to the four possible configurations in the cycloaddition products, i.e., with the substituted vinyl C atom joining to the ring C atom (giving the products **3** and **4**) or to the dicyanomethanide C atom. For TS structures, these positions are designated **r** for the former and **cn** for the latter. Each of these TS configurations can have two stereo orientations whereby the carbonyl is *endo* (as in **3** and **4**) or *exo*. The four configurations are designated **r-endo**, **r-exo**, **cn-endo**, and **cn-exo**. The **r-endo** configuration is pictured in the products **3** and **4**. The optimizations started with a dihedral angle of nearly 0° between the C=C and the C=O groups for

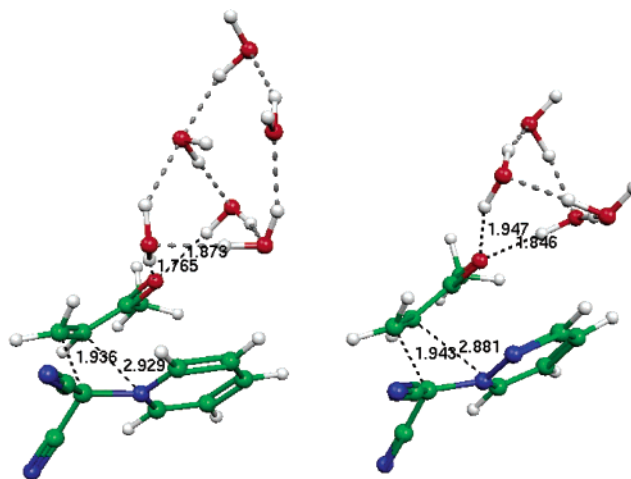


Figure 8. Rendering of the TS structure of MVK-5 with a 6-water cluster (on left) and a 4-water cluster on of MVK-2. Bond distances in Å.

the reactant dipolarophile and TS structures, as in our previous study.¹² As in other Diels–Alder reactions with carbonyl substituents on dienophiles, it was found in every case that the carbonyl group is preferred in a position over the ring and *endo*, i.e., **r-endo**. As this **r-endo** position is favored in the 0- and 4-water cluster case, it was the only one used in subsequent calculations with the larger basis set and in the calculations involving six waters (Figure 8).²⁸

Table 3 gives the calculated activation energies in kJ mol^{-1} and entropies in $\text{J mol}^{-1} \text{K}^{-1}$ for the various reactions studied here. Comparisons with the measured values from Table 2 are in the footnotes. Structures with two waters were calculated, but the four different positions of the dipolarophile gave different types of H-bonding between the reactants during the geometry optimizations. Structures were found with either one or two of the H atoms of the waters bonded to the carbonyl and the dipole, thus skewing the results for different **endo-exo** and **r** or **cn** positions of the carbonyls. Care was taken that the same positioning of the water cluster hydrogens was used in the reactants and the TS. The 4-water cages remained intact about the carbonyls, but the 6-water cages during the optimization procedure for MA-2 and MA-5 moved away from the C=O and remained as an intact unit situated over the dipolarophile. The 6-water unit remained attached in front of the carbonyl by two H-bonds with MVK-2 and MVK-5. This suggests a weaker interaction between the cluster in the TS structures involving the water-normal MA compared to that for water-super MVK.

There is a significant lowering of the activation energies with all of the 4-water clusters and with the MVK 6-water clusters compared with the values for 0-water (Table 3). The lowering with MVK is by 30.5 kJ mol^{-1} for dipole **2** and 40.0 kJ mol^{-1} for **5**. The lowering with MA is not as significant, 22.4 kJ mol^{-1} (for **2**) and 26.9 kJ mol^{-1} (for **5**). The pairs of values for **2** and **5** indicate that the presence of the second N atom in the pyridazinium ring versus the CH group in the pyridinium ring has little influence on the comparative MVK–MA activation energies or on the stabilization of the cluster. Increasing the

(25) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, 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, J.; 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. 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.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision A.1; Gaussian, Inc., Pittsburgh, PA, 2003.

(26) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev.* **1988**, *B37*, 785–789. (c) Miehlich, B.; Savin, A.; Stoll, H.; Preuss, H. *Chem. Phys. Lett.* **1989**, *157*, 200–206.

(27) (a) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257–2261. (b) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213–222.

(28) Flükiger, P.; Lüthi, H. P.; Portmann, S.; Weber, J. *MOLEKEL*, 4.3; Swiss Center for Scientific Computing: Manno, Switzerland, 2000–2002. Portmann, S.; Lüthi, H. P. *MOLEKEL: An Interactive Molecular Graphics Tool. CHIMIA* **2000**, *54*, 766–770.

Table 3. Activation Energies E_a , Entropies ΔS_a (298 K), and Free Energies ΔG_a (298 K) Calculated with the B3LYP/6-31G(d) Method^a

cluster	configuration	MVK-2			MVK-5			MA-2			MA-5		
		E_a	ΔS_a	ΔG_a	E_a	ΔS_a	ΔG_a	E_a	ΔS_a	ΔG_a	E_a	ΔS_a	ΔG_a
0 water	r-endo	66.0 ^b	-192.2 ^b	125.8	69.8	-183.1	127.0	70.7 ^d	-192.6 ^d	130.4	75.3	-186.4	133.0
(0 water)	(r-endo)	70.8 ^b	-194.1 ^b	132.4	73.4	-188.3	132.2	78.9 ^d	-193.7 ^d	137.2	83.1	-187.1	140.9
0 water	r-exo	71.1	-188.9	130.4	73.9	-184.3	131.7	74.2	-187.3	132.6	78.6	-182.2	135.2
0 water	cn-endo	71.2	-197.0	133.6	74.8	-193.0	135.7	111.8	-196.0	172.7	114.4	-191.5	173.6
0 water	cn-exo	72.2	-187.7	131.2	78.9	-192.4	131.7	76.5	-192.1	136.7	82.9	-187.2	141.3
4 water	r-endo	35.5 ^c	-225.0 ^c	103.5	29.8	-220.4	99.0	48.3 ^e	-230.3 ^e	118.5	48.4	-218.3	115.4
(4 water)	(r-endo)	44.5 ^c	x	x	x	x	x	62.0 ^e	x	x	x	x	x
4 water	r-exo	46.5	-224.8	116.7	46.2	-220.9	115.4	73.2	-194.4	133.2	74.2	-195.9	134.9
4 water	cn-endo	54.2	-221.4	123.8	57.9	-217.0	125.5	92.7	-222.6	161.8	95.9	-213.8	160.8
4 water	cn-exo	56.4	-198.0	118.0	65.0	-192.3	124.4	59.9	-209.5	124.4	68.4	-201.8	130.0
4 water, MeCN	r-endo	60.1 ^b	-197.8 ^b	122.2	x	x	x	64.5 ^d	-202.6 ^d	125.2	x	x	x
6 water	r-endo	41.1 ^c	-220.8 ^c	113.9	31.2	-222.4	104.4	xx	xx	xx	xx	xx	xx

^a The results for 6-311++G(d,p) are in the rows indicated by the cluster and configuration in parentheses. Energies in kJ mol^{-1} and entropies in $\text{J mol}^{-1} \text{K}^{-1}$. Entries marked x are for cases not calculated, xx for cases where the 6-water cluster disengaged from the TS C=O group. ^b Experimental values, E_a 51.7; ΔS_a -150, for EVK/MeCN (Table 2). ^c Experimental values, E_a 28.9; ΔS_a -181, for EVK/H₂O (Table 2). ^d Experimental values, E_a 59.8; ΔS_a -138, for MA/MeCN (Table 2). ^e Experimental values, E_a 55.1; ΔS_a -152, for MA/H₂O (Table 2).

basis set increases the activation energies uniformly. The activation free energies ΔG_a and activation entropies ΔS_a were calculated for 298.15 K. The difference in values between the E_a and ΔG_a reflect the large negative values of the activation entropies ΔS_a .

There is a trend in the calculated ΔS_a that is reflected in the experimental results. In all **r-endo** cases, the 4- and 6-water clusters show calculated ΔS_a values between -220 and -230 $\text{J mol}^{-1} \text{K}^{-1}$, while the **r-endo** 0-water cases are between -183 and -192 $\text{J mol}^{-1} \text{K}^{-1}$. This trend extends to any particular configuration whereby the 4-water cluster cases are more negative in ΔS_a than the 0-water cluster. In particular, the **r-endo** cases for both MVK and MA with **2** or **5**, the difference is ca. 20–30 $\text{J mol}^{-1} \text{K}^{-1}$ between the 4- and 6-water cases and the 0-water cases. At this level of theory it is not possible to distinguish between calculated transition-state entropies for cycloadditions with MVK and MA as does experiment; nevertheless, the calculated ΔS_a values do indicate a greater participation of the water cluster around the C=O group in the TS than in the reactant.

The geometries of MVK and MA were optimized along with one MeCN. The most favorable position detected was with the CN parallel to the C=O, whereby the Me end is loosely bonded to the carbonyl by a CH bond²⁹ and the N lone pair is interacting with the Me group in MVK and MA. These structures were then reoptimized with a 4-water cluster on the other side of the carbonyl. Activation energies were then calculated using these 4-water structures and **2** (Figure 9).²⁸ The E_a is raised (Table 3) for the 4-water–MeCN cluster and MVK (60.1 kJ mol^{-1}) nearly to the 0-water case (66.0) from the 4-water cluster case (35.5). The E_a is raised +24.5 kJ mol^{-1} upon adding MeCN to the 4-water cluster. This can be compared to the experimental raising of 28.9 (in H₂O) to 51.7 kJ mol^{-1} (MeCN) for MVK-**2** (Table 2) or +22.8 kJ mol^{-1} . For MA, the calculated barrier is raised less with the addition of MeCN to the 4-water cluster, from 48.3 to 64.5 kJ mol^{-1} (Table 3) or +16.2 kJ mol^{-1} , compared to +4.7 kJ mol^{-1} experimentally (Table 2). Hence, the disruptive presence of one MeCN molecule is consistent with the exponential nature of the water rate-enhancement plots of Figures 1–5.

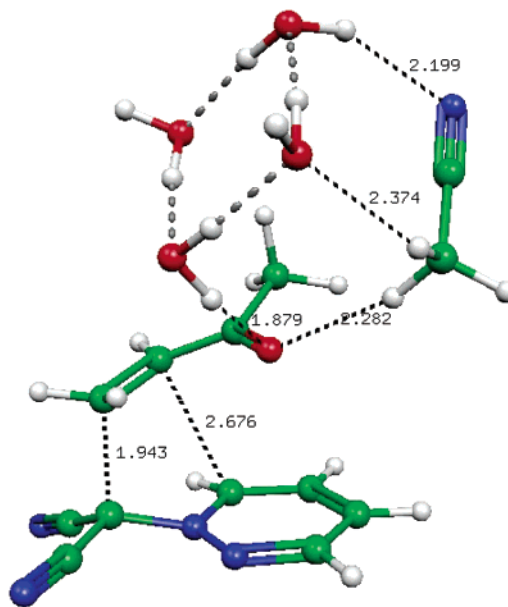


Figure 9. Rendering of the TS structure of MVK-**2** with a 4-water cluster and MeCN. The CN group is skewed to the C=O group and is H-bonded to the water cluster. Its Me end is H-bonded to the carbonyl. Bond distances in Å.

Overall, the results of the theoretical calculations support the implication from the experimental results that there is a large rate enhancement brought on by the participation of H-bonded clusters on the carbonyls. The E_a for 4-water–MeCN clusters give indications that this enhancement is different in magnitude for ketones and esters. A fuller explanation remains for the question about the differential solvation or aggregation of polar “aprotic” solvent molecules with carbonyls and other functional groups in the presence of water molecules. This question has even made its way into protein folding studies.²⁹

Experimental Section

Reagents and Solvents. The pyridazinium dicyanomethanide 1,3-dipole **2** (mp 208–210 °C) was prepared by procedures previously described^{12,30} and was recrystallized twice before use. Ethyl vinyl ketone (Aldrich, 97%) and methyl acrylate (Aldrich, 99%) were distilled before

(29) (a) Vargas, R.; Garza, J.; Dixon, D. A.; Hay, B. P. *J. Am. Chem. Soc.* **2000**, *122*, 4750–4755. (b) Domingo, L. R.; Andres, J. J. *Org. Chem.* **2003**, *68*, 8662–8668.

(30) Butler, R. N.; Farrell, D. M.; Pyne, C. S. *J. Chem. Res. (S)* **1996**, 418–419.

use. Acetonitrile, *tert*-butyl alcohol, and methanol were of spectrophotometric grade (Aldrich, >99.9%) and styrene (Aldrich, 99+%, 10–15 ppm stabiliser) were used without further purification. Acetone and ethanol were purified and dried according to standard procedures.³¹ Water was of Millipore grade.

Kinetic Measurements. The rate constants were measured by recording the disappearance of the pyridazinium dicyanomethanide dipole **2** at the maximum wavelength (λ_{max} , 413–429 nm in the solvent mixture under study). Spectra were measured using a Hewlett-Packard Agilent Technologies 8453 UV–vis spectrophotometer featuring an automatic changer for up to eight glass cuvettes of path length 1 cm. The temperature (± 0.2 °C) was maintained by means of a thermostat (Haake DC10)-controlled water bath, with a separate calibrated thermometer check. The reaction was monitored using pseudo-first-order conditions. The initial concentration of 1,3-dipole **2** was 3.2×10^{-5} M, and the dipolarophile concentrations were in excesses ranging from 600 to 30000-fold. Kinetic runs were performed at three different concentrations of dipolarophiles and repeated a minimum of three times. The length of time for the reaction ranged from 6 to 30 h, depending on the dipolarophile and conditions. The solution changed from yellow to colorless as the reaction progressed.

Typical Kinetic Run. First, 2 cm³ of the dipole solution was placed in a tightly capped cuvette of path length 1 cm and left to equilibrate to the temperature for 10 min. The dipolarophile solution (1 cm³) was added, the mixture was shaken and allowed to equilibrate, and the absorbance (*A*) measured. A plot of $\ln(A_t - A_\infty)$ versus time for more than 4 half-lives, gave a line whose slope was the pseudo-first-order rate constant. These lines typically gave *r* values of ≥ 0.999 . Plots of the pseudo-first-order rate constants versus the molarity of the dipolarophile, gave lines ($r \geq 0.995$) with slopes which were the second-order rate constants quoted. All second-order rate constants were measured at least three times and were reproducible to $\pm 1.5\%$.

(31) Vogel, A. I. In *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Furniss, B. S., Hannaford, A. J., Smith, P. W., Tatchell, A. R., Eds.; Prentice Hall: Harlow, UK, 1989; pp 400–402, pp 407–408.

Products

Synthetic procedures previously outlined¹² gave the products **3** and **4** from reactions in water and acetonitrile. The minor *exo* isomer was also present in the product solution, and the *endo/exo* ratio was determined by direct NMR analysis prior to workup. ¹H assignments were supported by NOE difference spectra, and ¹³C assignments were supported by DEPT spectra.

Compound 3: clear crystals (92% in water; 86% in acetonitrile). Mp = 110–112 °C. IR (Nujol mull, cm⁻¹) 2253 (C≡N), 1712 (C=O). ¹H NMR (400 MHz, CDCl₃) 1.09–1.12 (t, 3H, *J* = 7 Hz, CH₃), 2.54–2.61 (m, 2H, CH₂), 2.76–2.81 (dd, 1H, *J*_{gem} = 13.9, *J* = 8.8 Hz, H-2 *endo*), 3.02 (dd, 1H, *J*_{gem} = 13.9, *J* = 4.4 Hz, H-2 *exo*), 3.43–3.48 (m, 1H, H-1), 4.26 (d, 1H, *J* = 7.3, H-8a), 5.97 (d, 1H, *J* = 9.7, H-8), 6.12 (d, 1H, *J* = 9.7 Hz, H-7), 7.16 (s, 1H, H-6). ¹³C NMR (400 MHz, CDCl₃) 7.3 (CH₃), 37.0 (CH₂), 37.4 (C-2), 47.6 (C-1), 54.1 (C-3), 55.7 (C-8a), 113.0 (CN), 113.3 (CN), 120.3 (C-7), 127.9 (C-8), 142.4 (C-6), 207.4 (C=O). Anal. Calcd for C₁₂H₁₂N₄O: C, 63.2; H, 5.3; N, 24.6. Found C, 63.4; H, 4.9; N, 25.0; *endo/exo* = 12:1 (MeCN), 22:1 (water).

Compound 4: a brown oil (94% in water; 86% in acetonitrile). IR (Nujol mull, cm⁻¹) 2255 (C≡N), 1738 (C=O). ¹H NMR (400 MHz, CDCl₃) 2.82–2.88 (dd, 1H, *J*_{gem} = 14.1, *J* = 8.3 Hz, H-2 *endo*), 3.22–3.26 (dd, 1H, *J*_{gem} = 14.1, *J* = 2.9 Hz, H-2 *exo*), 3.31–3.36 (m, 1H, H-1), 3.76 (s, 3H, OCH₃), 4.23 (d, 1H, *J* = 7.3 Hz, H-8a), 5.96 (d, *J* = 10.2 Hz, H-7), 6.28 (d, 1H, *J* = 10.2 Hz, H-8), 7.16 (s, 1H, H-6). ¹³C NMR (400 MHz, CDCl₃) 37.1 (C-2), 41.6 (C-1), 52.2 (OCH₃), 53.0 (C-3), 55.8 (C-8a), 113.2 (CN), 133.3 (CN) 119.3 (C-7), 128.4 (C-8), 142.6 (C-6), 170.2 (C=O); *endo/exo* = 12:1 (MeCN), 1:0 (water).

JA040119Y