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Kinetic and synthetic influences of water and solvent-free conditions on 1,3-dipolar cycloaddition reactions: the phthalazinium and pyridazinium dicyanomethanide 1,3-dipoles: surprisingly successful synthetic methods†

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The influence of water on the kinetic and synthetic 1,3-dipolar cycloaddition reactions of phthalazinium-2-dicyanomethanide **1**, and pyridazinium dicyanomethanide **2**, with a wide range of dipolarophiles is reported. Water enhanced the rates of all reactions. The dipolarophiles were classified into two groups, water-normal and water-super. The former displayed rate enhancements of <20 times and the latter gave rate enhancements of >45 times, but more often some hundred times, on changing the solvent from acetonitrile to water. A ketone C=O conjugated to an alkene or alkyne constitutes a water-super dipolarophile. Esters, ethers, sulfones, nitriles and aryl rings conjugated to an alkene are water-normal dipolarophiles. The causes of these water effects are explored experimentally and with high level DFT. Hydrophobic effects and special hydrogen bonding interactions are the main factors involved. Synthetic implications are examined. Despite insolubility of the reactants in water successful high-yield reactions were achieved in water and under solvent-free conditions.

Since the early work of Breslow[1,2] on the influence of water on the Diels–Alder reaction there has been growing interest in the use of aqueous media for organic chemical synthesis. In recent years this has been immensely amplified by environmental and cost considerations.[3] Developing an understanding of organic reactions in water has become a field of intense study.[3–6] In the area of cycloaddition reactions much of this work[4,5] has focused on the Diels–Alder reaction. The economic factors mentioned have also promoted studies of organic synthesis under solvent free conditions.[7] One of the main factors influencing organic reactions in aqueous environments is the hydrophobic effect, the tendency of nonpolar species to aggregate in water.[2] Since the ultimate hydrophobic effect should be to push the organic reactants out of the medium entirely a comparison of solvent-free conditions with the water environment seems a natural progression. In the present work we have examined the influence of aqueous and solvent free conditions on the cycloaddition reactions of the 1,3-dipole, phthalazinium dicyanomethanide **1** and for comparison purposes the pyridazinium analogue **2**. We have previously reported a detailed kinetic-mechanistic study[8] and a synthetic-regiochemical and stereochemical study[9] of the dipole **1** with a wide range of alkene and alkyne dipolarophiles (Scheme 1). The 1,3-dipole **1** is a Sustmann type-II species,[10,11] (a normal or inverse demand 1,3-dipole) which may react *via* dipole HOMO-control or dipole LUMO-control depending on the dipolarophile which it encounters.

In contrast with the Diels–Alder reaction relatively little has been reported on the comparison between 1,3-dipolar cycloadditions in organic, aqueous and solvent-free environments. Cycloadditions of aromatic nitrile oxides in aqueous solutions[12–14] have received the most attention. Reactions of some nitrilimines in aqueous media have been reported[15] and water significantly increased the rates of cycloadditions of *C*,*N*-diphenylnitrone with dibutyl fumarate.[16] The influence of water on the cycloaddition reactions of iminium methanide 1,3-dipoles such as **1**, or on systems where the 1,3-dipole is embedded in an azine ring such as **1** and **2**, has not been reported to date. Since organic reactions of the type described herein are normally carried out in organic solvents the results obtained have wider implications than for the specific substrates used. They suggest that many organic synthetic reactions involving *water-insoluble* substrates may be successful both in water as solvent or under solvent-free conditions and that these types of conditions should be explored.

Results and discussion

(i) Kinetic effects

The influence of progressive introduction of water on the rates (measured by UV spectroscopy, Experimental) of the reactions of the dipoles **1** and **2** with a range of dipolarophiles in acetonitrile at 37 °C is shown in Table 1 and Fig. 1. Enhancement of the rates is observed in all cases. The experimental plots in Fig. 1 terminate at *ca.* 0.9 mol fraction of water for dipole **1** due to insolubility of the dipole which prevented further UV rate measurements. However we can expect a continuous extension of the plots to pure water. This was confirmed by removal of the benzeno moiety from the substrate **1**, thus using the pyridazine dicyanomethanide 1,3-dipole **2** which is soluble in water. This gave comparable plots up to 0.9 mol fraction of water and the plots extended in a continuous manner into pure water (Fig. 1, inset). Substrates of type **2** have been rationalised by Sauer *et al.*[17] to operate under dipole-LUMO control. Compound **2** is a close analogue of the dipole **1** and it responds similarly to the introduction of water to the medium. Based on the rate enhancements in water the dipolarophiles may be classified into two groups, water-normal and water-super dipolarophiles. For the dipoles **1** and **2** the former show rate

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† Electronic supplementary information (ESI) available: sample kinetic graphs and optimised transition state structures. See http://www.rsc.org/suppdata/p2/b2/b206028k/

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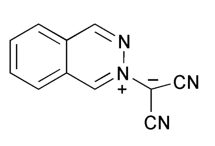

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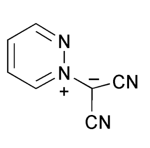

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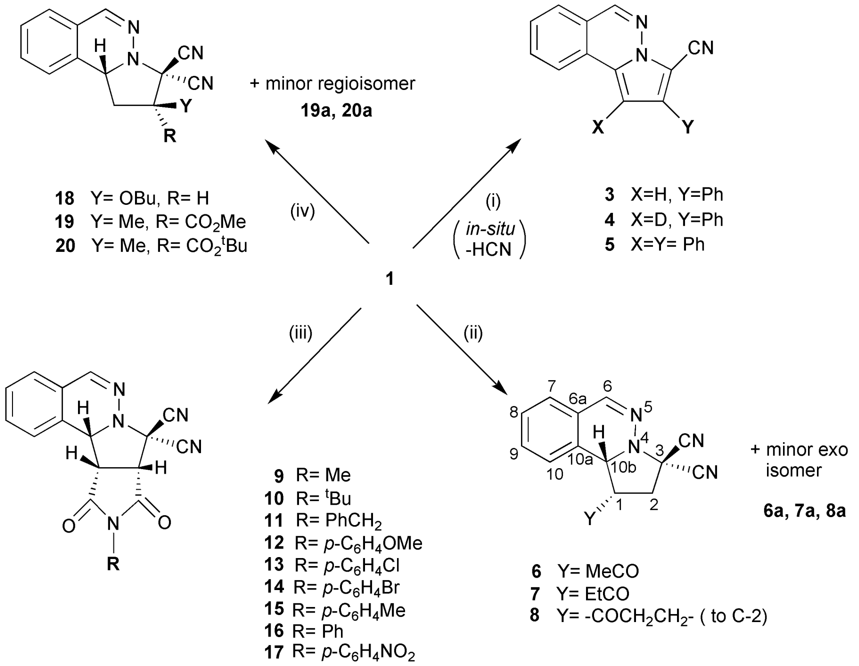

Scheme 1 Dipolarophiles; (i) X–C≡C–Y (ii) $YCH{=}CH_2$ (iii) *N*-(substituted) maleimides (iv) $Y{-}CR{=}CH_2$.

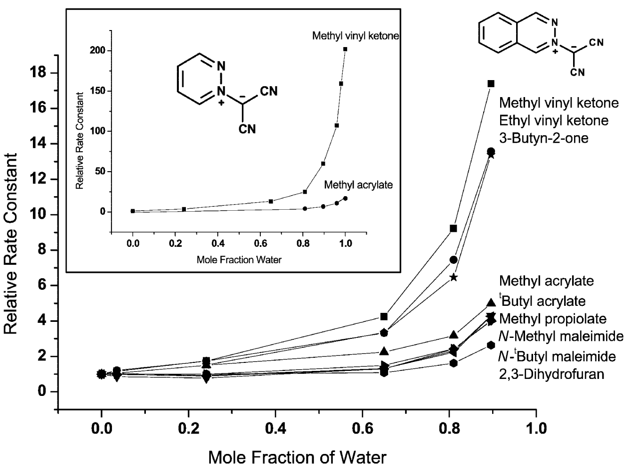

Fig. 1 Relative rate constants for a range of dipolarophiles and dipole **1** in various mol fractions of water in acetonitrile at 37 °C. Inlaid graph of dipole **2** in various mol fractions of water in acetonitrile at 37 °C.

enhancements of <20 times while the water-super group show rate enhancements of >45 times on changing the solvent from acetonitrile to water (Table 1). For example the reactions of methyl vinyl ketone, ethyl vinyl ketone and but-3-yn-2-one with the substrate **2** display rate enhancements of 202, 161 and 156 times respectively on changing from MeCN to H_2O (Table 1, entries 26–28). The result for methyl vinyl ketone parallels its behaviour in the Diels–Alder reaction with cyclopentadiene where the reaction rate is 730 times faster in water than in isooctane.[2]

Arrhenius activation data for a number of dipolarophiles (Table 2) show the expected decrease in ΔE_{act}, with that for the water-super dipolarophile methyl vinyl ketone being significantly greater than for the water-normal cases. The ΔS_{act} values are of interest. They suggest that the transition state for methyl vinyl ketone may be significantly more ordered than for the other cases since ΔS_{act} changes from −123 to −164 J mol^{-1} K^{-1} on changing the solvent from MeCN to 0.8 mol fraction of H_2O in MeCN. The corresponding decrease in ΔS_{act} is less than half for the water-normal cases. In future work we hope to identify further the structural parameters which distinguish the two groups. At present it is clear that a ketone, C=O, conjugated to an alkene or alkyne constitutes a water-super dipolarophile but an ester similarly conjugated is water normal (Table 1). Vinyl groups conjugated to ethers, sulfones, nitriles or aryl rings are also water-normal with these 1,3-dipoles (Table 1, entries 10–15). Also of significance from Fig. 1 is the almost exponential rise in the rates with water-super dipolarophiles for the last 10% of the change to pure water. This prompted us to explore synthetic reactions in water (below) despite the extreme insolubility of the substrates in water.

Rate enhancements of Diels–Alder reactions in water have been ascribed to three factors,[1–6] (i) hydrophobic effects, which aggregate the organic reactants, raising the energy of the ground state relative to the transition state and lowering the activation energy; (ii) a lowering of the activation energy by special hydrogen bonding in the transition state and (iii) an increase in the polarity for the cycloaddition transition state in water relative to that in organic solvents and consequent increased solvation stabilisation of the transition state by water. We have previously shown[8] that the cycloaddition reactions of the 1,3-dipole **1** with alkene and alkyne dipolarophiles in acetonitrile are concerted orbital controlled reactions with non-polar transition states which are highly insensitive to solvent polarity E_T values. Fig. 2 (Table 1, entries 18–25) shows Hammett plots for *N*-(*p*-substituted phenyl) maleimides in acetonitrile and water–acetonitrile (mol fraction 0.9 : 0.1). The small positive ρ values are unchanged and close to zero in both media indicating that there is no increase in the polarity of the transition state. Hence, we believe that the hydrophobic effect and hydrogen bonding effects are the main causes of the water

Table 1 Comparative kinetic data in acetonitrile, water and aqueous acetonitrile mixtures

Part (I)

Phthalazinium-2-dicyanomethanide **1** $k_2/10^{-3}$ dm^3 mol^{-1} s^{-1} at 37 °C

Entry	Dipolarophile	k_2 CH_3CN	k_2 H_2O–CH_3CN[a] 0.9 : 0.1	k_2 H_2O[b]	k_2 ratio[c]	k_2 ratio[d]
	Water super-dipolarophiles					
1	Methyl vinyl ketone (MVK)	62.0	1079	(3645)[b]	17.4	59
2	Ethyl vinyl ketone	76.9	1044	(3518)	13.6	45
3	But-3-yn-2-one	61.8	827	(2786)	13.4	45
4	1,4-Naphthoquinone	5.8	127.0	(428)	22.0	74
5	Cyclopent-2-en-1-one	0.55	15.3	(51.5)	27.8	94
6	Cyclohex-2-en-1-one	0.13	1.65	(5.55)	12.7	43
	Water normal-dipolarophiles					
7	Methyl acrylate (MAC)	37.7	187.9	(475)	4.9	12
8	*tert*-Butyl acrylate	19.1	82.2	(209)	4.3	11
9	Methyl propiolate	31.8	83.7	(213)	2.6	7
10	2,3-Dihydrofuran (DHF)	2.07	8.25	(21.0)	4.0	10
11	Acrylonitrile (ACN)	6.3	14.4	(36.7)	2.3	6
12	Phenyl vinyl sulfone	12.2	44.2	(112)	3.6	9
13	Methyl vinyl sulfone	5.37	9.90	(25.0)	1.8	5
14	Styrene (STY)	2.45	15.1	(38.5)	6.1	15
15	Isoprene	1.90	3.97	(10.0)	2.1	5
16	*N*-Methyl maleimide	317.7	1279	(3261)	4.0	10
17	*N*-*tert*-Butyl maleimide	202.5	864.4	(2204)	4.3	11
18	*N*-(*p*-Methoxyphenyl) maleimide	499	2140	(5457)	4.2	11
19	*N*-(*p*-Tolyl) maleimide	—	2161	—	—	—
20	*N*-(*p*-Ethylphenyl) maleimide	488	2248	(5732)	4.6	12
21	*N*-Phenyl maleimide	506	2225	(5673)	4.4	11
22	*N*-(*p*-Chlorophenyl) maleimide	568	2319	(5913)	4.1	11
23	*N*-(*p*-Bromophenyl) maleimide	—	2366	—	—	—
24	*N*-(*p*-Acetylphenyl) maleimide	—	2505	—	—	—
25	*N*-(*p*-Nitrophenyl) maleimide	650	2600	(6630)	4.0	10

Part (II)

Pyridazinium dicyanomethanide **2** $k_2/10^{-3}$ dm^3 mol^{-1} s^{-1} at 37 °C

Entry	Dipolarophile	k_2 CH_3CN	k_2 H_2O	k_2 Ratio[e]
	Water super-dipolarophiles			
26	Methyl vinyl ketone	0.464	93.6	202
27	Ethyl vinyl ketone	0.514	82.5	161
28	But-3-yn-2-one	0.243	37.9	156
	Water normal-dipolarophiles			
29	Methyl acrylate	0.106	1.76	16.6
30	Methyl propiolate	0.050	0.636	12.7

[a] Mol fraction. [b] Values in parentheses represent extrapolations to water using the measured change for the corresponding dipolarophile with dipole **2** over the same range. [c] Measured k_2 in H_2O–CH_3CN (0.9 : 0.1)/k_2 in CH_3CN. [d] Extrapolated k_2 in H_2O/k_2 in CH_3CN. [e] Measured k_2 in H_2O/k_2 in CH_3CN.

Table 2 Arrhenius data for reactions for dipole **1**

Dipolarophile	Solvent	$k_2/10^{-3}$ dm^3 mol^{-1} s^{-1} (T/K)[b]	ΔE_a/kJ mol^{-1}	ΔH_a/kJ mol^{-1}	ΔS_a/J mol^{-1} K^{-1}
Methyl vinyl ketone	CH_3CN	39.9 (301), 62.0 (310), 218 (331)	47.5	44.9	−123
	H_2O–CH_3CN 0.8 : 0.2[a]	397 (301), 572 (310), 1051 (331)	26.6	24.1	−164
Methyl acrylate	CH_3CN	30.7 (301), 37.7 (310), 193 (331)	53.2	50.6	−106
	H_2O–CH_3CN 0.8 : 0.2[a]	72.3 (301), 119.8 (310), 390 (331)	46.8	44.3	−120
2,3-Dihydrofuran	CH_3CN	1.33 (301), 2.07 (310), 10.5 (331)	58.4	55.9	−115
	H_2O–CH_3CN 0.8 : 0.2[a]	3.21 (301), 5.04 (310), 18.4 (331)	49.1	46.5	−130

[a] Mol fraction water in acetonitrile. [b] Rate constants are ± 2%.

promoted enhancements in the rates. Breslow[2] has suggested that hydrophobic effects can be monitored by the influence of added salts on the effects of water. Fig. 3 shows the influence of added LiCl (a water structure-making salt) and guanidinium chloride, (a water structure-breaking salt) on the water-kinetic effects for the water-normal dipolarophile methyl acrylate, and the water-super dipolarophile methyl vinyl ketone. Added LiCl increases the water rate enhancement by increasing the hydrophobic effect and guanidinium chloride decreases the water rate enhancement (through ion–molecule interactions[2]) paralleling their influences on the Diels–Alder reaction. Of interest here however is that the magnitude of these salt effects is essentially the same for both dipolarophiles, suggesting that the hydrophobic effect is similar for both. Hence the difference between methyl vinyl ketone and methyl acrylate may be due to a special hydrogen bonding effect in the cycloaddition transition state with the former which is absent with the latter along with similar hydrophobic effects for both dipolarophiles. This view has been adopted by some workers for the Diels–Alder reaction and calculated transition states showing special hydrogen bonding of water molecules have been described.[18–20] Our results are in agreement with it. However the nature of the plots in Fig. 1

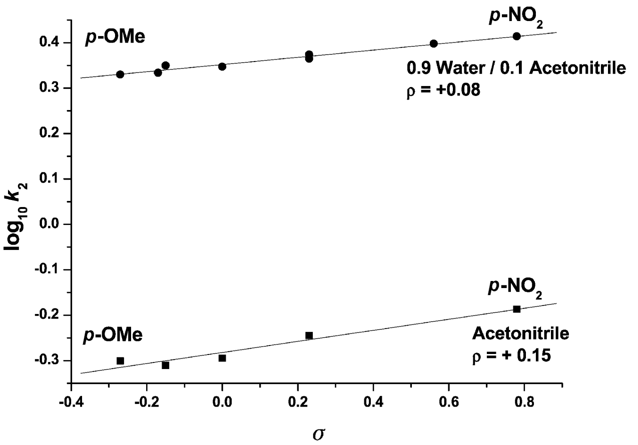

Fig. 2 Hammett plot dipole **1** and *N*-(*p*-substituted phenyl) maleimides at 37 °C.

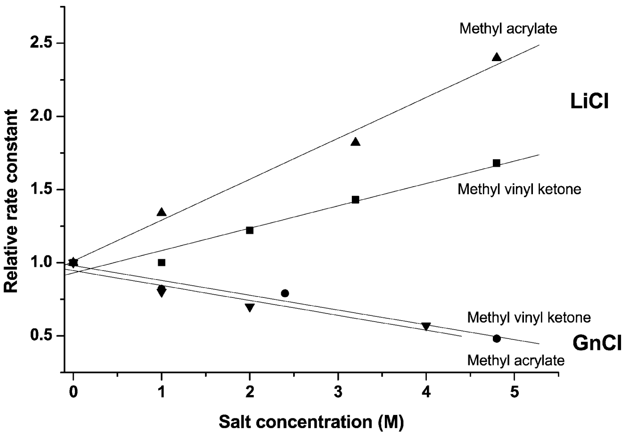

Fig. 3 Influence of lithium chloride (LiCl) and guanidinium chloride (GnCl) on methyl acrylate and methyl vinyl ketone for dipole **2**.

must not be overlooked. It is clear that the kinetic enhancement with water-super dipolarophiles becomes almost exponential as the last 10% of the organic solvent is removed on the change-over to pure water. Whatever special hydrogen bonding effects that could arise should be fully developed when 90% of the medium is water. So why should this rapid rate enhancement occur so late in the water addition? The question may be reversed; why should the presence of 0.1 mol fraction of MeCN in water cause such a dramatic drop in the rate of the cycloaddition? The presence of MeCN should certainly cause major disruption of the water structure. We believe that the balance between the hydrophobic effect and the special hydrogen bonding effects in these situations is not well understood and requires further study. The concept of a common small hydrophobic effect for most organic reactions involving small molecules in water seems over simplistic.

(ii) Theoretical calculations

The theoretical cycloadditions of **1** and **2** with five dipolarophiles were investigated, methyl vinyl ketone MVK, acrylonitrile ACN, methyl acrylate MAC, styrene STY, and 2,3-dihydrofuran DHF. A number of computational methods incorporated into the Gaussian98A9 series of programs were used in this study.[21] All geometry optimisations were carried out with the RB3LYP[22] DFT method. The standard split valence plus polarisation 6-31G(d) basis set[23] was used in all cases. Normal mode analysis was performed to ascertain the nature of all structures identified as stationary points. All structures identified here as transition states TS have only one imaginary vibrational frequency. Graphical inspection of its normal mode in each case showed it to be the motion expected for the concerted, asynchronous bond formation associated with cycloaddition. The activation energies for the lowest energy TS isomer of several species were reoptimised with the 6-311+G(d) basis set in order to assess the effect of the basis set. This basis set has diffuse functions that might more accurately describe the ionic nature of the dipole and TS. All values reported here are for the B3LYP/6-31G(d) method, except where noted for the larger basis set (noted lb in Table 3).

For MVK, the geometries of the C=O bond were optimised *cis* or *trans* to the C=C bond while the methyl C–H bond was either *cis* or *trans* to the C=O bond. Of these four combinations the *cis*,*cis* is the most favoured by *ca.* 4 kJ mol^{-1}. The quasi *cis*,*cis* combination was used as a starting point for the optimisation procedures for the transition states for MVK. A similar *cis*,*cis*,*cis* combination was used for MAC. All TS structures were calculated for the four stereo products involving MVK, ACN, STY, and the two stereo products involving DHF (*endo*- and *exo* forms of both possible regioisomers). Since we previously reported[8] the differences in energies for the four stereoisomeric transition states of **1** with several dipolarophiles, only the lowest activation energies are reported here for MVK, MAC, ACN, and STY. It has been argued by Mattay[24] and Houk[25] that the *cis*–*trans* equilibrium of the dipolarophile has an important part in determining *endo*–*exo* selectivity. Our purpose is to report the theoretical, gas phase calculations within a series of dipolarophiles to explore the effect of substituents and hydrated substituents.

The ground state of MVK and MAC and the four TS structures for dipoles **1** and **2** with MVK or MAC were recalculated with one and two H_2O molecules around the carbonyl O atom (see Fig. 4). It was found that the single H-bonded H_2O is more stable on the O lone pair next to the C=C bond than on the CH_3 or OCH_3 side. This position was maintained in the TS structures, however the other non H-bonded H atom was placed away from the incoming dipole. This affords a uniform comparison of the effect of one H_2O with only one H-bond. In most cases another TS structure can be found where there is a second H-bond from the H_2O to the N atom in the ring or nitrile of the dipole. The second H_2O molecule was placed on the other carbonyl lone pair, also with the second H atom pointing away from the dipole. The optimisation procedure using analytical derivatives at every step leads to many combinations of the H_2O molecules having one or two H-bonds. For uniformity we have chosen to report the 10b-CH/*endo* combination for MVK and MAC and the 3-C(CN)$_2$/*exo* combination for STY and DHF since they give the lowest activation energy without H_2O and structures could be found with the extra H atoms both pointing away from **2**.

Only one H_2O molecule was found to bond directly to the O atom in DHF. Optimisation procedures bring the second H_2O molecule to a placement where it is H-bonded to the first H_2O molecule bonded to the ring O atom. Therefore, only a geometry optimisation of the monohydrated DHF was attempted for the transition state. Even in this case the optimisation process brought the H_2O molecule from on top of the DHF partner to where it was H-bonded to one of the nitrile N atoms.

All calculated energies and entropies for structures are available as supplementary material. Computer output is available at http://camchem.rutgers.edu/~burke. The calculated activation energies ΔE^{act}, and entropies ΔS^{act} for these isomers are given in Table 3. The activation energies and entropies for structures involving one or two H_2O molecules (1W, 2W) are calculated as the difference between the H-bonded TS and the sum of the dipole and H-bonded dipolarophile. The theoretical values for the activation energies ΔE^{act} compare favourably with the experimental values reported here for three dipolarophiles in CH_3CN, each being less by 3 kJ mol^{-1} (Table 2, Table 3). As is the case for concerted cycloadditions the calculated ΔS^{act} values are at least 50% more negative than experiment.

Table 3 B3LYP/6-31G(d) calculations for cycloaddition transition states with one and two molecules of water (/1W,/2W), experimental values (from Table 2) in parentheses

	ΔE^{act}/kJ mol^{-1}	ΔG^{act}/kJ mol^{-1}	ΔS^{act}/J (mol K)$^{-1}$
1 + MVK	50.13 (47.5)	110.51	−193.29 (−123)
1 + MVK/1W	46.81		
1 + MVK/2W	34.20 (26.6)		
1 + MVK-lb[a]	53.56		
1 + MAC	51.10 (53.2)	111.44	−190.25 (−106)
1 + MAC/1W	55.01 (46.8)		
1 + MAC/2W	–[b]		
1 + MAC-lb	56.83		
1 + ACN	52.67	112.61	−190.30
1 + STY	55.10	115.74	−193.01
1 + DHF	54.38 (58.4)	118.27	−202.69 (−115)
2 + MVK	65.96	125.76	−192.06
2 + MVK/1W	60.69	121.88	−197.16
2 + MVK/2W	37.33	106.50	−221.42
2 + MVK-lb	68.46		
2 + MVK/2W-lb	40.85		
2 + MAC	70.70	130.48	−192.96
2 + MAC/1W	73.44	130.41	−195.38
2 + MAC/2W	54.10		
2 + MAC-lb	76.09		
2 + MAC/2W-lb	60.22		
2 + ACN	70.46	130.30	−192.31
2 + ACN (lb)	76.95	137.19	−184.90
2 + STY	77.28	137.34	−192.07
2 + DHF	75.11	138.31	−201.75

[a] lb, large basis set: reoptimized geometry using B3LYP/6-311G(d). [b] No two singly H-bonded water molecules could be found.

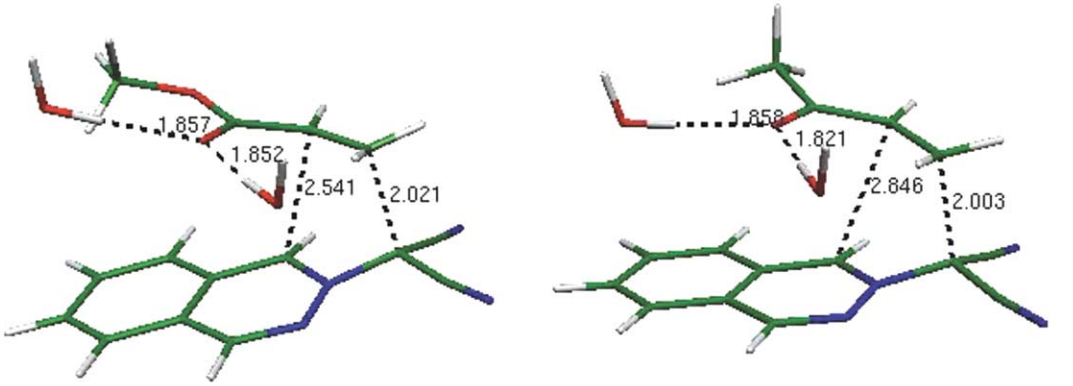

Fig. 4 B3LYP/6-31G(d) optimised transition state structure for the cycloaddition in the CH/*endo* orientation of **1** and MAC and **1** and MVK with two H_2O molecules. Dotted lines show the distances (Å) of the new bonds between the dipole and dipolarophile in the TS. The carbonyl O atom is H-bonded to each of the two waters leaving a free OH directed away from the dipole. (Green C; blue N; red O atoms).

The activation energies and entropies follow certain trends. The calculated ΔE^{act} for adducts with **2** are greater than with **1** as is reflected in the experimental rate constants $k_2 < k_1$. At 310 K for MVK in CH_3CN the experimental k_1/k_2 is 62.0/0.464 = 134. Using the relationship[26] from Transition State Theory that for similar reactions in the same solvent and at ~298 K

$$\Delta E^{act} = \Delta E^{act}_1 - \Delta E^{act}_2 \approx 5.73\ \text{kJ mol}^{-1} * \log(k_1/k_2)$$

a ratio of 134 gives ΔE^{act} = 12.2 kJ mol^{-1}. The theoretical ΔE^{act} is 65.96(65.96) − 50.13(53.56) = 15.8(12.4, 6–311+G*). Likewise for MAC, the ratio of the experimental k_1/k_2 = 37.7/0.106 gives ΔE^{act} ≈14.6 while the theoretical ΔE^{act} is 19.6(19.2). It thus appears that the theoretical ΔE^{act} follow the experimental trend for the rates in CH_3CN and that Transition State Theory indicates similar mechanisms for the cycloaddition to dipoles **1** and **2**.

Using Molecular Dynamics simulations on *ab initio* TS structures of MVK and cyclopentadiene, Jorgensen *et al.*[18] calculated a stabilisation of the free energy of the TS by water of 18 kJ mol^{-1} relative to reactants. They attributed the enhanced stabilisation of the TS to stronger H-bonds. A similar finding is obtained here from a calculation of the interaction energy between two H_2O molecules and MVK or MAC and two with the TS. These interaction energies are given in Table 4. The calculated free energy interaction using the B3LYP/6-31G* method is 19 kJ mol^{-1}. The difference in interaction energies between MVK2W and its TS2W are all negative and greater in absolute value for those of MAC2W and its TS2W. The free energy interaction for both MVK2W and MAC2W are positive

Table 4 Water interaction energies[a] by two water molecules, calculated with the B3LYP/6-31G(d) method

Species	ΔE/kJ mol^{-1}	ΔG/kJ mol^{-1}	ΔS/J (mol K)$^{-1}$
int en[a] MVK	−71.19	16.02	−240.89
int en TS	−99.82	−3.24	−270.25
Δ int en MVK	−28.63	−19.26	−29.36
int en MAC	−67.94	18.17	−236.30
int en TS	−84.54	5.44	−252.63
Δ int en MAC	−16.60	−12.73	−16.33

[a] Water interaction energy (int en) is the difference in energy between a hydrated molecule (or transition state) and the sum of energies of the isolated molecule (or TS) and water(s).

Table 5 Reactions of dipole **1** with various dipolarophiles

Entry	Dipolarophile	Compound	Mp/°C[a]	Yield (%) CH_3CN[d]		Yield (%) H_2O[d]		Yield (%) solvent free[h]	
1	Phenylacetylene	**3**	210–212[b]	82[e]		78[e]		75	
2	Phenylacetylene d^1	**4**	213–214[b]	86[e]		87[e]		—	
3	Diphenylacetylene	**5**	213–214[b]	60[e]		71[e]		—	
4	Methyl vinyl ketone	**6**	152–154	96 (3 : 1)[f]		95 (7 : 1)[g]		—	
5	Ethyl vinyl ketone	**7**	123–125	94 (3 : 1)[f]		96 (11 : 1)[g]		83 (4 : 1)[f]	
6	Cyclopent-2-en-1-one	**8**	228–229	80 (3 : 1)[c,f]		95 (16 : 1)[e,g]		65 (4 : 1)[f]	
7	*N*-Methyl maleimide	**9**	233–235	87		89		—	
8	*N*-*tert*-Butyl maleimide	**10**	212–214	80		90		75	
9	*N*-Benzyl maleimide	**11**	205–207	81		91		—	
10	*N*-(*p*-Methoxyphenyl) maleimide	**12**	215–216	91		95		—	
11	*N*-(*p*-Chlorophenyl) maleimide	**13**	238–239	92		94		—	
12	*N*-(*p*-Bromophenyl) maleimide	**14**	235–236	85		93		—	
13	*N*-(*p*-Tolyl) maleimide	**15**	222–223	89		91		—	
14	*N*-Phenyl maleimide	**16**	252–254	88		96		—	
15	*N*-(*p*-Nitrophenyl) maleimide	**17**	226–228	90		95		—	
16	Butyl vinyl ether	**18**	140–141	86[e]		87[f]		80	
17	Methyl methacrylate	**19**	138–139[c]	*Major*	*Minor*	*Major*	*Minor*	*Major*	*Minor*
				62	13	56	19	66	22
18	*tert*-Butyl methacrylate	**20**	119–120[c]	*Major*	*Minor*	*Major*	*Minor*	*Major*	*Minor*
				62	17	63	20	63	13

[a] Recrystallised from ethanol unless otherwise stated. [b] Recrystallised from acetonitrile. [c] Mp of major isomer. [d] Stirred at ambient temperature unless otherwise stated. [e] Stirred under reflux. [f] *endo–exo* ratio determined by ^{1}H NMR, reaction heated at 80 °C. [g] Stirred at 81 °C. [h] Heated at 80 °C.

but the TS2W for MVK is slightly negative and for MAC positive. This gives an overall preference of 6.5 kJ mol^{-1} in free energy to the doubly H-bonded TS for MVK (Fig. 1) relative to MAC. The theoretical calculations suggest that special hydrogen bonding effects in the transition state play an important role in rate enhancements with water-super dipolarophiles. These effects are indicated by the considerable lowering of the activation energies for mono- or dihydrated MVK and the slight lowering or raising of the activation energies (Table 3) for the cases of MAC and DHF.

(iii) Synthetic implications

(a) Reactions in water. The 1,3-dipole **1** is insoluble in water with solubility <5.0 × 10^{-6} M as determined from its UV absorption at λ_{max} 411 nm. The alkene and alkyne dipolarophiles are also insoluble in water. When heterogeneous mixtures of the substrate **1** with a range of dipolarophiles in water were stirred at the same temperature as in acetonitrile (ambient or 81 °C) high yields of the cycloadducts were obtained (Scheme 1). The yields (Table 5) were equal to or better than those under homogeneous conditions in acetonitrile solvent.[9] The work-up conditions were more adventitious since the solid products could be collected by simple filtration. The only difference observed in the product distribution was an increase in the *endo–exo* ratio when both isomers were formed (Table 5). This phenomenon has also been noted for Diels–Alder reactions in water[5] and has been ascribed to a favouring of the more compact *endo*-transition state by the hydrophobic effect and the polarity of the water medium.[5,27,28] The reactions may be occurring through very low concentrations of the reactants in solution or at the surface of the solid 1,3-dipole particles. The structures, regiochemistry and stereochemistry of the products (Scheme 1) have been established previously[9] from their spectra and some X-ray crystal structures. A number of new products not previously reported have similar structures and are included in the Experimental.

(b) Reactions under solvent-free conditions. Since the hydrophobic effects which increase the reaction rates, arise through aggregation of the organic reactant molecules in water the ultimate hydrophobic effect should be aggregation of the reactants in the absence of a solvent, *i.e.* solvent-free conditions. In order for reaction conditions to be described as solvent-free it requires the reactants to be present in equimolar proportions. Otherwise the excess of one reagent becomes the solvent. Hence we examined synthetic reactions under these conditions. The solid dipole **1**, in a tube, was treated dropwise with an equimolar quantity of the liquid dipolarophile and the mixture was heated at 80 °C for a short time. The cycloaddition products were obtained in excellent yields (Table 5). In this case *endo–exo* isomer ratios obtained were similar to those in acetonitrile solvent for reactions at ambient temperatures and under reflux (81 °C). The reactions under solvent-free conditions did not occur at ambient temperatures and since temperature could influence the *endo–exo* ratio the comparison of these ratios for the solvent-free reactions at 80 °C are more meaningful for the cases in acetonitrile under reflux (81 °C) even though the similarity extends to the reactions at ambient temperatures also (Table 5). These surprising synthetic results are of interest beyond the reactions described. They merit exploration for other organic reactions where the reactants are insoluble but also unreactive towards water.

Experimental

Mp's were measured on a electrothermal apparatus. IR spectra were measured with a Perkin Elmer Spectrum 1000 spectrophotometer and Microanalysis on a Perkin Elmer Model 240 CHN analyser. NMR spectra were measured on a JEOL GXFT 400 instrument with tetramethylsilane as an internal reference and either deuteriochloroform or hexadeuteriomethyl sulfoxide as a solvent. The structures were examined also using COSY, NOEDS and DEPT. *J* values are given in Hertz. The dipole **1** was prepared as previously described.[29] The pyridazinium dicyanomethanide dipole **2** was prepared by the same procedure. The phenyl-substituted maleimides were prepared according to the literature procedure.[30] The other dipolarophiles were purchased from Aldrich. Water used for synthesis was Millipore grade. Solvent free reactions were preformed in a stoppered test tube at 80 °C (CAUTION: use safety shield). Compounds **3**, **4**, **9**, **10**, **11**, **13**, **16**, **17**, **18**, **19**, **20** have been previously reported.[9] The stereochemistries of the *endo* products **6**, **7**, **8** and their *exo*-isomers **6a**, **7a** and **8a** were established from NOE difference spectra which showed strong (7–10%) enhancements from H-10b to the *cis*-H-1 in the *endo* compounds **6**, **7**, **8** and the absence of a through-space enhancement for the products **6a**, **7a**, **8a**.

Kinetics

The kinetics were measured by recording the disappearance of the dipole **1** at 420 nm using its UV–VIS spectrum. Spectra were measured using a Hewlett Packard Agilent Technologies 8453 UV–VIS spectrophotometer featuring an automatic changer for up to eight glass cuvettes of pathlength 1 cm. The temperature was maintained at 37 °C. The reaction was monitored under pseudo-first order conditions. The dipole **1** was recrystallised twice before use. The liquid dipolarophiles were distilled before use. The solvents used were HPLC grade and the water was Millipore grade. The initial concentration of the dipole **1** was 3.2×10^{-5} M and the dipolarophiles were used in excess ranging from 500 to 10000 M. The reactions were monitored using the π–π* transition of the dipole **1** at 420 nm and 413 nm for 0.80 and 0.90 mole fraction water–acetonitrile. The pyridazinium dicyanomethanide dipole **2** was monitored using the π–π* transition at 427 nm in acetonitrile and 413 nm for 0.80 to 1.0 mol fraction water in acetonitrile. The same procedure for dipole **1** was used for dipole **2**. Kinetic runs were performed at three different concentrations of dipolarophiles and repeated a minimum of three times. The rate constants were reproducible to ± 2%. The length of time for the reaction varied from 10 min to 12 h depending on the dipolarophile. The solutions changed from yellow to colourless as the rates progressed. Sample kinetic graphs for Table 1, entries 5, 7, 12, 27 and 29 are supplied as supporting information.†

Synthetic procedures

The following are typical examples of synthetic reactions in acetonitrile, in water and under solvent free conditions:

1,2-Diphenyl-3-cyanopyrrolo[2,1-*a*]phthalazine 5

A suspension of dipole **1** (0.30 g, 1.54 mmol) in acetonitrile (20 cm^3) was treated with diphenylacetylene (2.74 g, 15.4 mmol) and stirred under reflux for 24 hours. After which time the product precipitated from solution and was filtered to give compound **5**. Yield (60%, 0.32 g) Mp 213–214 °C (acetonitrile) (Found C, 82.5; H, 4.8; N, 12.3. $C_{24}H_{15}N_3$ requires C, 82.3; H, 5.1; N, 12.5%); ν_{max}cm^{-1} (Nujol mull) 2216 (C≡N); δ_H (DMSO-d^6 60 °C) 7.31–7.64 (m, 13H, H-7 to H-9, H-2′ to H-4′ and H-2″ to H-4″), 8.06 (d′ 1H, *J* 7.3, H-10), 8.95 (s, 1H, H-6); δ_C (DMSO-d^6 60 °C) 112.5 (C≡N), 116.3 (C-3), 120.9 (C-2), 121.2 (C-10), 123.1 (C-1), 126.0 (C-10b), 127.6, 127.9, 128.6, 128.7, 129.0, 130.6, 130.8, 132.1 (C-7 to C-9, C-1′ to C-4′ and C-1″ to C-4″ some overlap of signals), 146.1 (C-6).

Synthesis in water. Product **5** was prepared at 81 °C in water as described for acetonitrile (reflux 81 °C) and isolated by direct filtration, Yield (%) 71.

1-*endo*-Acetyl-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]-phthalazine 6 and 1-*exo*-acetyl-3,3-dicyano-1,2,3,10b-tetrahydro-pyrrolo[2,1-*a*]phthalazine 6a

A suspension of dipole **1** (0.30 g, 1.54 mmol) in acetonitrile (20 cm^3) was treated with an excess of methyl vinyl ketone (0.64 cm^3, 7.7 mmol) and stirred at ambient temperature for 4 hours to give a pale yellow solution. The solvent was removed under reduced pressure and the residue when treated with ethanol (5 cm^3) gave compound **6**; Yield (72%, 0.31 g) Mp 152–154 °C (ethanol) (Found C, 68.0; H, 4.3; N 21.2. $C_{15}H_{12}N_4O_2$ requires C, 68.2; H, 4.5; N, 21.2%); ν_{max}cm^{-1} (Nujol mull) 1715 (C=O); δ_H (CDCl$_3$) 2.05 (s, 3H, CH$_3$), 3.63–3.67 (m, 1H, H-1$_{exo}$), 2.93 (dd, 1H, *J* 3.4, 14.6, H-2$_{endo}$), 3.09 (dd, 1H, *J* 8.7, 14.6, H-2$_{exo}$), 4.80 (d, 1H, *J* 6.8, H-10b), 7.27–7.46 (m, 3H, H-7 to H-9), 7.65 (s, 1H, H-6); δ_C (CDCl$_3$) 29.4 (CH$_3$), 38.5 (C-2), 50.5 (C-1), 55.2 (C-3), 58.5 (C-10b), 113.1, 113.3 (C≡N), 124.6 (C-10a), 127.1, 129.3, 124.8 (C-8 to C-10), 130.7 (C-6a), 132.0 (C-7), 145.3 (C-6), 205.5 (C=O).

The filtrate was placed on a flash column of silica gel (230–400 mesh ASTM) and eluted with dichloromethane to give compound **6a** as a gummy residue

Compound **6a**; Yield (23%, 0.098 g gum (recolumned crude sample)); ν_{max}cm^{-1} (CCl$_4$ liquid cell) 1716 (C=O); δ_H (CDCl$_3$) 2.93 (s, 3H, CH$_3$), 2.95 (dd, 1H, *J* 5.8, 13.9, H-2 *endo*), 3.10 (dd, 1H, *J* 11.7, 13.9, H-2$_{exo}$), 3.55–3.58 (m, 1H, H-1*endo*), 4.53 (d, 1H, *J* 9.2, H-10b), 7.03 (d, 1H, *J* 6.8, H-10), 7.28–7.48 (m, 3H, H-7 to H-9), 7.76 (s, 1H, H-6); δ_C (CDCl$_3$) 29.2 (CH$_3$), 37.8 (C-2), 49.8 (C-1), 57.6 (C-10b), 112.8, 113.1 (C≡N), 123.5 (C-10), 124.8 (C-10a), 126.2 (C-9), 128.9 (C-8), 129.3 (C-6a), 131.2 (C-7), 146.4 (C-6), 203.9 (C=O).

Synthesis in water. The products **6** and **6a** were prepared and isolated as described using water as solvent; **6**, **6a**, overall yield (%), 95 (ratio 7 : 1).

1-*endo*-Propionyl-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo-[2,1-*a*]phthalazine 7 and 1-*exo*-propionyl-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine 7a

A suspension of dipole **1** (0.30 g, 1.54 mmol) in acetonitrile (20 cm^3) was treated with ethyl vinyl ketone (0.76 cm^3, 7.7 mmol) and stirred at room temperature for 4 hours. After which time the solvent was removed under reduced pressure and the residue dissolved in dichloromethane (3 cm^3). The residue was placed onto a column of flash silica gel (230–400 mesh ASTM) and eluted with a mixture of dichloromethane–petroleum spirit (bp 40–60 °C) in the gradient 1 : 1 to 1: 0.

Synthesis in water. A suspension of dipole **1** (0.30 g, 1.54 mmol) in water (20 cm^3) was treated with excess ethyl vinyl ketone (0.76 cm^3, 7.7 mmol) and stirred rapidly at ambient temperature for 4 hours. The product was extracted into dichloromethane (2×10 cm^3) and dried over MgSO$_4$. The solvent was removed under reduced pressure and the residue dissolved in dichloromethane (2 cm^3) and placed onto a column of flash silica gel (230–400 mesh ASTM) and eluted with a mixture of dichloromethane–petroleum spirit (bp 40–60 °C) in the gradient 1 : 1 to 1: 0.

Solvent free synthesis. The dipole **1** (0.1 g, 0.51 mmol) was placed into a stoppered test-tube and treated with ethyl vinyl ketone (0.049 cm^3, 0.51 mmol) which was dropped onto the dipole. The test-tube was stoppered and heated at 80 °C until the dipole was fully reacted. (CAUTION: use safety shield). After which time the residue was dissolved in dichloromethane (2 cm^3) and placed onto a column of flash silica gel (230–400 mesh ASTM) and eluted with a mixture of dichloromethane–petroleum spirit (bp 40–60 °C) in a 5% (v/v) changing gradient 1 : 1 to 1 : 0.

The first product to elute from the column was compound **7a**; Yield (23% 0.098 g gum (recolumned crude sample)), ν_{max}cm^{-1} (CCl$_4$ liquid cell) 1725 (C=O); δ_H (CDCl$_3$) 1.16 (t, 3H, *J* 6.8, CH$_3$), 2.65 (q, 2H, *J* 6.8, CH$_2$), 2.92 (dd, 1H, *J* 6.3, 13.9, H-2$_{endo}$), 3.06 (dd, 1H, *J* 10.9, 13.9, H-2$_{exo}$), 3.55–3.62 (m, 1H, H-1$_{endo}$), 4.60 (d, 1H, *J* 9.3, H-10b), 6.99 (d, 1H, *J* 7.3, H-10), 7.26–7.49 (m, 3H, H-7 to H-9), 7.76 (s, 1H, H-6); δ_C (CDCl$_3$) 7.5 (CH$_3$), 35.7 (CH$_2$), 38.3 (C-2), 49.1 (C-1), 58.1 (C-10b), 112.5, 113.1 (C≡N), 123.2 (C-10a), 125.6 (C-10), 126.3 (C-9), 128.7 (C-6a), 132.0 (C-7), 146.2 (C-6), 206.7 (C=O); C-3 and C-8 signals overlapped.

Compound **7**; Yield (71% 0.31 g) Mp 123–125 °C (ethanol) (Found C, 68.6; H, 5.1; N, 19.9. $C_{16}H_{14}N_4O$ requires C, 69.0; H, 5.0; N, 20.1%), ν_{max}cm^{-1} (Nujol mull) 1712 (C=O); δ_H (CDCl$_3$) 0.79 (t, 3H, *J* 7.3, CH$_3$), 2.34 (q, 2H, *J* 7.3, CH$_2$), 2.92 (dd, 1H, *J* 3.9, 14.2, H-2), 3.05 (dd, 1H, *J* 9.2, 14.2, H-2), 3.65–3.69 (m, 1H, H-1$_{exo}$), 4.82 (d, 1H, *J* 7.3, H-10b), 7.08 (d, 1H, *J* 6.8, H-10), 7.26–7.45 (m, 3H, H-7 to H-9), 7.62 (s, 1H, H-6); δ_C (CDCl$_3$) 7.3 (CH$_3$), 35.6 (CH$_2$), 38.8 (C-2), 49.8 (C-1), 58.7 (C-10b), 113.2, 113.3 (C≡N), 124.9 (C-10a), 125.0 (C-10), 127.0 (C-9), 129.3 (C-8), 130.9 (C-6a), 131.9 (C-7), 144.8 (C-6), 208.3 (C=O); C-3 signal overlapped.

endo-8,8-Dicyano-11-oxo-8a,9,10,11,11a,11b-hexahydrocyclopenta[3,4]tetrahydropyrrolo[2,1-*a*]phthalazine 8 and *exo*-8,8-dicyano-11-oxo-8a,9,10,11,11a,11b-hexahydrocyclopenta[3,4]-tetrahydropyrrolo[2,1-*a*]phthalazine 8a ‡

A suspension of dipole **1** (0.30 g, 1.54 mmol) in acetonitrile (20 cm^3) was treated with an excess of cyclopentenone (0.64 cm^3, 7.7 mmol) and was stirred under reflux for 24 hours. The solvent was removed under reduced pressure and the residue dissolved in dichloromethane (3 cm^3). This was placed on a column of flash silica gel (230–400 mesh ASTM) and eluted with a petroleum spirit (bp 40–60 °C) dichloromethane mixture in the gradient 1 : 1 to 0 : 1. The products were eluted from the column as follows; Compound **8** Yield (61%, 0.27 g) Mp 228–229 °C (ethanol) (Found C, 69.8; H, 4.1; N, 19.8. $C_{16}H_{12}N_4O_2$ requires C, 69.5; H, 4.4; N, 20.2%); ν_{max}cm^{-1} (Nujol mull) 1748 (C=O); δ_H (DMSO-d^6) 2.08–2.58 (m, 4H, H-3′ and H-4′), 3.55 (dd, 1H, H-1), 3.80–3.82 (m, 1H, H-2), 4.72 (d, 1H, *J* 6.3, H-10b), 7.37–7.55 (m, 3H, H-7 to H-9), 7.56 (d, 1H, *J* 7.3, H-10), 7.82 (s, 1H, H-6); δ_C(DMSO-d^6) 24.5 (C-3′), 38.2 (C-2), 38.5 (C-4′), 47.6 (C-1), 60.5 (C-10b), 112.8, 113.5 (C≡N), 124.4 (C-10a), 126.6 (C-10), 127.1 (C-9), 130.7 (C-8), 131.3 (C-7), 131.2 (C-6a), 146.6 (C-6), 213.6 (C=O); C-3 signal overlapped.

Compound **8a**; Yield (20%, 0.09 g Gum (recolumned crude sample)); ν_{max}cm^{-1} (CCl_4 Liquid cell) 1734 (C=O); δ_H (DMSO-d^6) 2.20–2.52 (m, 4H, H-3′ and H-4′), 3.49 (dd, 1H, H-1), 3.83–3.85 (m, 1H, H-2), 4.19 (d, 1H, *J* 9.2, H-10b), 7.34–7.78 (m, 4H, H-7 to H-10), 7.89 (s, 1H, H-6); δ_C (DMSO-d^6) 22.9 (C-3′), 37.8 (C-4′), 51.1 (C-1), 57.0 (C-10b), 60.4 (C-3), 112.2, 114.3 (C≡N), 124.5 (C-10), 126.3 (C-9), 128.9 (C-8), 132.5 (C-7), 133.2 (C-6a), 146.7 (C-6), 211.2 (C=O); C-2 and C-10a signals overlapped.

Synthesis in water. The products **8** and **8a** were prepared and isolated as described using water as solvent at 81 °C; **8**, **8a**, overall yield (%), 95 (ratio 16 : 1).

Solvent free synthesis. The products **8** and **8a** were prepared and isolated as described using no solvent; **8**, **8a**, overall yield (%) 65 (ratio 4 : 1).

endo-1,2-(Dicarboxy-*N*-*p*-methoxyphenylimido)-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine 12

A suspension of dipole **1** (0.30 g, 1.54 mmol) in acetonitrile (20 cm^3) was treated with *N*-(*p*-methoxyphenyl) maleimide (0.31 g, 1.54 mmol) and stirred at ambient temperature for 24 hours. During this time the product precipitated from solution and was collected by filtration to give compound **12**; Yield (91%, 0.55 g); Mp 215–216 °C (ethanol) (Found C, 66.7; H, 3.9; N, 17.6. $C_{22}H_{15}N_5O_3$ requires C, 66.5; H, 3.8; N, 17.6%); ν_{max}cm^{-1} (Nujol mull) 1779, 1709 (C=O); δ_H (DMSO-d^6) 3.74 (s, 3H, OMe), 4.27 (dd, 1H, *J* 7.8, 7.9, H-1), 4.63 (d, 1H, *J* 7.8, H-2), 5.06 (d, 1H, *J* 7.8, H-10b), 6.99–7.05 (m, 4H, H-2′ and H-3, *p*-OMeC_6H_4), 7.42–7.57 (m, 3H, H-7 to H-9), 7.71 (d, 1H, *J* 8.1, H-10), 7.95 (s, 1H, H-6); δ_C (DMSO-d^6) 45.0 (C-2), 51.1 (C-1), 55.3 (OMe), 59.0 (C-3), 59.6 (C-10b), 110.7, 112.3 (C≡N), 123.9 (C-10a), 127.6, 127.0, 128.8 (C-8 to C-10), 159.2, 114.4, 129.6, 123.5 (*p*-OMeC_6H_4 C-1′, C-2′, C-3′, C-4′, resp.), 129.1 (C-6a), 131.8 (C-7), 146.7 (C-6), 170.7, 173.3 (C=O).

Synthesis in water. Product **12** was prepared in water as described and isolated by direct filtration, Yield (%) 95.

The following cycloadducts were prepared in acetonitrile and water as described.

endo-1,2-(Dicarboxy-*N*-*p*-bromophenylimido)-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine 14

Compound **14**; Yield (85%, 0.62 g), Mp 235–236 °C (ethanol), (Found C, 56.5; H, 2.7; N, 15.7. $C_{21}H_{12}N_5O_4Br$ requires C, 56.5; H, 2.7; N, 15.7%), ν_{max}cm^{-1} (Nujol mull)

1780, 1714 (C=O); δ_H (DMSO-d^6) 4.30 (dd, 1H, *J* 7.7, 7.8, H-1), 4.69 (d, 1H, *J* 8.0, H-2), 5.07 (d, 1H, *J* 8.0, H-10b), 7.06 (d, 2H, *J* 7.7, H-2′ of N–BrC_6H_4), 7.44–7.72 (m, 5H, H-7 to H-10 and H-3′ of N–BrC_6H_4), 7.96 (s, 1H, H-6); δ_C (DMSO-d^6) 43.3 (C-2), 51.2 (C-1), 59.2 (C-10b), 59.8 (C-3), 110.6, 112.2 (C≡N), 123.5 (C-10a), 129.5 (C-6a), 131.8 (C-7), 130.7, 128.5, 132.2, 121.9 (N–C_6H_4Br C-1′, C-2′, C-3′, C-4′ respectively), 127.7, 129.2, 127.1 (C-8 to C-10), 169.9, 172.7 (C=O).

endo-1,2-(Dicarboxy-*N*-*p*-methylphenylimido)-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine 15

Compound **15**. Yield (89%, 0.53 g), Mp 222–223 °C (ethanol) (Found C, 69.4; H, 3.8; N, 18.2. $C_{22}H_{15}N_5O_2$ requires C, 69.3; H, 4.0; N, 18.4%); ν_{max}cm^{-1} (Nujol mull) 2195 (C≡N), 1782, 1714 (C=O), δ_H (DMSO-d^6) 2.30 (s, 1H, CH_3), 4.28 (dd, 1H, *J* 7.9, 7.8, H-1), 4.64 (d, 1H, *J* 8.3, H-2), 5.06 (d, 1H, *J* 7.8, H-10b), 6.96 (d, 2H, *J* 8.3, H-2′ of $CH_3C_6H_4$), 7.25 (d, 2H, *J* 8.3, H-3′ of N–$C_6H_4CH_3$), 7.40–7.57 (m, 3H, H-7 to H-9), 7.71 (d, 1H, *J* 7.8, H-10), 7.95 (s, 1H, H-6); δ_C (DMSO-d^6) 20.6 (CH_3), 45.1 (C-2), 51.1 (C-1), 59.1 (C-10b), 59.6 (C-3), 110.7, 112.3 (C≡N), 123.5 (C-10a), 124.5 (C-6a), 131.7 (C-7), 127.0, 127.7, 129.1 (C-8 to C-10), 138.4, 128.9, 126.1, 129.6 (N–$C_6H_4CH_3$ C-1′, C-2′, C-3′, C-4′ resp.) 170.3, 172.2 (C=O).

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