

Understanding “On-Water” Catalysis of Organic Reactions. Effects of H⁺ and Li⁺ Ions in the Aqueous Phase and Nonreacting Competitor H-Bond Acceptors in the Organic Phase: On H₂O versus on D₂O for Huisgen Cycloadditions

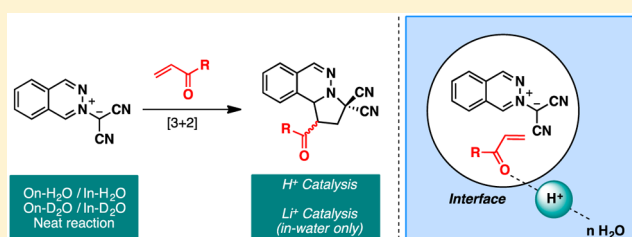
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S Supporting Information

ABSTRACT: For a typical Huisgen cycloaddition, carried out on water, the behavior of water molecules at the oil–water interface depended on the properties of the reactants. With weakly basic reactants, a small quantity of added H⁺ (HClO₄, 0.0001–0.01 M) present in the aqueous phase had negligible effects, but larger quantities of H⁺ (HClO₄, 0.1–3.0 M) increased the catalytic effect and caused protons to cross the water–organic interface and affect the products. Added Li⁺ ions (LiClO₄, 0.1–3.0 M) had no effect for on-water reactions but enhanced the rates and endo products for in-water reactions. For these cycloaddition reactions, the product endo:exo ratios, when compared to those in organic solvents, can be used to distinguish between the on-water and in-water modes. Comparisons of organic reactions on H₂O and on D₂O indicate that on-water catalysis ranges from weak to strong trans-phase H-bonding for reactants with basic pK_a < ca. –6 and to interfacial proton transfer for reactants with higher basic pK_a > ca. 2 (pK_a of conjugate acid). Water shows a chameleon-type response to organic molecules at hydrophobic surfaces.



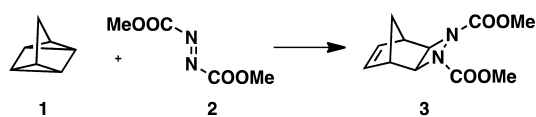
INTRODUCTION

Following the pioneering work of Breslow on the influence of water on the Diels–Alder reactions and his recognition and exploration of the hydrophobic effect as central to the understanding of organic reactions in water, there has been an ever-growing interest in using water as a medium for organic reactions.^{1–8} The subsequent recognition that water-insoluble organic compounds could also be induced to undergo reactions in the water medium by Sharpless, Fokin and their co-workers, named the “on-water” phenomenon, further increased the drive toward extensive use of water as a medium for organic synthesis.^{9–16} The on-water catalytic effect, however, is not well understood, despite the fact that there have been extensive theoretical studies focusing on the oil–water interface. Trans-phase H-bonding from dangling OH_{free} groups at the interface to H-bond acceptor sites on the organic reactants was proposed by Jung and Marcus to be the key contribution to the catalytic effect.¹⁷ Experimental kinetic and thermodynamic studies by Manna and Kumar supported these conclusions.¹⁸ Using quantum mechanical/molecular mechanical modeling, Jorgensen and co-workers concluded that the Diels–Alder reactions were less accelerated on the surface of water than in the bulk water.¹⁹ Kühne and co-workers, using extended Car–Parrinello molecular dynamics, concluded that H-bonds from OH_{free} groups at the aqueous–organic interface play a much smaller role in on-water catalysis than has been suggested.²⁰ However, they also state that their results do not exclude the possibility of

certain preferential orientations or increased strengths of H-bonds leading to faster reactions at the water–organic interface. Experimental results also give rise to varied opinions. Sela and Vigalok reported that neat conditions or other “non-solvents” are better than on-water reactions for some Passerini reactions and amine epoxide ring openings.²¹ Zhou, Wang, and co-workers report highly efficient on-water reactions with substrates containing C–F bonds where trans-facial H-bonding by OH_{free} groups to fluorine atoms is important.²² Zuo and Qu have emphasized that small levels of water solubility for organic reactants are a necessary requirement in order to achieve on-water reactions.²³ Among the theoretical studies there has been a considerable focus on the cycloaddition reaction of quadricyclane (1) with dimethyl azodicarboxylate (2) (Figure 1). This reaction is a complicated two-stage mechanism with a large polar character in the gas phase, and it is likely to be more complicated under on-water conditions.²⁴ In our opinion, the literature has overlooked an important result reported by Sharpless, Fokin, and their co-workers, namely, the difference for on H₂O and on D₂O, concerning which these researchers stated, “Interestingly a significant solvent isotope effect was also observed; the reaction slowed noticeably when D₂O was used in place of water.”⁹ The Beattie and McErlean research groups have proposed that on-water catalysis involves a proton transfer

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Solvent	Conc [M]	Time to completion
Neat	4.53	48 h
H ₂ O	4.53	10 min
D ₂ O	4.53	45 min

Figure 1. Cycloaddition reaction of quadricyclane and dimethyl azodicarboxylate under neat conditions, H₂O, and D₂O.⁹

across the organic–water interface, giving rise to acid catalysis.^{25,26} They have provided compelling evidence for this with strong D/H isotope effects measured for on-water Claisen rearrangements of allyl aryl amines.²⁶

Herein we examine Huisgen cycloadditions in different environments: (a) neat (no solvent), (b) in an organic solvent (MeCN), (c) in water (dissolved in bulk water), (d) on water (highly water insoluble reactants), and (e) using water with very small (0.0001 M) to large (3.0 M) quantities of H⁺ and Li⁺ (0.1 and 3.0 M) present and also adding non-reacting, competing H-bond acceptors to the organic phase. Previously, we have established an experimental distinction between in-water and on-water reactions for aqueous suspensions of organic reactants.²⁷ Diels–Alder and Huisgen 1,3-dipolar cycloadditions that occur in water show enhanced endo:exo product ratios arising from the Breslow hydrophobic effect, which favors endo-transition states in bulk water. Reactions that occur in aqueous suspensions by the on-water mode do not show enhancements of product endo:exo ratios because they take place in the organic phase under trans-phase on-water catalysis and are not experiencing the Breslow hydrophobic effect of bulk water. In choosing substrates for the on-water reactions herein, attention was paid to the sensitivity of isomeric endo:exo mixtures to acid. Acid may isomerize endo

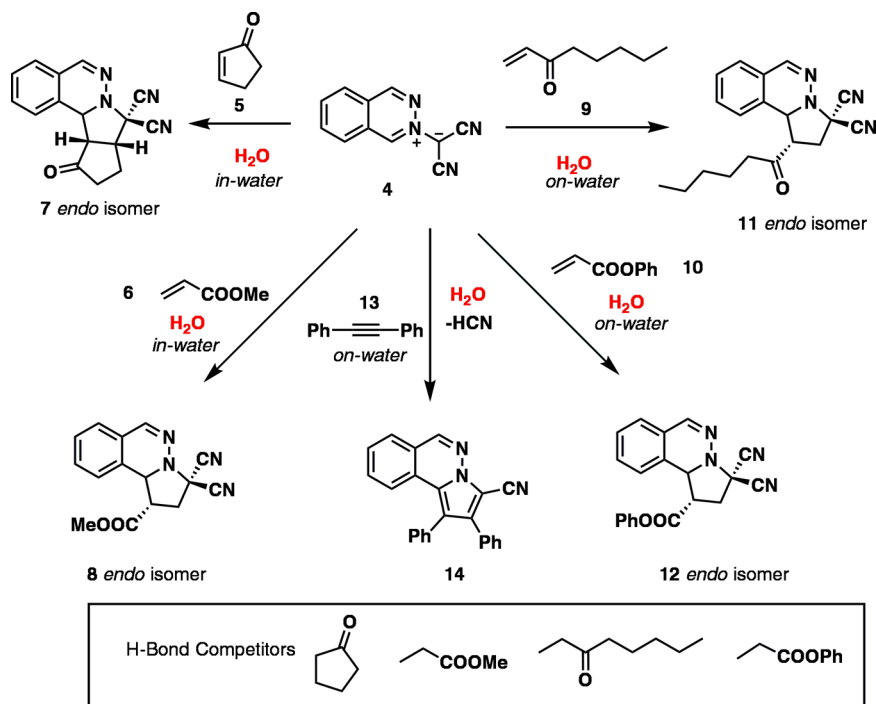
Table 1. (A) In-Water Reaction of Phthalazinium-2-dicyanomethanide ($s \leq 5 \times 10^{-6} \text{ mol L}^{-1}$) (4) with 2-Cyclopenten-1-one (5) and Methyl Acrylate (6) and (B) On-Water Reaction of Phthalazinium-2-dicyanomethanide (4) with 1-Octen-3-one (9), Phenyl Acrylate (10), and Diphenylacetylene (13)

(A) In-Water										
			 (s = 0.27 molL ⁻¹)				 (s = 0.46 molL ⁻¹)			
Entry	Medium	Additive ^a	Time (h) ^c	Temp (°C)	Yield (%)	endo:exo	Time (h) ^c	Temp (°C)	Yield (%)	endo:exo
1	Neat ^b	-	12	20	84	8.9:1	1.25	20	79	5:1
2	MeCN	-	48	20	96	5.1:1	12	20	65	8.3:1
3	H ₂ O	-	36	20	95	42:1	12	20	91	9.8:1
4	D ₂ O	-	36	20	99	52:1	12	20	85	9.9:1
5	H ₂ O	5 mol	36	20	89	33:1	12	20	84	5.2:1
6	H ₂ O	10 mol	36	20	87	37:1	12	20	83	6.1:1

(B) On-water														
			 (s = 0.016 molL ⁻¹)				 (s = 0.012 molL ⁻¹)				 (s = 0.0042 molL ⁻¹)			
Entry	Medium	Additive ^a	Time (h) ^c	Temp (°C)	Yield (%)	endo:exo	Time (h) ^c	Temp (°C)	Yield (%)	endo:exo	Time (h) ^c	Temp (°C)	Yield (%)	endo:exo
7	Neat ^b	-	1.5	20	74	7:1	0.5	20	87	4.3:1	24	82	92	-
8	MeCN	-	1.25	20	99	8.7:1	1.0	20	88	7.8:1	24	82	60	-
9	H ₂ O	-	1	20	92 ^d	8.2:1	0.5	20	90	6.8:1	24	82	71	-
10	D ₂ O	-	1	20	85	7.6:1	0.5	20	93	5.8:1	24	82	69	-
11	H ₂ O	5 mol	1	20	88	8.8:1	0.83	20	80	5.1:1	-	-	-	-
12	H ₂ O	10 mol	1	20	81	9.0:1	0.83	20	78	7.7:1	-	-	-	-

^aAdded corresponding unreactive H-bonding competitor, cyclopentaneone, methyl propionate, octane-3-one, and phenyl propionate, respectively.

^bThe term neat refers to the identical reaction as with MeCN, H₂O, or D₂O however with no solvent present. ^cThe completion time is the time to maximum yield when no further products are appearing. ^dSee Figure 3 for the transition from conversion yield to completion yield for this reaction.

Scheme 1. Huisgen 1,3-Dipolar Cycloaddition Reaction with a Range of Dipolarophiles^a

^aThese reactions are normal-electron-demand 4π -HOMO-controlled cycloadditions with catalytic H-bonding at the 2π dipolarophiles 5, 6, 9, and 10. The reaction with diphenylacetylene (13) is an inverse-electron-demand 4π -LUMO-controlled cycloaddition with H-bonding at the CN groups of the 1,3-dipole 4.¹⁵

isomers to the thermodynamic exo-forms, thereby providing a marker for protons crossing the interface to the organic phase.

RESULTS AND DISCUSSION

i. On-Water vs In-Water Reactions; Competitor H-Bond Acceptors in the Organic Phase. Phthalalazine-2-dicyanomethanide (4) is a high-melting yellow solid (mp 252–254 °C dec) that is highly insoluble in water ($s \leq 5 \times 10^{-6}$ mol L⁻¹ at 37 °C). The nature of its Huisgen cycloaddition reactions with liquid 2π -dipolarophiles in water depends on the water solubility of the dipolarophile. For dipolarophiles with water solubilities >0.1 mol L⁻¹, the reactions occur in water. The dissolved 2π -reactant facilitates an equilibrium transport of the 1,3-dipole through the solution prior to the separation of the highly insoluble products. In physical appearance the yellow suspension of reactants gradually changes to a sticky white suspension of products (see Supporting Information, Figure S5). Two examples of such reactions of 4, with 2-cyclopenten-1-one (5) and methyl acrylate (6), are shown in Table 1 and Scheme 1. When the water solubility of the 2π -reactant is an order of magnitude lower, ca. 0.01 mol L⁻¹, the reactions occur by the on-water mode, although the physical appearance in the reaction flask is no different (see Supporting Information, Figure S5).²⁷ Three examples of such on-water reactions, with 1-octen-3-one (9), phenyl acrylate (10), and diphenylacetylene (13) are shown in Table 1 and Scheme 1. Reactions that occur in water, where the transition states experience the bulk water environment, display the result of the Breslow hydrophobic effect.^{2,3} This favors endo-transition states and enhances the endo:exo ratio of the cycloaddition products. Reactants with large hydrophobic surfaces, such as 2-cyclopenten-1-one (5) show large enhancements of the endo:exo product ratio in water relative to organic solvents or neat, e.g. 5.1 in MeCN and

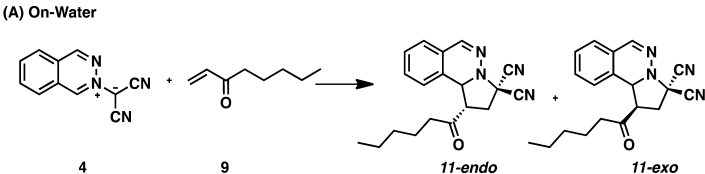
42 in water (Table 1, entries 2, 3), while the endo enhancement for reactants with little hydrophobic surface area, such as methyl acrylate (6), show smaller endo:exo enhancements, e.g., 8.3 in MeCN and 9.8 in water (Table 1). Reactions that occur by the on-water mode show no endo enhancement because they occur at the organic side of the organic–water interface and do not experience the hydrophobic effect of bulk water. Hence, the product endo:exo ratios for the reactions of 4 with 1-octen-3-one (9) (8.4 ± 0.2) and phenyl acrylate (10) (7.3 ± 0.5) are the same in MeCN and water (Table 1).

Also shown in Table 1 are the “neat” reactions of 4 with the dipolarophiles concerning the points raised by Sela and Vignalok.²¹ For these reactants the neat reactions are faster than the in-water cases but the on-water reactions are slightly faster or similar to the neat reactions. The term “neat” here means a necessary 10 molar quantity of liquid 2π -reactant to one mole of the insoluble solid 4π -reactant 4 with separation and workup procedures required to isolate the products. Such neat reactions are not more efficacious or efficient than on-water reactions.

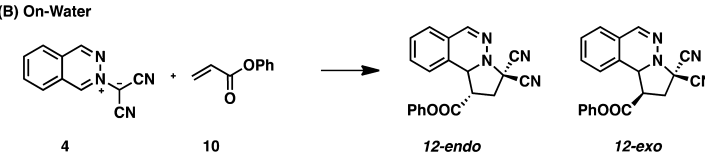
If on-water catalysis arises from H-bonding across the water–organic interface from dangling OH_{free} groups to H-bond acceptor sites on the reactants, it follows that if an excess of a competitor H-bond acceptor molecule were introduced, which did not interfere with the reaction, then it should inhibit the on-water reaction. Having explored possible competitors for H-bond acceptance, it became clear that the requirement of not interfering with the reactants or the reaction was essential, and hence, the saturated versions of the alkene dipolarophiles were chosen as the most suitable competitors for trans-interphase H-bonds. Thus, octan-3-one and phenyl propionate were introduced to compete with the on-water reactions of 1-octen-3-one (9) and phenyl acrylate (10). In Table 1 (entries

Table 2. Effects of H⁺ and Li⁺ in the Aqueous Phase on the Reaction of 1,3-Dipole 4 with (A) 1-Octen-3-one (9) and (B) Phenyl Acrylate (10) at 20 °C

(A) On-Water



(B) On-Water



Entry	Water Phase	Time	Yield (%)	endo:exo	Comment
1	H ₂ O	1 h	92	8.2:1	-
2	HClO ₄ (0.0001 M)	1 h	84	9.2:1	
3	HClO ₄ (0.001 M)	1 h	85	9.3:1	H ^{δ+} -OH ^{δ-} . nH ₂ O at phase interface
4	HClO ₄ (0.01 M)	1 h	83	9.2:1	
5	HClO ₄ (0.1 M)	45 min	85	4.3:1	H ⁺ . nH ₂ O at phase interface
6	HClO ₄ (1.0 M)	30 min	90	2.9:1	H ⁺ crosses phase interface
7	HClO ₄ (2.0 M)	9 min	80	1.8:1	
8	HClO ₄ (3.0 M)	4 min	82	0.63:1	
9	LiClO ₄ (0.1M)	1 h	86	8.4:1	Li ⁺ . nH ₂ O in bulk water only
10	LiClO ₄ (1.0M)	1 h	83	8.7:1	
11	LiClO ₄ (3.0M)	1 h	81	8.7:1	

Entry	Water Phase	Time	Yield (%)	endo:exo	Comment
12	H ₂ O	30 min	90	6.8:1	-
13	HClO ₄ (0.0001 M)	20 min	85	6.5:1	
14	HClO ₄ (0.001 M)	15 min	88	6.3:1	H ^{δ+} -OH ^{δ-} . nH ₂ O at phase interface
15	HClO ₄ (0.01 M)	15 min	83	6.1:1	
16	HClO ₄ (0.1 M)	15 min	88	6.4:1	
17	HClO ₄ (1.0 M)	10 min	90	6.0:1	
18	HClO ₄ (2.0 M)	10 min	81	4.8:1	H ⁺ . nH ₂ O, crossing interface
19	HClO ₄ (3.0 M)	6 min	82	4.8:1	
20	LiClO ₄ (0.1M)	30 min	82	6.7:1	Li ⁺ . nH ₂ O in bulk water only
21	LiClO ₄ (1.0M)	30 min	87	6.5:1	
22	LiClO ₄ (3.0M)	30 min	81	5.1:1	

11 and 12) are shown the effect of adding these to the organic phase. Up to 10 molar excesses of the additives caused a 10–12% reduction in the yields of products for the cycloadditions with compound 4. As the molar excesses of the additives were

increased into the range of 15–50 mol, the additives took on the role of an organic solvent, and further inhibitions of the reactions were not observed.

Table 3. Effects of H⁺ and Li⁺ in the Aqueous Phase on the Reaction of 1,3-Dipole 4 with (A) Methyl Acrylate (6) and (B) 2-Cyclopenten-1-one (5) at 20 °C

(A) In-Water

4 + 6 → 8-endo + 8-exo

Entry	Water Phase	Time	Yield (%)	endo:exo	Comment
1	H ₂ O	12 h	91	9.8:1	-
2	HClO ₄ (0.0001 M)	12 h	83	11:1	-
3	HClO ₄ (0.001 M)	12 h	82	11:1	-
4	HClO ₄ (0.01 M)	12h	80	11:1	-
5	HClO ₄ (0.1 M)	12h	85	11:1	-
6	HClO ₄ (1.0 M)	10 h	89	17:1	-
7	HClO ₄ (2.0 M)	5.5 h	80	18:1	-
8	HClO ₄ (3.0 M)	3 h	82	17:1	H ⁺ and Li ⁺ complexed to endo TS in-water
9	LiClO ₄ (0.1M)	12 h	83	17:1	-
10	LiClO ₄ (1.0M)	12 h	81	18:1	-
11	LiClO ₄ (3.0M)	3.5 h	80	16:1	-

(B) In-Water

4 + 5 → 7-endo + 7-exo

Entry	Water Phase	Time	Yield (%)	endo:exo	Comment
12	H ₂ O	36 h	95	42:1	-
13	HClO ₄ (0.0001 M)	36 h	97	44:1	-
14	HClO ₄ (0.001 M)	24 h	95	52:1	-
15	HClO ₄ (0.01 M)	20 h	95	54:1	-
16	HClO ₄ (0.1 M)	13 h	96	48:1	-
17	HClO ₄ (1.0 M)	1 h	95	44:1	-
18	HClO ₄ (2.0 M)	30 min	89	43:1	H ⁺ and Li ⁺ complexed to endo TS in-water
19	HClO ₄ (3.0 M)	20 min	84	48:1	-
20	LiClO ₄ (0.1M)	36 h	91	42:1	-
21	LiClO ₄ (1.0M)	24 h	89	38:1	-
22	LiClO ₄ (3.0M)	7 h	84	24:1	-

ii. Effects of H⁺ and Li⁺ in the Aqueous Phase. *a. On-Water Reactions.* There have been extensive studies of the catalytic effects of Li⁺ ions on the Diels–Alder [4 + 2] cycloadditions as well as [2 + 2] cycloadditions and a range of other important reactions, including aldol reactions, Michael reactions, Alder–ene reactions, sigmatropic rearrangements, and Mannich reactions.^{28–39} Lithium perchlorate in diethyl ether has been widely used but other salts, such as lithium trifluoromethanesulfonate and trifluoromethane sulfonimide in

solvents such as acetone and acetonitrile, have also been explored.^{30,40} In the context of on-water chemistry, it is of particular interest to explore the presence of H⁺ and the related charge intensive Li⁺ ion as additives in the aqueous layer. In Table 2 are shown the results of adding low to high concentrations of HClO₄ and LiClO₄ to the on-water and in-water reactions in Scheme 1. The results for on-water reactions are significantly different from the in-water cases. For the on-water reactions with 1-octen-3-one (9) and phenyl acrylate

(10), small quantities of added acid, 0.0001–0.01 M, had negligible or small effects on the reactions (Table 2, entries 1–4 and 12–16). Hence, the presence of small quantities of protons in the bulk water did not influence events at the water–organic interface. However, as the quantity of added acid was increased, significant effects were encountered. For the reaction with 1-octen-3-one (9), increasing the concentration of HClO₄ in the water layer from 0.1 to 3.0 M reduced the reaction completion times, eventually to a few minutes, accompanied by a decline and eventual collapse of the endo:exo ratio of the products (Table 2, entries 5–8). A similar effect was observed for the reaction of phenyl acrylate (10) for 1.0–3.0 M concentrations of HClO₄ in the aqueous layer, (Table 2, entries 17–19).

Separate control exposure of the normal isolated endo:exo product mixtures to aqueous HClO₄ solutions showed that the product endo-isomer for the 1-octen-3-one cycloadduct 11 was rapidly isomerized to the thermodynamic exo isomer in >0.1 M HClO₄ and more slowly for the phenyl acrylate product endo-12 in >1.0 M HClO₄. The 1-octen-3-one endo cycloadduct 11 was particularly prone to acid isomerization, in a clean reaction with no more than 5% decomposition (Table S2, Supporting Information). These results indicate that with 0.1 M HClO₄ in the water layer, hydrated protons are present at the water–organic interface and give rise to stronger on-water catalysis. When the concentration of HClO₄ in water surpasses 1.0 M, these protons are crossing the water–organic interface, reducing the reaction completion times and causing isomerization of the endo-isomers (Table 2). In contrast to the in-water reactions, introduction of LiClO₄ (0.1–3.0 M) to the aqueous phase of the on-water reactions had no effect. The presence of Li⁺ ions in the bulk water did not influence the reactions occurring at the water–organic interface for these systems (Table 2).

b. In-Water Reactions. For the in-water reactions of methyl acrylate (6), the presence of small quantities of HClO₄ (0.0001–0.1 M) caused no increase in the rate of the reaction with a small increase in the product endo:exo ratio (Table 3, entries 2–5). Increasing the concentration of HClO₄ from 0.1 to 3.0 M in the solution gave significantly shorter reaction completion times and further increases in the product endo:exo ratios (Table 3, entries 6–8). The presence of LiClO₄, 0.1 and 3.0 M, in the solution gave similar reduction in the reaction completion times (Table 3, entries 9–11). The in-water cycloaddition of 4 with 2-cyclopenten-1-one (5) showed small reductions in the times to completion for 0.0001–0.1 M HClO₄ (Table 3, entries 13–16) in the solution, but for higher concentrations of 1.0–3.0 M, the reaction times were again shortened considerably (Table 3, entries 17–19). The presence of LiClO₄ (0.1–3.0 M) also significantly shortened the reaction completion times (Table 3, entries 20–22). For these in-water reactions, the product endo:exo ratio is influenced by the bulk water hydrophobic effect, particularly for compound 5, and the effect of the added salt on this ratio is complicated by the contrast in the effect of the ions (Li⁺, pro-hydrophobic; ClO₄⁻ anti-hydrophobic). These results are consistent with an expected complexation of the hydrates H⁺·*n*H₂O and Li⁺·*n*H₂O with O atoms of the 2π-organic molecules in the in-water transition states.⁴¹ Importantly, these effects did not arise for the on-water reactions, where the ions are confined to the water phase and not in contact with the reaction transition states.

iii. On H₂O versus on D₂O. The synthetic results for the on-water reactions in Table 1 suggest that there is no difference between on H₂O and on D₂O for these cycloaddition reactions.

Normal kinetic measurements show that there is no D/H isotope effect for the in-water reactions, for example, between phthalazinium-2-dicyanomethanide 4 and water-soluble methyl vinyl ketone (Figure 2 and Table S3, Supporting Information).

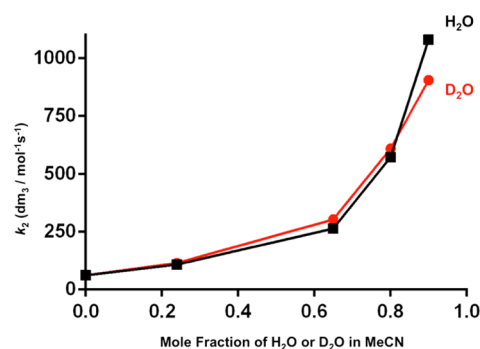


Figure 2. Comparison of the rate of cycloaddition reaction of phthalazinium-2-dicyanomethanide (4) and methyl vinyl ketone in varying mole fractions of H₂O (black) or D₂O (red) in acetonitrile at 37 °C.

This is expected, since there are no bonds involving H atoms active in the transition state. The on-water reactions are taking place in multiphase sticky mixtures of solids (products and reactants), organic oil, and water (Figure S5, Supporting Information). Normal solution kinetic measurements cannot be made, and extracts suitable for quantitative NMR analysis cannot be acquired.

Also the comparative rates of appearance of the insoluble products cannot be measured spectroscopically. In Figure 3 we

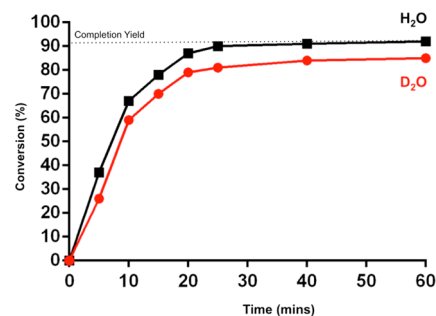


Figure 3. Comparison of the cycloaddition reaction of phthalazinium-2-dicyanomethanide (4) and 1-octen-3-one (9) in both H₂O (black) or D₂O (red) over the reaction time period of 60 min at 20 °C (see Table 1, entry 9).

show a plot of the rate of growth of products from the cycloaddition reaction of phthalazinium-2-dicyanomethanide (4) with 1-octen-3-one (9) on H₂O and on D₂O. The results in Figure 3 were acquired by setting up many reactions that were identical in every respect but with H₂O and D₂O as the aqueous phase (see Table S4, Supporting Information). The reactions were allowed to run for the times shown and worked up, and the products were isolated and quantified.

The product endo:exo ratios were constant (8.0 ± 0.5) across all the runs. The results showed conclusively that there is no D/H isotope effect in these on-water reactions. If the small experimental error range were to be considered an isotope effect, the maximum H/D rate effect would be 1.08. This laborious approach was necessary. It is also reflective of the single result quoted by Sharpless, Fokin, and co-workers for the

on-water reaction for dimethyl azodicarboxylate (Figure 1) and for the plots presented by Beare and McErlean for the on-water Claisen rearrangements of allylarylamines mentioned above, where strong D/H isotope effects were discovered.^{9,26} Alkylarylamines are significant bases with basic pK_a values of 3–5 (pK_a of conjugate acid).⁴² Azo compounds in general have a basic pK_a values of ca. 2.^{42,43} For these reactants, on-water catalysis involves proton transfer across the water–organic interface. The reactants herein, ketones and esters, have basic pK_a values of -6 to -7 and are 8–10 orders of magnitude weaker bases.⁴² On-water catalysis of their reactions involve trans-phase H-bonding and no proton transfer. These results show that on-water catalysis responds to the nature and properties of the organic reactants. Basic and nucleophilic sites in organic molecules can facilitate proton transfer across the water organic interface, and they should also facilitate the appearance of dangling OH_{free} groups prior to any potential proton transfer. It has recently been shown by Ben-Amotz and co-workers that for water in contact with hydrophobic surfaces the extent of OH_{free} groups depends on the surface area and the electrostatic nature of the surface, with a higher probability of dangling OH groups near regions of negative polarity.⁴⁴ The results of Beare and McErlean and Sharpless, Fokin, and co-workers combined with these herein point in the same direction.^{9,26} They suggest a chameleon-type of behavior for water at hydrophobic surfaces. This has significant implications for the interactions of water with hydrophobic regions in biological systems, such as protein surfaces, grooves in DNA, and ion-transport mechanisms.

CONCLUSION

In the realm of on-water chemistry, “on-water catalysis” is an interfacial interaction across the water–organic interface. The interaction varies in intensity with the properties of the molecules in the organic phase and can range from weak to strong H-bonds or proton transfer. Water at the hydrophobic organic surface displays chameleon-type behavior by responding to the properties of the organic reactant molecules.

EXPERIMENTAL SECTION

Melting points were measured on an electrothermal apparatus. IR spectra were measured using an FT-IR instrument. All the NMR spectra were measured on either a 400 or 500 MHz instrument for ^1H NMR and 100 or 125 MHz for ^{13}C NMR. The NMR spectra were measured with tetramethylsilane as an internal reference and either CDCl_3 or $\text{DMSO}-d_6$ as a solvent. The structures were also examined using COSY, NOEDS, and DEPT. J values are given in hertz (Hz). Water used for synthesis was ultrapure grade. The stereochemistries of the endo products and their exo-isomers were established from NOE difference spectra (NOEDS), which showed strong (7–10%) enhancements from H-10b to the *cis*-H-1 in the endo compounds and the absence of a through-space enhancement for the exo products. Endo:exo isomer ratios for product were determined by ^1H NMR analysis using integration of the H-10b signals, and the error for these measurements was typically $\pm 3\%$ to $\pm 5\%$. For reactions in the water medium, the water-insoluble product mixtures were separated and each product isolated as described after prior NMR estimation of the isomer ratio, unless otherwise stated. Throughout the work the isolated product yields were accurate to $\pm 1\%$ to $\pm 3\%$, with most being at the lower end of this range. Because of the low water solubilities of the reactants, the reaction milieu appeared as insoluble multiphase mixtures and suspensions in water (Figure S5, Supporting Information). All reactions were carried out in identical glassware, with a stirring speed of 1200 rpm. This stirring speed was necessary to ensure that there was sufficient mixing of the reactants. The solubility

of 1,3-dipole **4** in water was $\leq 5 \times 10^{-6}$ mol L^{-1} from UV spectra of saturated water solution at λ_{max} of 413 nm using the extinction coefficient of homogeneous solutions in $\text{H}_2\text{O}:\text{MeCN}$ (9:1 v/v). The water solubilities of dipolarophiles **5**, **6**, **9**, **10**, and **13** were obtained computationally from the chemical search engine SciFinder, where the solubility of organic compounds for any searchable compound within the CAS database are calculated using the ACD lab software.

Synthesis of Tetracyanoethylene Oxide.⁴⁵ A solution of tetracyanoethylene (3.0 g, 34 mmol) in acetonitrile (22 mL) was cooled to -5 °C in an acetone–ice bath. Hydrogen peroxide (30%) (2.66 mL, 34 mmol) was added dropwise at such a rate that the temperature of the reaction remained between 10 and 12 °C. When the addition was complete, the reaction mixture was stirred for a further 5 min and then diluted with ice-cold water (150 mL). The precipitated solid was collected by filtration and washed with water. The solid was left to dry on a suction pump for 1 h and then used immediately. The product was obtained as a white solid (3.62 g, 74%): mp 177–179 °C (sealed tube) (lit. mp 177–178 °C). Found C, 50.0; N, 38.7. $\text{C}_6\text{N}_4\text{O}$ requires C, 50.0; N, 38.9.

Caution: All operations must be carried out in a fumehood.

Phthalazinium-2-dicyanomethanide 1,3-Dipole (4).⁴⁵ A solution of phthalazine (0.91 g, 7.0 mmol) in ethyl acetate (40 mL) was cooled to below 0 °C in an ice bath. This was treated dropwise with a cooled ethyl acetate solution (5 mL) of TCNEO (1.0 g, 7.0 mmol). The yellow product precipitated immediately and was collected by filtration (1.25 g, 92%): mp 263–265 °C (acetonitrile); ^1H NMR δ_{H} (400 MHz, $\text{DMSO}-d_6$, 80 °C) 7.92–7.96 (m, 1H), 8.02–8.06 (m, 1H), 8.18–8.24 (m, 2H), 9.40 (s, 1H), 9.60 (s, 1H); ^{13}C NMR δ_{C} (100 MHz, $\text{DMSO}-d_6$, 80 °C) 63.5, 117.2, 122.8, 126.4, 128.0, 129.8, 132.8, 135.5, 150.9, 153.9; IR ν_{max} (mull)/ cm^{-1} 2191, 2159 ($\text{C}\equiv\text{N}$). Found C, 67.9, H, 3.1; N, 28.7. $\text{C}_{11}\text{H}_6\text{N}_4$ requires C, 68.0, H, 3.1, N, 28.9.

endo-3,3-Dicyano-1,2-cyclopentano-5-one-1,2,3,10b-tetrahydropyrrolo[2,1-a]phthalazine and exo-3,3-Dicyano-1,2-cyclopentano-5-one-1,2,3,10b-tetrahydropyrrolo[2,1-a]phthalazine (7).²⁷ A suspension of compound **4** (0.010 g, 0.051 mmol) in water (0.66 mL) was treated with an excess of 2-cyclopenten-1-one **5** (0.021 mL, 0.257 mmol) and stirred at room temperature to give a white suspension. The reaction was extracted into dichloromethane (3×10 mL), and the organic layer was dried over Na_2SO_4 . The solvent was removed under reduced pressure, and the residue was placed on a flash column of silica gel (230–400 mesh ASTM) and eluted with a petroleum spirit (bp 40–60 °C)–dichloromethane mixture in the gradient from 1:1 to 0:1. The products were eluted from the column as follows.

Endo-isomer: white solid, mp 228–229 °C (ethanol); ^1H NMR δ_{H} (400 MHz, $\text{DMSO}-d_6$) 2.08–2.58 (m, 4H), 3.55 (dd, 1H), 3.80–3.82 (m, 1H), 4.72 (d, J 6.3, 1H), 7.37–7.55 (m, 3H), 7.56 (d, J 7.3, 1H), 7.82 (s, 1H); ^{13}C NMR δ_{C} (100 MHz, $\text{DMSO}-d_6$) 24.5, 38.2, 38.5, 47.6, 60.5, 112.8, 113.5, 124.4, 126.6, 127.1, 130.7, 131.3, 131.2, 146.6, 213.6; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (Nujol mull) 1748 ($\text{C}=\text{O}$). Found C, 69.8; H, 4.1; N, 19.8. $\text{C}_{16}\text{H}_{12}\text{N}_4\text{O}$ requires C, 69.5; H, 4.4; N, 20.2.

Exo-isomer: gum (recolumned crude sample); ^1H NMR δ_{H} (400 MHz, $\text{DMSO}-d_6$) 2.20–2.52 (m, 4H), 3.49 (dd, 1H), 3.83–3.85 (m, 1H), 4.19 (d, J 9.2, 1H), 7.34–7.78 (m, 4H), 7.89 (s, 1H); ^{13}C NMR δ_{C} (100 MHz, $\text{DMSO}-d_6$) 22.9, 37.8, 51.1, 57.0, 60.4, 112.2, 114.3, 124.5, 126.3, 128.9, 132.5, 133.2, 146.7, 211.2; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (CCl_4 liquid cell) 1734 ($\text{C}=\text{O}$).

endo-1-Methoxycarbonyl-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-a]phthalazine and exo-1-Methoxycarbonyl isomer and endo-2-Methoxycarbonyl-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-a]phthalazine (8).²⁷ A suspension of the compound **4** (0.010 g, 0.051 mmol) in water (0.66 mL) was treated with methyl acrylate **6** (0.023 mL, 0.257 mmol) and stirred at ambient temperature, giving a pale yellow solution. The reaction was extracted into dichloromethane (3×10 mL), and the organic layer was dried over Na_2SO_4 . The solvent was removed under reduced pressure, and the residue was placed on a flash column of silica gel (230–400 mesh ASTM) and eluted with a petroleum spirit (bp 40–60

°C)–dichloromethane mixture in the gradient from 1:1 to 0:1. The products from the column were isolated in the following order.

2-endo Isomer: gum (recollected crude sample); ^1H NMR δ_{H} (400 MHz, CDCl_3) 2.53–2.98 (m, 2H), 3.96 (s, 1H), 3.90–3.96 (m, 1H), 4.34 (dd, J 8.6, 8.5, 1H), 7.13–7.53 (m, 4H), 7.81 (s, 1H); IR ν_{max} (CCl_4 liquid cell)/ cm^{-1} , 1742 (C=O).

This isomer was formed in a yield of 2% and was not included in the endo:exo ratios that are mentioned in the tables.

1-exo Isomer: gum (recollected crude sample); ^1H NMR δ_{H} (400 MHz, CDCl_3) 3.00–3.22 (m, 2H), 3.86 (s, 3H), 3.54–3.59 (m, 1H), 4.46 (d, J 8.8, 1H), 7.40–7.61 (m, 4H), 7.89 (s, 1H); ^{13}C NMR δ_{C} (100 MHz, CDCl_3) 42.3, 58.7, 113.2, 113.5, 123.4, 124.9, 126.0, 128.8, 131.5, 145.8; IR ν_{max} (CCl_4 liquid cell)/ cm^{-1} , 1751 (C=O).

1-endo Isomer: white crystalline solid, mp 132–133 °C (ethanol); ^1H NMR δ_{H} (400 MHz, CDCl_3) 2.99–3.05 (m, 1H), 3.12–3.16 (m, 1H), 3.55 (s, 3H), 3.63–3.68 (m, 1H), 4.82 (d, J 6.6, 1H), 7.26–7.45 (m, 4H), 7.66 (s, 1H); ^{13}C NMR δ_{C} (100 MHz, CDCl_3) 39.2, 42.9, 52.4, 55.8, 59.2, 113.3, 113.9, 124.7, 125.1, 126.1, 127.1, 129.7, 130.2, 144.4, 170.6; IR ν_{max} (mull)/ cm^{-1} 1742 (C=O). Found: C, 63.9; H, 4.3; N, 19.9. $\text{C}_{15}\text{H}_{12}\text{N}_4\text{O}_2$ requires C, 64.3; H, 4.3; N, 19.9.

1-endo-Hexanoyl-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-a]phthalazine and 1-exo-Hexanoyl-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-a]phthalazine (11).²⁷ A suspension of compound 4 (0.010 g, 0.051 mmol) in water (0.66 mL) was treated with an excess of 1-octen-3-one 9 (0.038 mL, 0.0255 mmol) and stirred at ambient temperature to give a pale yellow solution. The reaction was extracted into dichloromethane (3 × 10 mL), and the organic layer was dried over Na_2SO_4 . The solvent was removed under reduced pressure, and the residue was placed on a flash column of silica gel (230–400 mesh ASTM) and eluted with a petroleum spirit (bp 40–60 °C)–dichloromethane mixture in the gradient from 1:1 to 0:1. The endo:exo isomers proved difficult to isolate. The characterization given is for the mixture of the endo and exo isomers and the ratio of endo:exo isomers was determined through integration of the H-10b signals.

1-endo And 1-exo isomers: gum; ^1H NMR δ_{H} (500 MHz, CDCl_3) 0.75 (t, 3H, endo), 0.87–0.98 (m, 2H, endo, 3H, exo), 1.06–1.14 (m, 2H, endo), 1.22–1.36 (m, 2H, endo, 2H, exo), 1.64–1.73 (m, 2H, exo), 2.25–2.30 (m, 2H, exo), 2.29–2.32 (m, 2H, endo, 2H, exo), 2.88–2.92 (m, 1H endo; 1H exo), 3.03 (dd, J 13.8, 9.1, 1H, endo), 3.10 (dd, J 13.8, 11.2, 1H, exo), 3.55–3.60 (m, 1H, endo), 3.64–3.68 (m, 1H, exo), 4.50 (d, J 9.4, 1H, exo), 4.81 (d, 1H, J 7.5, 1H, endo), 6.97 (d, J 7.8, 1H, exo), 7.09 (d, J 7.4, 1H, endo), 7.26–7.53 (m, 3H, endo; 3H, exo), 7.57 (s, 1H, endo), 7.73 (s, 1H, exo); ^{13}C NMR δ_{C} (125 MHz, CDCl_3) 13.8 (endo), 13.9 (exo), 22.1 (endo), 22.7 (exo), 23.1 (exo), 22.3 (endo), 30.8 (exo), 30.9 (endo), 38.2 (exo), 38.8 (endo), 42.5 (endo), 42.3 (exo), 49.2 (exo), 50.0 (endo), 55.9 (endo), 58.0 (exo), 58.9 (exo), 112.9, 113.3 (exo), 113.1, 113.6 (endo), 123.6 (exo), 124.6 (endo), 125.3 (endo), 126.2 (exo), 127.0 (endo), 128.9 (exo), 129.3 (endo), 130.5 (endo and exo), 131.8 (endo), 132.0 (exo), 144.5 (endo), 146.3 (exo), 207.1 (exo), 208.0 (endo); HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{20}\text{N}_4\text{O}$ ($M + \text{H}$)⁺ 321.1716, found 321.1725.

The terms endo and exo refer to the isomers to which the signal belongs. Some of the exo isomer peaks are missing in the ^{13}C NMR due to overlap with the major endo isomer.

endo-1-Phenoxycarbonyl-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-a]phthalazine and exo-1-Phenoxycarbonyl-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-a]phthalazine (12).²⁷ A suspension of compound 4 (0.010 g, 0.051 mmol) in water (0.66 mL) was treated with an excess of phenyl acrylate (10) (0.035 mL, 0.257 mmol) and stirred at ambient temperature to give a pale yellow solution. The reaction was extracted into dichloromethane (3 × 10 mL), and the organic layer was dried over Na_2SO_4 . The solvent was removed under reduced pressure, and the residue was placed on a flash column of silica gel (230–400 mesh ASTM) and eluted with a petroleum spirit (bp 40–60 °C)–dichloromethane mixture in the gradient from 1:1 to 0:1. The products from the column were isolated in the following order.

1-exo Isomer: gum; ^1H NMR δ_{H} (500 MHz, CDCl_3) 3.14 (m, 1H), 3.27 (dd, J 14.2, 5.3, 1H), 3.68–3.74 (m, 1H), 4.55 (d, J 9.2, 1H), 6.74

(d, J 8.6, 1H), 7.09–7.48 (m, 6H), 7.74 (s, 1H); IR ν_{max} (neat)/ cm^{-1} 1750 (C=O).

1-endo Isomer: off-white solid, mp 126–128 °C (ethanol); ^1H NMR δ_{H} (500 MHz, CDCl_3) 3.11 (dd, J 13.7, 8.1, 1H), 3.24 (dd, J 13.7, 3.1, 1H), 3.82–3.86 (m, 1H), 4.97 (d, 1H, J 6.7, 1H), 6.60 (d, J 7.8, 2H), 7.16 (d, J 7.3, 1H), 7.23–7.26 (m, 2H), 7.31–7.33 (m, 1H), 7.40–7.48 (m, 3H), 7.60 (s, 1H); ^{13}C NMR δ_{C} (125 MHz, CDCl_3) 39.6, 43.7, 55.3, 59.5, 113.1, 113.9, 120.9, 124.8, 125.8, 126.4, 126.9, 129.4, 129.9, 131.7, 144.1, 149.9, 169.0; IR ν_{max} (neat)/ cm^{-1} 1748 (C=O). Found C, 70.2; H, 4.2; N, 16.5. $\text{C}_{20}\text{H}_{14}\text{N}_4\text{O}_2$ requires C, 70.1; H, 4.1; N, 16.4.

1,2-Diphenyl-3-cyanopyrrolo[2,1-a]phthalazine (14).²⁷ A suspension of compound 4 (0.010 g, 0.051 mmol) in water (0.66 mL) was treated with diphenylacetylene (13) (0.091 g, 0.51 mmol) and stirred under reflux for 24 h. The reaction was extracted into dichloromethane (3 × 10 mL), and the organic layer was dried over Na_2SO_4 . The solvent was removed under reduced pressure, and the residue was placed on a flash column of silica gel (230–400 mesh ASTM) and eluted with a petroleum spirit (bp 40–60 °C)–dichloromethane mixture in the gradient from 1:1 to 0:1: off-white solid, mp 213–214 °C (acetonitrile); ^1H NMR δ_{H} (400 MHz, $\text{DMSO}-d_6$, 60 °C) 7.31–7.64 (m, 13H), 8.06 (d, J 7.3, 1H), 8.95 (s, 1H); ^{13}C NMR δ_{C} (100 MHz, $\text{DMSO}-d_6$, 60 °C) 112.5, 116.3, 120.9, 121.2, 123.1, 126.0, 127.6, 127.9, 128.6, 128.7, 129.0, 130.6, 130.8, 132.1 (some overlap of signals), 146.1; IR ν_{max} / cm^{-1} (Nujol mull) 2216 (C≡N); HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{15}\text{N}_3$ ($M + \text{H}$)⁺ 346.1345, found 346.1349.

Caution: All operations must be carried out in a fumehood.

Kinetics. The kinetics were measured by recording the disappearance of phthalazinium-2-dicyanomethanide (4) 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 path length 1 cm. The temperature was maintained at 37 °C. The reaction was monitored under pseudo-first-order conditions. The 1,3-dipole 4 was recrystallized twice before use. The solvents used were HPLC grade and the water was Millipore grade. The initial concentration of the 1,3-dipole 4 was 3.2×10^{-5} M and the dipolarophiles were used in excess ranging from 100 to 700 times. The reactions were monitored using the π – π^* transition of the 1,3-dipole 4 at 420 and 413 nm for 0.80 and 0.90 mole fraction water–acetonitrile. Kinetic runs were performed at three different concentrations of dipolarophiles and repeated a minimum of three times. The rate constants were reproducible to $\pm 2\%$. The solutions changed from yellow to colorless as the rates progressed, and typical run times were on the order 5 min to 1 h, depending on the dipolarophile concentration. The results of the kinetics are shown in Figure 2, and the rate data are given in the Supporting Information (Table S3).

■ ASSOCIATED CONTENT

📄 Supporting Information

Influence of the concentration of HClO_4 (Table S1), exploring the stability of the cycloaddition products (Table S2), details on the rates of reactions from Figure 2 (Table S3) and the yields obtained that are shown in Figure 3 (Table S4), graphs showing the influence of the concentration of HClO_4 on the various reactions (Figures S1–S4), photos showing the reaction progress (Figure S5), ^1H and ^{13}C NMR spectra for 11 and 12, and selected NOEDS enhancements for compounds 7 and 8. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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