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Diaminomethylenemalononitriles and Diaminomethyleneindanediones as Dual Hydrogen Bond Donors for Anion Recognition

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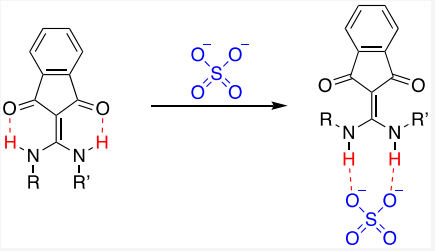
ABSTRACT: Diaminomethylenemalononitriles (DMMs) and diaminomethyleneindanediones (DMIs) are dual H-bond donors that have previously been used as organocatalysts, but their anion binding ability has not been investigated. We report the synthesis of both alkyl- and aryl-substituted DMMs and DMIs, together with a comparison of their anion binding ability with that of the analogous thioureas. The DMMs display affinity for monovalent anions, with similar anion binding affinities observed to that of the thioureas in acetonitrile, albeit with differing trends for the *N,N′*-dialkyl versus *N,N′*-diaryl compounds. In contrast, the DMIs do not bind to monovalent anions under similar conditions as a result of conformational locking through the formation of intramolecular H-bonds. This can be overcome upon addition of sulfate ions, and binding of sulfate is enhanced in a more competitive solvent (DMSO).



INTRODUCTION

Dual hydrogen bond donors, such as (thio)ureas and squaramides, have been widely investigated as binding motifs in anion recognition[1,2] and have also been exploited as organocatalysts for a wide range of reactions.[3−6] They provide a good geometrical match for oxoanions (e.g., carboxylates) and for oxygen-rich functional groups (e.g., nitro groups, sulfones, and phosphonates), which can be exploited both to provide receptors able to discriminate between anionic species[2,3,7−12] and to bind to reaction intermediates, thereby facilitating reactions. Notably, dual hydrogen bond donors show greater hydrogen bond donicity compared to single hydrogen bond donors of similar acidity which makes them more suitable for binding to basic anions or reaction substrates.[13]

The parallel (but for the most part, separate) searches for more potent anion receptors and more effective organocatalysts have led to the recent investigation of a number of alternative dual hydrogen bond donors (e.g., thiosquaramides,[14] croconamides,[14−16] deltamides,[15,17] cyanoguanidines,[18] diaminomethylenemalonitriles,[19−28] and diaminomethyleneindanediones[29,30]). In general, where both properties have been investigated, there is a correlation between potent anion receptors and effective organocatalysts, and this has been attributed to the relative hydrogen bonding ability of the different motifs.[6,31,32] This hydrogen bonding ability is governed by a combination of factors including the Brønsted acidity[17,33] and the conformational preferences of the dual hydrogen bond donor motifs.[2,16,17,34] Both of these factors are important when designing anion receptors and organocatalysts; energetic penalties apply if a conformational change is required for the formation of both H-bonds to a guest or substrate, while it is generally accepted that increased Brønsted acidity correlates with an increase in hydrogen bond strength[2] that is required for effective substrate binding.

In recent work, Miura and co-workers have evaluated both diaminomethylenemalonitriles[19−28] DMMs) and diaminomethyleneindanediones[29,30] (DMIs) as organocatalysts for a range of asymmetric conjugate addition reactions and found them to be superior to the analogous thiourea and squaramide catalysts. However, the anion binding properties of these dual hydrogen bond donor motifs have not been reported. Given the correlations between effective organocatalysts and powerful anion receptors identified above, we decided to investigate the anion binding abilities of both DMMs and DMIs. This was of particular interest since *N,N′*-(*p*-nitrophenyl) diaminomethylenemalonitrile has been reported to be relatively acidic (pK_{a1} = 7.72 in water)[35] suggesting that this motif should therefore be a powerful hydrogen bond donor. For comparison, the pK_a of the comparable *N,N′*-(*p*-nitrophenyl) squaramide has been calculated to be 10.0 in DMSO[15] (which can be converted to a pK_a of 5.40 in water using a recently described empirical method[36]).

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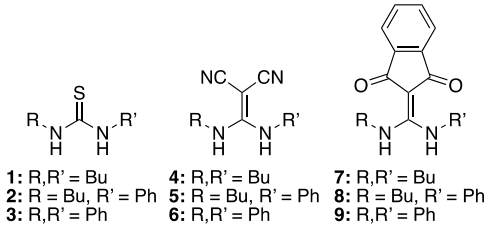
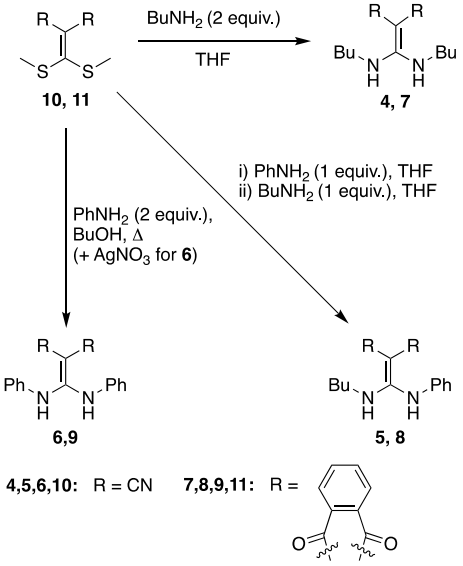
RESULTS AND DISCUSSION

Since it is well established that the presence of either alkyl or aryl substituents can impact the anion binding ability of dual hydrogen bond donors, such as the thioureas **1**−**3**, we chose to prepare three derivatives of the DMM (**4**−**6**) and DMI (**7**−**9**) cores, bearing *N*,*N*′-dibutyl, *N*-butyl, *N*′-phenyl, or *N*,*N*′-diphenyl substituents, as well as the analogous thiourea compounds (**1**−**3**), to allow a direct comparison of their anion binding properties. Thioureas **1**−**3** have all been previously reported and were readily prepared according to literature methods.[37,38]



The synthesis of DMMs **4**−**6** and DMIs **7**−**9** commenced with the known dithioether derivatives **10** and **11**, respectively (Scheme 1).[37,39] Treatment of **10** and **11** with 2 equiv of butylamine at 25 °C gave the dibutyl derivatives **4** and **7**, respectively. Compound **9** was similarly obtained upon treatment of **11** with 2 equiv of aniline in THF at reflux, while the synthesis of **8** exploited the relative rates of reactivity for the first and second substitution reactions of **11**. Hence, treatment of **11** with 1 equiv of aniline was followed by subsequent reaction with butylamine to provide **8**. Reaction of the malononitrile derivative **10** with aniline required more forcing conditions. Treatment of **10** with 2 equiv of aniline in refluxing THF for 24 h provided only the monosubstituted compound **12**. Subsequent reaction with butylamine provided moderate yields of **5**. In order to prepare **6**, a higher boiling solvent (1-butanol) was required, together with the addition of a stoichiometric amount of silver nitrate to trap the methanethiolate leaving group. Under these more forcing conditions, **6** was isolated in moderate yield.

Scheme 1. Synthesis of DMM and DMI Receptors 4−**9**



Initial screening of the anion binding abilities of the diphenyl substituted receptors **3**, **6**, and **9** was performed by the addition of 20 equiv of a range of monovalent anions (F^-, Cl^-, Br^-, I^-, NO_3^-, $H_2PO_4^-$, HSO_4^-, TsO^-, AcO^-) as the tetrabutylammonium (TBA^+) salts to solutions of the receptors in CD_3CN and analysis of the resulting differences observed in their ^1H NMR spectra (Figure 1, Figures S1−S3). Similar results were observed for the DMM and thiourea compounds, where addition of Cl^-, Br^-, NO_3^-, HSO_4^-, and TsO^- all resulted in downfield shifts of the signals attributable to the NH protons, whereas no changes were observed upon addition of I^-, suggesting that this anion is too diffuse to bind to these receptors under these conditions. Upon addition of AcO^- or F^-, similar changes to the NMR spectra were observed for **3** and **6**, with the disappearance of the NH signals attributed to deprotonation.[40−43] In the case of $H_2PO_4^-$, the disappearance of the NH signals was attributed to anion−anion proton transfer.[44] In contrast, in CD_3CN solution, no changes were observed in the ^1H NMR spectra of **9** upon addition of Cl^-, Br^-, I^-, NO_3^-, HSO_4^-, or TsO^-, suggesting these anions do not interact with the receptor under these conditions, whereas addition of AcO^-, F^-, and $H_2PO_4^-$ all resulted in the loss of the signals attributable to the NH protons, indicative of deprotonation.

^1H NMR titrations in CD_3CN were then performed to determine the binding affinities of **1**−**6** to relevant anions, with the resulting titration isotherms fitting best to 1:1 binding models in all cases (see Figure 2 for a representative example). Attempts to fit the binding data to 1:2 and 2:1 models gave irreproducible results for duplicate titrations. Inspection of the residuals suggests that the 1:1 model is valid for all compounds at low anion concentrations (5 equiv of anion relative to the receptor), but for some of the receptor−anion combinations, more complicated binding behavior occurs as the anion concentrations are increased.[45−48] The resulting binding affinities (Table 1) indicate that chloride binds with the highest affinity to all six of these receptors, presumably due to the relatively high charge density of chloride in comparison to the other anions evaluated. Whereas the thioureas follow the expected trend for binding affinities with the diphenyl compound **3** having a significantly higher affinity for chloride (K_a = 1600 M^{-1}) than the dibutyl compound **1** (K_a = 150 M^{-1}), the results for the DMM compound series are not so clear-cut, with all three compounds **4**−**6** displaying similar affinities for chloride (150−210 M^{-1}).

This difference in binding trends between the DMM derivatives and the thioureas may be a result of a combination of the relative acidities of the NH protons and the conformational preferences of these compounds. In order to bind to anions through both H-bond donors, the receptors need to adopt the *anti-*,*anti*-conformation (Figure 3). To investigate the conformational preferences of the thiourea receptors **1**−**3** and DMM receptors **4**−**6**, we performed DFT calculations in MeCN (at the M06-2X/6-31G(d) level of theory). For the thioureas, in all cases the *syn-*,*anti*-conformer is calculated to have the lowest energy. The 'reorganizational energy penalty' for dibutylthiourea (**1**) to adopt the *anti-*,*anti*-conformation required for formation of two H-bonds to an anionic guest is considerably lower than that of the diphenyl analogue **3** (2.8 kJ mol^{-1} for **1** vs 8.3 kJ mol^{-1} for **3**), so if this was the only factor involved, it would be expected that **3** should have lower affinity for anions than **1**. However, the dibutylthiourea (**1**) is approximately 8 pK_a units less acidic

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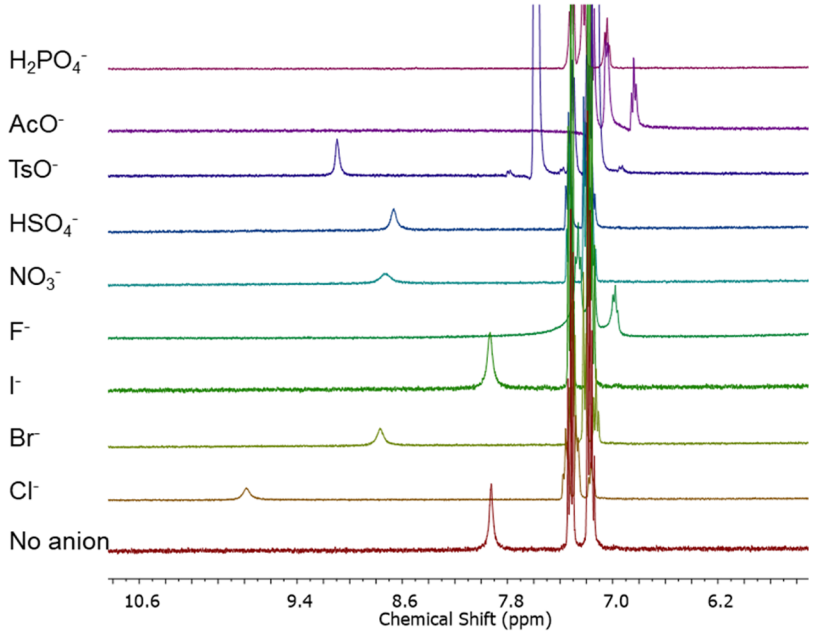

Figure 1. Anion binding screen of **6** in CD_3CN. All anions added as tetrabutylammonium (TBA^+) salts, 20 equiv.

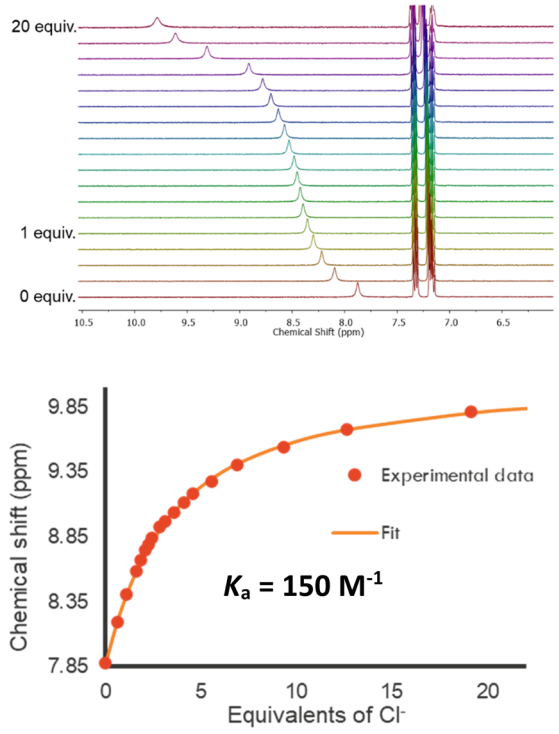

Figure 2. (Top) Representative stack plot of **6** (2.4 mM) titration with TBACl, CD_3CN. (Bottom) Binding isotherm of the NH proton signal, fit to a 1:1 binding model.

than **3**,[17] and so the increased acidity of the NH protons in the diaryl compound results in a higher binding affinity than that of the dialkyl analogue, despite the higher reorganizational energy penalty.

Crystals suitable for single crystal X-ray crystallography were obtained from an acetonitrile solution for each of **4**–**6** (Figure 4). These show that, for **5** and **6**, the *syn-,syn-* conformer is preferred in the solid state, whereas, for **4**, the *syn-,anti-* conformer is preferred. While we note that crystal packing

Table 1. Association Constants (K_a/M^{-1}) Determined by ^1H NMR Spectroscopy in CD_3CN at 300 K[a]

	Binding affinity (K_a/M^{-1})				
Receptor	Cl^-	Br^-	NO_3^-	HSO_4^-	TsO^-
1 (Bu, Bu)	150	60	20	30	40
2 (Bu, Ph)	340	110	30	50	60
3 (Ph, Ph)	1600	170	50	80	150
4 (Bu, Bu)	170	30	20	20	30
5 (Bu, Ph)	210	30	20	40	50
6 (Ph, Ph)	150	20	20	20	40

[a]All anions were added as their tetrabutylammonium (TBA^+) salts. All K_a's were rounded to two significant figures. Estimated errors in K_a < 15%.

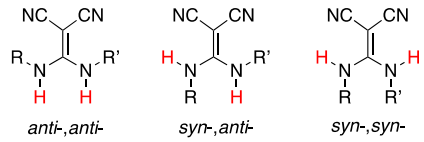

Figure 3. Conformations of malononitrile receptors.

effects may influence the conformations obtained in the solid state, these conformers reflect the lowest energy conformations obtained using DFT calculations in MeCN (performed at the M06-2X/6-31G(d) level of theory) suggesting that the conformers observed in the solid state are indicative of the preferred conformations of these compounds. However, in contrast to the thiourea derivatives, for **4**–**6**, the reorganizational energy penalties are similar for the diaryl and dialkyl derivatives (9.9 kJ mol^{-1} for **6** and 8.0 kJ mol^{-1} for **4**) and the trend in the experimentally determined chloride binding affinities is mirrored by these calculated energy differences between the lowest energy conformers and the *anti-,anti-* conformation required for anion binding.

The reorganizational energy penalties (31.8–41.0 kJ mol^{-1}) calculated for the DMI derivatives to adopt the *anti-,anti-*

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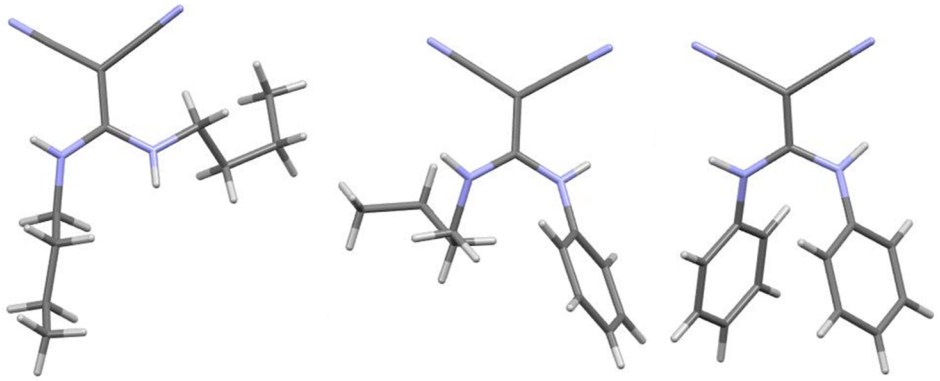

Figure 4. X-ray crystal structures of **4**, **5**, and **6**, respectively obtained from acetonitrile.

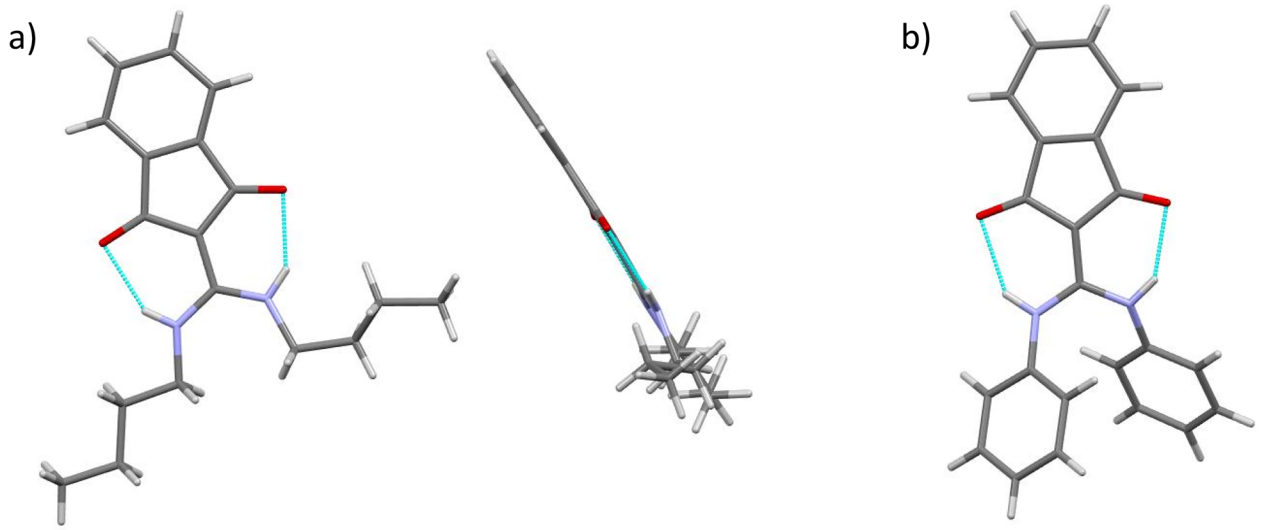

Figure 5. X-ray crystal structures of (a) **7** (front and side view, showing planarity of the DMI unit resulting from intramolecular hydrogen bonding interactions) and (b) **9**, obtained from acetonitrile.

conformations required for anion binding are significantly higher than those for the comparable thioureas (2.8−8.3 kJ mol^{-1}) or DMM derivatives (7.8−9.9 kJ mol^{-1}). This may explain the lack of observed anion binding in the ^{1}H NMR screen above and is attributed to conformational "locking" of the DMI motif in the *syn-,syn*-conformation through the formation of intramolecular hydrogen bonds between the NH protons and the indanedione carbonyl groups when in this conformation. Single crystals of **7** and **9** were obtained from MeCN solution, and X-ray crystallography of these confirmed the presence of these intramolecular hydrogen bonds (Figure 5).

We postulated that this conformational lock might be exploited to provide selective binding of anions with higher intrinsic binding affinity for the dual hydrogen bond motif and therefore evaluated the ability of **7**−**9** to bind to divalent sulfate ions, which, given their divalent charge and appropriate geometry, are expected to have increased affinity for dual H-bond donors in comparison to monovalent anions. Pleasingly, upon titration of **7**, **8**, and **9** with sulfate in CD_3CN, we observed changes in the ^{1}H NMR spectra, with binding of **8** and **9** to sulfate displaying fast exchange on the NMR time scale. While the resulting titration isotherms do not fit particularly well to a 1:1 binding model, this provides a better fit than other models and the poor fits are attributed to a combination of line broadening and conformational changes that occur upon binding (apparent K_a = 380 M^{-1} for **9** and 110 M^{-1} for **8**). Upon addition of sulfate to **7**, slow exchange was observed, providing good evidence for a 1:1 binding stoichiometry (K_a = 10 M^{-1}, as calculated directly from the relative concentrations of each species in solution[49]). The observed trend in anion binding affinities (aryl > alkyl) is consistent with the "usual" trend for (thio)ureas and squaramides.[2,15]

We envisaged that DMSO-d_6, which is a strong hydrogen bond acceptor and known to facilitate rearrangement of dual hydrogen bond donors to the *anti-,anti*-conformer,[16,34] might disrupt the intramolecular hydrogen bonding interactions and facilitate anion binding.[50] We therefore screened binding of **7**−**9** to a range of anions (Cl^-, Br^-, I^-, F^-, NO_3^-, HSO_4^-, $H_2PO_4^-$, AcO^-, TsO^-) in DMSO-d_6. Only addition of sulfate resulted in significant downfield shifts of the signals attributable to the NH protons, but ^{1}H NMR titrations and fitting of the resulting binding isotherms to 1:1 binding models provided sulfate binding affinities for **7** and **8** that were an order of magnitude larger than those obtained in CD_3CN (Table 2) indicating that, in contrast to the expected behavior in moving from CD_3CN to DMSO, which is itself a hydrogen bond acceptor and therefore expected to result in decreased anion binding affinity, disruption of the intramolecular

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Table 2. Association Constants (K_a/M^{-1}) Determined by ^1H NMR Spectroscopy at 300 K[a]

	SO_4^{2-} Binding affinity (K_a/M^{-1})[b]		
	7	8	9
CD_3CN	10[c]	110[dc]	380[e]
DMSO-d_6	180[c]	1100[c]	–[f]

[a]Sulfate added as the tetrabutylammonium (TBA^+) salt. All K_a's were rounded to two significant figures. [b]Estimated error K_a < 15%. [c]Slow exchange binding value calculated directly from concentrations. [d]Fitted to a 1:1 model for NH and ArH. [e]Fitted to a 1:1 binding model for ArH. [f]Probable deprotonation.

hydrogen bonds results in significantly higher binding affinities for sulfate in the more polar solvent. The conformational lock therefore provides a useful means of increasing the selectivity of these simple receptors for sulfate ions.

CONCLUSIONS

In summary, we have synthesized dual H-bond donor motifs, previously employed as organocatalysts, in the form of DMMs and DMIs, and evaluated their anion binding ability for the first time. The DMMs show H-bonding interactions with a range of anions. However, binding is generally weaker than that of the comparable thioureas, which is attributed to a combination of the relative reorganizational energy penalties and innate H-bond donicity of these motifs. In contrast, the DMIs do not display significant binding affinity for monovalent anions in acetonitrile. This is attributable to "conformational locking" of these dual H-bond donors in the *syn-,syn*-conformation as a result of the formation of intramolecular H-bonds. This conformation lock can be overcome by addition of sulfate anions and is enhanced by the use of a more competitive solvent, providing a novel approach for the development of sulfate selective anion receptors and demonstrating that, in the presence of an appropriate anionic guest (or reaction substrate), H-bond formation is possible with this motif.

These findings suggest that, in contrast to established examples, where increased anion binding affinities of dual hydrogen bond donors such as (thio)squaramides are well-correlated to improved organocatalytic properties,[6,31,32] these two properties of DMMs and DMIs are not correlated and this warrants further investigation. They also indicate that in the nonpolar solvents (e.g., toluene, *m*-xylene) previously employed in the conjugate addition reactions of carbonyl compounds to maleimides, catalyzed by DMIs,[29,30] the preferred conformational locking of these motifs through intramolecular hydrogen bonding would prevent dual hydrogen bonding to the carbonyl group of a maleimide, suggesting that the proposed mechanism for DMI organocatalysts[30] may need to be revised.

EXPERIMENTAL SECTION

General Experimental Methods. Nuclear magnetic resonance (NMR) spectra were recorded at 300 K using either a Bruker Avance DPX 400 or a Bruker Avance 300 spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded at the indicated frequencies. Chemical shifts are expressed as parts per million (ppm) and are referenced to solvent residual signals. The data are reported as chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, m = multiplet), coupling constant *J* in Hz, and relative integral. Low resolution mass spectra were recorded on a Bruker amaZon SL mass spectrometer using electrospray ionization (ESI, positive or negative mode). High resolution mass spectra were recorded on a Bruker Apex II Fourier Transform Ion Cyclotron Resonance (FTICR) mass spectrometer with a 7.0 T magnet, fitted with an off-axis Analytic electrospray source with quadrupole mass analyzer, and are reported as *m*/*z* (relative intensity). Infrared (IR) absorption spectra were recorded on a Bruker Alpha-E FT-IR spectrometer using attenuated total reflection (ATR) of either a solid or a thin film. Notable vibrational wavenumbers are recorded in cm^{-1}.

Tetrahydrofuran, acetonitrile, methanol, dichloromethane, and *N,N*-dimethylformamide were purified and dried using an Innovative Technology, Inc., Pure-solve solvent purification system. Compounds **1**,[38,51] **2**,[51,52] **3**,[51] 2-[bis(methylthio)methylene]malononitrile,[53] and 2-[bis(methylthio)methylene]-1*H*-indene-1,3(2*H*)-dione[54] were prepared according to literature methods.

*2-[N,N′-Di(butylamino)methylene]malononitrile (**4**).* 2-(Bis(methylthio)methylene)malononitrile (0.20 g, 1.2 mmol), THF (10 mL), and butylamine (0.2 g, 3 mmol) were stirred at room temperature for 2 min. The solution was heated to reflux in a heating block on a hot plate and stirred overnight before being cooled. The solvent was then removed under removed pressure to give a brown oil, and the residue was diluted with dichloromethane (20 mL) and washed with 1 M aqueous HCl (30 mL). The organic layer was collected, and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The organic layers were combined and dried with $MgSO_4$, and the solvent was removed under reduced pressure. The resulting brown solid was washed with hexane which gave a white solid as the product (0.15 g, 60%). Mp 58−61 °C; ^1H NMR (400 MHz, CD_3CN) δ 5.68 (s, 2H), 3.33−3.28 (m, 4H), 1.61−1.55 (m, 4H), 1.42−1.33 (m, 4H), 0.97−0.93 (t, *J* = 8, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_3CN) δ 164.4, 119.8, 44.1, 32.1, 20.4, 13.9; IR (solid) ν_{max} 3285, 2960, 2935, 2870, 2199, 2169, 1590, 1567 cm^{-1}; HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{12}H_{20}N_4Na$ 243.1586, found 243.1583.

*2-[N-Butylamino, N′-anilino)methylene]malononitrile (**5**).* A solution of 2-(Bis(methylthio)methylene)malononitrile (0.20 g, 1.2 mmol), THF (10 mL), and aniline (0.22 g, 2.4 mmol) was heated to reflux on a hot plate stirrer overnight before being cooled to room temperature. Butylamine (0.2 g, 3 mmol) was added, and the solution was heated to reflux in a heating block on a hot plate and stirred for a further 24 h. The solvent was then removed under reduced pressure, and the residue was diluted with dichloromethane (20 mL) and washed with 1 M aqueous HCl (30 mL). The organic layer was removed, and the aqueous layer was extracted with DCM (3 × 30 mL) before the organic layers were combined and the solvent was removed under reduced pressure. The resulting off-white solid was recrystallized in $CHCl_3$/hexane (1:1) to afford the desired product as a white powder (0.16 g, 67%). Mp 172−175 °C; ^1H NMR (CD_3CN, 400 MHz) δ 7.55 (s, 1H), 7.44−7.40 (m, 2H), 7.27−7.23 (m, 1H), 7.21−7.19 (m, 1H), 6.01 (s, 1H), 3.30−3.25 (m, 2H), 1.58−1.53 (m, 2H), 1.35−1.30 (m, 2H), 0.94−0.90 (t, *J* = 8 Hz, 3H). $^{13}C\{^1H\}$ NMR (CD_3CN, 100 MHz) δ 162.7, 137.6, 129.5, 125.8, 123.5, 117.3, 43.7, 35.9, 31.1, 19.4, 12.9; IR (ATR) ν_{max} 3228, 3065, 3033, 2954, 2926, 2872, 2209, 2184, 1607, 1586 cm^{-1}; HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{14}H_{16}N_4Na$ 263.1267; found 263.1267.

*2-[N,N′-Di(anilino)methylene]malononitrile (**6**).* 2-(Bis(methylthio)methylene)malononitrile (0.20 g, 1.2 mmol), *n*-butanol (10 mL), pyridine (0.46 mL, 5.9 mmol), aniline (0.56 g, 4.7 mol), and powdered silver nitrate (0.50 g, 2.9 mmol) were stirred and heated to reflux in a heating block on a hot plate and stirred overnight. The solution was then cooled to room temperature, the solvent was removed under reduced pressure, and the residue was diluted with dichloromethane (30 mL) and washed with 1 M aqueous HCl (50 mL). The aqueous layer was extracted with dichloromethane (3 × 50 mL), the organic layers were combined and dried, and the solvent was removed under reduced pressure. The resulting dark brown solid was recrystallized from dichloromethane/methanol (19:1) which gave the product as a white solid precipitate (0.08 g, 26%). Mp 250−253 °C (decomposition); ^1H NMR (CD_3CN, 400 MHz) δ 8.0 (s, 2H, NH), 7.3 (m, 4H), 7.1 (m, 6H); $^{13}C\{^1H\}$ NMR (CD_3CN, 400 MHz) δ 160.7, 137.5, 129.2, 125.7, 123.0, 116.5, 40.2; IR (ATR) ν_{max} 3232,

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3006, 2967, 2881, 2209, 2181, 1620, 1583 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{12}N_4Na$ $[M + Na]^+$ 283.0954, found 283.0954.

*2-[N,N′-Di(butylamino)methylene]-1H-indene-1,3(2H)-dione (**7**).* 2-(Bis(methylthio)methylene)-*1H*-indene-1,3(2*H*)-dione (0.21 g, 0.84 mmol) was dissolved in THF (5 mL) with triethylamine (0.1 mL) and stirred at room temperature for 5 min. Butyl amine (0.39 g, 4.2 mmol) was added to the reaction mixture which was heated to reflux in a heating block on a hot plate and stirred overnight. After 24 h the solution was cooled to room temperature, and the solvent was removed from the dark yellow solution under reduced pressure. The resulting residue was dissolved in dichloromethane (30 mL) and then washed with 1 M aqueous HCl. The organic layer was extracted and dried with $MgSO_4$, and solvent was removed to afford a yellow solid. The crude product was then recrystallized from hot ethanol to give yellow crystals (0.16 g, 57%). Mp 87−90 °C; ^{1}H NMR (400 MHz, CD_3CN) δ 8.95 (s, 2H), 7.54−7.49 (m, 4H), 3.56−3.52 (m, 4H), 1.72−1.65 (m, 4H), 1.53−1.48 (m, 4H), 1.01−0.98 (t, J = 8 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_3CN) δ 191.3, 160.3, 138.7, 132.0, 119.8, 93.0, 43.9, 31.9, 19.4, 12.9; IR (solid) ν_{max} 2957, 2927, 2971, 1658, 1630, 1594, 1485, 1429, 1382, 1359 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{25}N_2O_2$ $[M + H]^+$ 301.1911; found 301.1912.

*2-[(N-Butylamino, N′-anilino)methylene]-1H-indene-1,3(2H)-dione (**8**).* 2-(Bis(methylthio)methylene)-*1H*-indene-1,3(2*H*)-dione (0.15 g, 0.65 mmol) was dissolved in THF (5 mL) with triethylamine (0.1 mL) at room temperature. Aniline (0.11 g, 1.1 mmol) was added to the reaction mixture which was stirred at room temperature. After 6 h, butyl amine (0.1 g, 1.4 mmol) was added to the reaction mixture, and this was stirred for a further 24 h. The solvent was removed under reduced pressure, and the resulting oil was dissolved in dichloromethane, which was then washed with 1 M aqueous HCl (3 × 30 mL). The organic layer was collected and dried with $MgSO_4$, and solvent was removed *in vacuo* to afford a yellow solid. The crude product was then recrystallized from ethanol to give yellow crystals (0.09 g, 42%). Mp 94−97 °C; ^{1}H NMR (400 MHz, CD_3CN) δ 10.50 (s, 1H), 9.10 (s, 1H), 7.58 (s, 4H), 7.49−7.45 (m, 2H), 7.37−7.33 (m, 3H), 7.88−7.83 (m, 2H), 1.52−1.45 (m, 2H), 1.31−1.23 (m, 2H), 0.85−0.81 (t, J = 8 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_3CN) δ 191.7, 158.5, 138.9, 137.8, 132.4, 129.4, 126.6, 125.0, 120.2, 93.6, 44.1, 31.1, 19.3, 12.7. IR (solid) ν_{max} 3049, 2966, 2935, 2880, 2885, 1659, 1623, 1687, 1493, 1458, 1431 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{21}O_2N_2$ $[M + H]^+$ 321.1598, found 321.1594.

*2-[N,N′-Di(anilino)methylene]-1H-indene-1,3(2H)-dione (**9**).* 2-(Bis(methylthio)methylene)-*1H*-indene-1,3(2*H*)-dione (0.21 g, 0.84 mmol) was dissolved in *n*-butanol (5 mL) with triethylamine (0.1 mL) at room temperature. Aniline (0.39 g, 4.2 mmol) was added to the reaction mixture which was heated to reflux in a heating block on a hot plate and stirred overnight. After 24 h, the solvent was removed from the dark yellow solution under reduced pressure and the resulting residue was dissolved in ethyl acetate (30 mL) and then washed with 1 M aqueous HCl (2 × 15 mL). The organic layer was retained and dried with $MgSO_4$, and solvent was removed to afford a yellow solid. The crude product was then recrystallized from hot ethanol to give bright yellow crystals (0.16 g, 50%). Mp 204−207 °C; ^{1}H NMR (400 MHz, CD_3CN) δ 10.80 (s, 2H), 7.66−7.64 (m, 4H), 7.10−7.03 (m, 8H), 7.00−6.96 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 192.6, 155.1, 139.0, 136.1, 132.6, 128.6, 125.7, 123.5, 120.9, 94.6; IR (solid) ν_{max} 3050, 1660, 1632, 1581, 1462 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{22}H_{16}O_2N_2Na$ $[M + Na]^+$ 363.1104; found 363.1104.

General Method for NMR Titration Experiments. NMR titrations were performed by additions of aliquots of the desired anionic guest as the tetrabutylammonium (TBA) salt (0.1−0.2 M) made up in a solution of the receptor (2.5−4.0 mM) in either MeCN-d_3 or DMSO-d_6 (0.5% water). Both the anion salt and receptor were dried under high vacuum over P_4O_{10} to remove residual water and solvent, respectively. ^{1}H NMR spectra were recorded on a Bruker Avance DPX 500 spectrometer or a Bruker Avance DPX 400 spectrometer and calibrated to the residual proton solvent peak in MeCN-d_3 (δ = 1.94 ppm) or DMSO-d_6 (δ = 2.50 ppm) at 300 K. Stack plots were made using MestReNova Version 6.0. Where possible, nonlinear least-squares curve fitting of the titration data to a 1:1 binding model using bindfit v0.5[45,47] enabled the calculation of association constants (K_a). The obtained K_a values represent the average of two independent titrations. Errors for each set of titration data are provided in the Supporting Information and were determined as the higher value of (i) the error provided through the Bindfit program for data fitting or (ii) the standard deviation determined from duplicate measurements.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02801.

Reproduction of the ^{1}H, and ^{13}C NMR spectra of all novel compounds; details of computational methods; ^{1}H NMR binding studies and fitted titration data; details of the crystal structure determinations of **4** (CCDC # 2044087), **5** (CCDC # 2044086), **6** (CCDC # 2044085), **7** (CCDC # 2044484), and **9** (CCDC # 2044084) (PDF)

Accession Codes

CCDC 2044084−2044087 and 2044484 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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