Probing Persistent Intramolecular C−H···X (X = O, S, Br, Cl, and F) Bonding in Solution Using Benzyl Meldrum's Acid Derivatives

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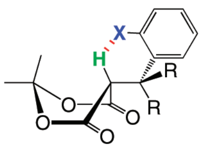

X = OMe, SMe, Br, Cl, F
R = alkyl

Persistent intramolecular interactions between acidic C−H hydrogens and a variety of acceptors (X) (X = O, S, Br, Cl, and F) in solution were probed by ^{1}H NMR experiments, using 5-benzyl Meldrum's acid derivatives. To bring about formation of intramolecular C−H···X bonding, *ortho*-substituted benzyl Meldrum's acids were designed, for which hydrogen bonding occurred through a six-membered ring. Introduction of substituents on the aromatic moiety and in the tether allowed variation of electronic and steric factors. The superior acidity of Meldrum's acids impacted the ability of the C−H hydrogen to engage in nonclassical C−H···X bonds and drove the conformational properties of benzyl Meldrum's acid, in combination with steric factors, namely A^{1,3}-allylic strain. Further understanding of intramolecular C−H···X bonds was gained by characterization of benzyl Meldrum's acids in the solid state, by X-ray analysis, and by the conformation correlated to the observations made in solution.

Introduction

Nonclassical C−H···X (where X = O and N) hydrogen bonds are prominent and well documented in the solid state.[2] However, limited experimental evidence supports persistent C−H···X hydrogen bonds in solution, which have been postulated to be of particular importance in a wide array of biological phenomena, as well as in supramolecular chemistry. Infrared and proton magnetic resonance spectroscopy have been utilized to survey the propensities of haloforms and related compounds to act as proton donors in intermolecular hydrogen bond with DMSO, pyridine, acetone, and Et_3N.[3,4] Other reports, using ^{1}H NMR, concern intramolecular *o*-carboranyl C−H···N and C−H···O interactions.[5] Further evidence of C−H···X bonding in this system has been extended to acceptors such as Br, Cl, and F.[6] The common feature of the haloforms and the *o*-carboranes is the relatively high acidity of the hydrogen involved. Consequently, the formation of persistent C−H···X bonds in solution should be promoted by enhancing the acidity of the C−H donor and thus its ability to hydrogen bond.[7,8]

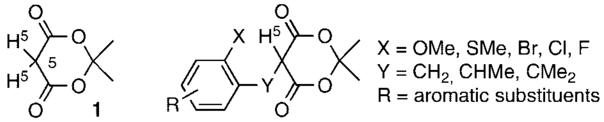

FIGURE 1. Meldrum's acid (**1**) and 5-benzyl derivatives.

Meldrum's acid (**1**) and derivatives are valuable reagents in organic synthesis (Figure 1), serving as powerful acylating agents in C−C,[9] C−O, and C−N bond forming reactions[10] and as building blocks in the synthesis of numerous natural

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(2) For reviews on the C−H···O bond in the solid state, see: (a) Castellano, R. K. *Curr. Org. Chem.* **2004**, *8*, 845–865. (b) Steiner, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 48–76. (c) Desiraju, G. R; Steiner, T. *The Weak Hydrogen Bond in Structural Chemistry and Biology*; Oxford University Press: Oxford, UK, 1999.

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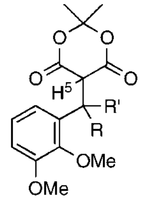
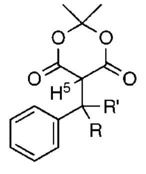
(8) In the solid state, the acidity of the X−H bond affects the lengths of the X−H···O (X = C, N, O) hydrogen bonds rather than the oxygen atom basicity, see: Taylor, R.; Kennard, O. *J. Am. Chem. Soc.* **1982**, *104*, 5063–5070.

10.1021/jo802311w CCC: $40.75

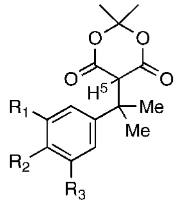
TABLE 1. **^1H NMR Chemical Shifts of Benzyl Meldrum's Acid and Benzyl Malonate Derivatives**



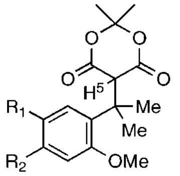
2, R = R' = H
3, R = H; R' = Me
4, R = R' = Me



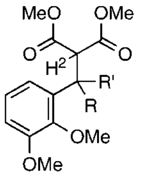
5, R = R' = H
6, R = H; R' = Me
7, R = R' = Me



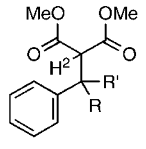
8, $R_1 = R_2$ = MeO; R_3 = H
9, $R_1 = R_3$ = MeO; R_2 = H
10, $R_1 = R_3$ = H; R_2 = MeO



11, R_1 = H; R_2 = MeO
12, R_1 = MeO; R_2 = H
13, $R_1 = R_2$ = H



14, R = R' = H
15, R = H; R' = Me
16, R = R' = Me



17, R = R' = H
18, R = H; R' = Me
19, R = R' = Me

entry	compd	H(5) chemical shift[a,b,c]	Δ ppm[e]
1	**2**	4.13 (4.63) (t)	0.39 (−0.14) (**2**−**5**)
2	**3**	4.29 (4.45) (d)	0.62 (−0.27) (**3**−**6**)
3	**4**	5.38 (5.18) (s)	1.80 (0.62) (**4**−**7**)
4	**5**	3.74 (4.77) (t)	
5	**6**	3.67 (4.72) (d)	
6	**7**	3.58 (4.56) (s)	
7	**8**	3.47 (s)	−0.11 (**8**−**7**)
8	**9**	3.59 (s)	0.01 (**9**−**7**)
9	**10**	3.50 (s)	−0.08 (**10**−**7**)
10	**11**	5.29 (s)	1.71 (**11**−**7**)
11	**12**	5.05 (s)	1.47 (**12**−**7**)
12	**13**	5.21 (5.04) (s)	1.63 (0.48) (**13**−**7**)
13	**14**[d]	3.75 (t)	0.09 (**14**−**17**)
14	**15**[d]	3.83 (d)	0.21 (**15**−**18**)
15	**16**[d]	4.60 (s)	0.78 (**16**−**19**)
16	**17**[d]	3.66 (t)	
17	**18**[d]	3.62 (d)	
18	**19**[d]	3.82 (s)	

[a] ^1H NMR chemical shifts in $CDCl_3$. [b] H(5) multiplicity is in parentheses. [c] ^1H NMR chemical shifts in DMSO-d_6 are in parentheses. [d] H(2) chemical shift. [e] Δ ppm in DMSO-d_6 and the compared compounds are in parentheses.

products.[11] Considerable attention has also been paid to the exceptionally high C−H acidity of **1**.[12] The hydrogens located α to the two carbonyl groups (5-position), with a remarkable pK_a of 4.83−4.93[13] (7.3 in DMSO),[14] confer unique chemical properties to Meldrum's acid (**1**), one of them being the ability to participate in hydrogen bonding. X-ray structural determination of this atypical carbon-based Brønsted acid revealed the presence of a nonclassical intermolecular C−H···O bond (2.43 Å) between the oxygen atom of the carbonyl group and the pseudoaxial hydrogen H(5) at the 5-position.[15,16] Toward an understanding of the interactions between acidic C−H hydrogens and a variety of acceptors (X), we set out to probe persistent hydrogen bonding in solution using Meldrum's acid derivatives. To bring about formation of an unprecedented intramolecular hydrogen bond, *ortho*-substituted benzyl Meldrum's acids were designed for which hydrogen bonding would occur through a six-membered ring. As illustrated in Figure 1, introduction of substituents (R) on the aromatic moiety and in the tether (Y) would allow variation of electronic and steric factors.

Herein, we document benzyl Meldrum's acid derivatives as a class of compounds newly identified as displaying persistent intramolecular C−H···X bonds (X = O, S, Br, Cl, and F) (Figure 1) in solution, as evidenced by ^1H NMR experiments and solid-state X-ray analysis.

Results and Discussion

1. Characterization of Persistent Intramolecular C−H···X (X = O, S, Br, Cl, and F) Bonds in Solution with ^1H NMR Spectroscopy. (a) Identification of Anomalous Chemical Shift Differences in Benzyl Meldrum's Acid Derivatives. In the course of our studies using Meldrum's acids as acylating agents in the catalytic intramolecular Friedel−Crafts reaction, 5-(2,3-dimethoxybenzyl) Meldrum's acids **2**−**4** were prepared, in which the degree of substitution at the benzylic position was varied (Table 1).[9f] It was noted that the ^1H NMR chemical shift difference for H(5) spanned 1.25 ppm; as substitution increased at the benzylic position, so did deshielding of H(5) (entries 1−3). To determine if the origin of this unexpected chemical shift variation was attributable to the *gem*-dimethyl group, unsubstituted counterparts **5**−**7** were synthesized. The latter showed

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(9) (a) Fillion, E.; Dumas, A. M. *J. Org. Chem.* **2008**, *73*, 2920–2923. (b) Fillion, E.; Dumas, A. M.; Hogg, S. A. *J. Org. Chem.* **2006**, *71*, 9899–9902. (c) Fillion, E.; Wilsily, A. *J. Am. Chem. Soc.* **2006**, *128*, 2774–2775. (d) Fillion, E.; Dumas, A. M.; Kuropatwa, B. A.; Malhotra, N. R.; Sitler, T. C. *J. Org. Chem.* **2006**, *71*, 409–412. (e) Fillion, E.; Fishlock, D. *J. Am. Chem. Soc.* **2005**, *127*, 13144–13145. (f) Fillion, E.; Fishlock, D.; Wilsily, A.; Goll, J. M. *J. Org. Chem.* **2005**, *70*, 1316–1327. (g) Fillion, E.; Fishlock, D. *Org. Lett.* **2003**, *5*, 4653–4656.

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(15) Pfluger, C. E.; Boyle, P. D. *J. Chem. Soc., Perkin Trans. II* **1985**, 1547–1549.

(16) A survey of the Cambridge Crystallographic Database revealed a very limited number of Meldrum's acids monosubstituted at the 5-position. From these, a single example of intramolecular C−H···O bond, which occurs via a seven-membered ring, was found, see: Snyder, C. A.; Selegue, J. P.; Dosunmu, E.; Tice, N. C.; Parkin, S. *J. Org. Chem.* **2003**, *68*, 7455–7459.

TABLE 2. Concentration Data for Meldrum's Acid 13 in $CDCl_3$

entry	concn (M)	^{1}H NMR chemical shift of H(5) (ppm)
1	0.044	5.22
2	0.16	5.22
3	0.35	5.23
4	0.70	5.24
5	1.38	5.26

an insignificant variation of 0.16 ppm (entries 4−6). A direct comparison of compounds **2**−**4** with **5**−**7** (Δ ppm in Table 1) revealed that the largest ^{1}H NMR chemical shift difference, 1.80 ppm, was observed for *gem*-dimethyl-substituted Meldrum's acid **4** versus **7**. Obviously, the presence of the *gem*-dimethyl group had a large influence on the chemical shift of H(5) in **2**−**4**. However, since increasing substitution at the benzylic position of Meldrum's acids **5**−**7** had a slight shielding effect on H(5), an additional factor had to be involved. It was hypothesized that the methoxy group present at the ortho position of the aromatic moiety was key in deshielding H(5). Indeed, ^{1}H NMR chemical shifts of 3,4-dimethoxybenzyl, 3,5-dimethoxybenzyl, and 4-methoxybenzyl Meldrum's acids **8**, **9**, and **10** revealed no significant difference when related to **7** (entries 7−9). The influence of the *o*-methoxy group on the chemical shift of H(5) was further confirmed with Meldrum's acids **11**−**13**. The introduction (entries 10 and 11) or absence (entry 12) of an additional electron-donating methoxy group substituent at various positions of the aromatic had little influence on the chemical shift of H(5), which remained unusually deshielded for a C−H bond of this type, with a Δ ppm between 1.47 and 1.71 when compared with **7**.

These observations were unique to 5-benzyl Meldrum's acids. As shown in Table 1 (entries 13−18), the chemical shift variations of H(2) for malonate analogues **14**−**16** and their corresponding derivatives **17**−**19** lacking the methoxy substituents revealed a similar dependence of benzylic substitution. However, with a maximum Δ ppm of 0.78 for **16**, this effect was much lower than that observed with 5-benzyl Meldrum's acids. Therefore, the greater C−H acidity of Meldrum's acids in comparison to malonates likely plays a role in deshielding H(5) when the *ortho* position of the aromatic moiety is substituted with a methoxy group.

From these results, the polarization of the C−H bond and the ensuing deshielding of H(5) in Meldrum's acids bearing a methoxy group at the *ortho* position of the aromatic moiety suggested a persistent intramolecular C−H···O bond in solution. The ability of Meldrum's acid to engage in nonclassical C−H···O hydrogen bonds as a result of its superior acidity, in combination with steric factors, deserved thorough investigation.

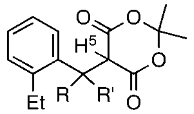
(b) Distinguishing Between van der Waals Interactions and Hydrogen Bonding as Causes of H(5) Chemical Shift Changes. From these premises, we set out to probe persistent intramolecular hydrogen bonding in solution by studying the insensitivity of proton chemical shift to concentration and temperature changes on benzyl Meldrum's acid derivatives **2**, **3**, **4**, and **13**. As shown in Table 2, varying the concentration of **13** from 0.044 to 1.38 M had no impact on the ^{1}H chemical shift of H(5), which remained deshielded.

For acids **2**−**4**, the effect of temperature on H(5) chemical shift was minimal as judged by the slight variation over a range of 105 °C (Table 3). While the above results suggested the formation of persistent intramolecular C−H···O bonds in Meldrum's acids **2**−**4**, compounds **2** and **3** showed nonsubstantial deshielding of H(5) compared to **4**, with Δ ppm values of 0.39 and 0.62, respectively, versus 1.80 ppm (Table 1, entries 1 and 2 versus 3). It was then determined if the H(5) chemical shift variations observed for acids **2** and **3** in $CDCl_3$ were the result of van der Waals contacts rather than persistent intramolecular hydrogen bonding. The influence on the chemical shift of H(5) by a non-hydrogen bond acceptor group located at the *ortho* position of the aromatic was estimated by preparing compounds **20**−**22** (Table 4). While slightly larger, the ethyl group was rationally selected to mimic the hydrogen bond acceptor methoxy group.

TABLE 3. Temperature Effect on Meldrum's Acids 2−4 in $CDCl_3$

entry	Meldrum's acid	H(5) chemical shift (ppm) at −50 °C	H(5) chemical shift (ppm) at 55 °C	Δ ppm [−50 °C − 55 °C]
1	**2**	4.31	4.07	0.24
2	**3**	4.49	4.18	0.31
3	**4**	5.59	5.25	0.34

TABLE 4. Van der Waals Contacts Contribution of Ortho Substituent to Δ ppm in $CDCl_3$ and DMSO-d_6



			H(5) chemical shift (ppm)		Δ ppm	
entry	R	R′	in $CDCl_3$	in DMSO	in $CDCl_3$	in DMSO
1	H	H (**20**)	3.69	4.66	−0.05[a]	−0.11
2	Me	H (**21**)	3.63	4.47	−0.04[b]	−0.25
3	Me	Me (**22**)	4.13	4.45	0.55[c]	−0.11

[a] Compared with **5**. [b] Compared with **6**. [c] Compared with **7**.

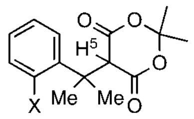
A substantial effect was only observed for **22**, which bears a benzylic *gem*-dimethyl group (Table 4, entry 3). In $CDCl_3$, the ethyl group deshielded H(5) in **22** when compared with **7** by 0.55 ppm. Once again, the *gem*-dimethyl compound displayed a unique behavior, which likely indicates that the presence of the benzylic substituents forces the group at the ortho position of the aromatic to be in close proximity with H(5). Indeed, in $CDCl_3$, a nOe between the methylene of the ethyl groups and H(5) was observed.

The fact that H(5) in Meldrum's acids **20** and **21** relative to **5** and **6** is slightly shielded, while **2** and **3** relative to **5** and **6** is deshielded, suggests that van der Waals interactions do not account for the increased chemical shift of H(5) in **2** and **3**. Considering that the only difference between **2** and **20**, and **3** and **21**, respectively, is the presence of an oxygen atom versus a methylene group, it is logical to conclude that this deviation in chemical shift is caused by hydrogen bonding. In the same vein, while H(5) of **22** is deshielded by 0.55 ppm relative to **7**, the much larger difference between H(5) of **4** compared to **7** (1.80 ppm) must be caused by a significant intramolecular C−H···O bond in solution.

In solution, it was then concluded that the chemical shift variations of H(5) in **2**−**4**, in comparison to their unsubstituted analogues **5**−**7**, were due to hydrogen bonding between the *o*-methoxy group and H(5), in accordance with the temperature studies. These data undoubtedly established that Meldrum's acids **2**−**4** form a persistent C−H···O bond in solution, the strength of this interaction being enhanced by increasing substitution at the benzylic position.

Van der Waals interactions as the sole cause of the H(5) chemical shift changes were further ruled out by studying the

TABLE 5. ^{1}H NMR Spectroscopic Data for 5-(2-Substituted Benzyl) Meldrum's Acids in CDCl$_3$ and DMSO-d_6



entry	X	H(5) chemical shift[a] (ppm)	Δ ppm[b,c]
1	H (**7**)	3.58 (4.56)	
2	OMe (**13**)	5.21 (5.04)	1.63 (0.48)
3	Et (**22**)	4.13 (4.45)	0.55 (−0.11)
4	Me (**23**)	4.18	0.60
5	F (**24**)	4.56 (4.57)[b]	0.98 (0.01)
6	Cl (**25**)	5.50	1.92
7	Br (**26**)	5.73	2.15
8	SMe (**27**)	6.50 (6.27)[b]	2.92 (1.71)

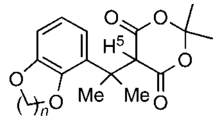
[a] ^{1}H NMR chemical shifts in DMSO-d_6 are in parentheses. [b] All the compounds were compared with **7**. [c] Δ ppm in DMSO-d_6 are in parentheses.

effect of other potential H-bond acceptors. Thus, electronic factors controlling the formation of persistent C−H···X (X = S, Br, Cl, and F) through a six-membered ring were then explored in detail. As the chemical shift difference was most pronounced between **4** and **7**, this effect was studied using *gem*-dimethylbenzyl-substituted Meldrum's acid derivatives **22**−**27**. As depicted in Table 5, the chemical shift values of H(5) were determined and compared with reference compound 5-benzyl Meldrum's acid **7**. The ethyl-substituted 5-benzyl Meldrum's acid **22** discussed previously, and the methyl derivative **23**, which lack the ability to hydrogen bond but are also more sterically demanding than **7**, slightly affected the chemical shift of H(5) (entries 3 and 4).[17] Halogens, also considered strong hydrogen bond acceptors, interacted effectively with H(5) (entries 5−7), bromide and chloride leading to substantial deshielding of H(5). Thiomethoxy-substituted Meldrum's acid **27** induced the strongest effects on H(5) chemical shift (entry 8).[18]

5-(2-Alkylbenzyl) Meldrum's acids **22** and **23** showed a Δ ppm between 0.55 and 0.60 compared to control model **7**. On the other hand, Meldrum's acids **24**−**27**, which contain potential hydrogen bond acceptors, show greater chemical shift differences, ranging from 0.98 to 2.92 ppm. Were this difference caused solely by van der Waals interactions, the chemical shift should increase with the van der Waals radius of the involved atom. However, comparing **22** and **23** to **24**, in which a smaller fluoride atom (1.47 Å)[19] causes a greater chemical shift difference than a larger carbon atom (1.70 Å), suggests that hydrogen bonding accounts for the deshielding of H(5). The same is true of **26** versus **27**, in which smaller sulfur (1.80 Å) deshields more strongly than larger Br (1.85 Å). The fact that Δ ppm correlates to polarizability of the involved atom rather than van der Waals radius is further proof of intramolecular hydrogen bonding in 5-(2-substituted benzyl) Meldrum's acids.

Aside from the presence of a hydrogen bond accepting atom as a requirement for their formation, hydrogen bonds have been shown to depend on the directionality of the involved lone pair.[20]

TABLE 6. Spectroscopic Data for 28 and 29 in CDCl$_3$



entry	*n*	H(5) chemical shift (ppm)	Δ ppm[a]
1	1 (**28**)	4.69	1.11
2	2 (**29**)	5.06	1.48

[a] The compounds were compared with **7**.

Conformationally constrained systems **28** and **29** displayed a smaller ^{1}H NMR chemical shift difference, compared with dimethoxy substrate **4**, likely a result of a nonoptimal orientation of the oxygen lone pairs in the C−H···O interaction (Table 6). This further rules out van der Waals contacts as the cause of the increased chemical shift of H(5), as these should be relatively unaffected by such a conformational change.

(c) Contribution of Geminal Benzylic Substituents to the Presence of C−H···X (X = O, S, F) Bonding. The effect of the nature of the geminal benzylic substituents on hydrogen bond formation was then examined (Table 7). Sterically congested diethyl ester and diallyl derivatives **30** and **31** displayed deshielded H(5) when compared with analogous compounds **39** and **40**, respectively (entries 1 and 2 versus entries 10 and 11). Similar observations were made for cyclopentene, cyclopentane, and cyclohexane derivatives **32**, **33**, and **34** (entries 3−5), and dimethoxy cyclohexane substrate **45** (entry 16). In all these models, the chemical shift differences (Δ ppm) in CDCl$_3$ were not as sizable as that observed for the dimethyl counterpart **13**, indicating that the greater steric hindrance afforded by the *gem*-diester, *gem*-diallyl groups, and geminal cyclic substituents had a direct impact on the ability of the ortho substituent to interact with H(5) in solution. Nonetheless, the Δ ppm values in CDCl$_3$ were indicative of persistent intramolecular C−H···O bonding in solution for **30**−**34** and **45**, but to a less extent than in *gem*-dimethyl systems **4** and **13**. This hypothesis was corroborated by studying the effect of an ethyl group located at the ortho position of the aromatic on the chemical shift of H(5), in the cyclohexyl series, with Meldrum's acid **35** (entry 6). The Δ ppm of 0.20 in CDCl$_3$ for **35** was almost 3-fold lower than the one observed for **22** (0.55), despite detecting a NOE between the methylene of the ethyl groups and H(5), and was inferior to the Δ ppm values for all Meldrum's acids **30**−**34** and **45**. Therefore, van der Waals contacts arguments did not account for the observed chemical shift variations for **30**−**34** and **45** in CDCl$_3$; it was concluded that intramolecular hydrogen bonding was key in the deshielding of H(5). The smaller Δ ppm values for this series of compounds seem to indicate that adverse steric effects were introduced, which counterbalanced the formation of a persistent C−H···O bond in solution. As a result, for compounds **30**−**34** and **45**, an equilibrium of intramolecular hydrogen bonded versus non-bonded benzyl Meldrum's acid species was formed to a variable degree, similar to **2** and **3**, thus furnishing less deshielded H(5) chemical shifts. In contrast, compounds **4** and **13** which have larger Δ ppm values in CDCl$_3$ suggest that a greater percentage of the molecules were present in the hydrogen bonded form.[21,22]

The effect of other potential H-bond acceptors was investigated. A negligible Δ ppm of 0.17, comparable to that of ethyl derivative **35** (Δ ppm = 0.20), was observed for fluoro Meldrum's acid derivative **36** and suggested the absence of a

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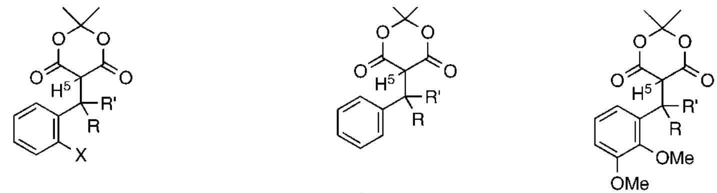
[17] Similarly to the observations made with **22**, strong nOe between the methyl group located on the aromatic moiety and H(5) was measured for **23**.

[18] For intramolecular C−H···X (X = O, S) interactions in *N*-acyl-4-isopropyl-1,3-thiazolidine-2-thiones and related 1,3-oxazolidin-2-ones, see: Cosp, A.; Larrosa, I.; Anglada, J. M.; Bofill, J. M.; Romea, P.; Urpí, F. *Org. Lett.* **2003**, *5*, 2809–2812.

[19] Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441–451.

[20] Steiner, T.; Saenger, W. *J. Am. Chem. Soc.* **1992**, *114*, 10146–10154.

TABLE 7. Effect of Benzylic Substituents on the ^{1}H NMR Chemical Shifts of Benzyl Meldrum's Acids



30, R = R' = CO_2Et; X = OMe
31, R = R' = $CH_2CH{=}CH_2$; X = OMe
32, R—R' = $CH_2CH{=}CHCH_2$; X = OMe
33, R—R' = $(CH_2)_4$; X = OMe
34, R—R' = $(CH_2)_5$; X = OMe
35, R—R' = $(CH_2)_5$; X = CH_2CH_3
36, R—R' = $(CH_2)_5$; X = F
37, R—R' = $(CH_2)_5$; X = SMe
38, R—R' = $CH{=}CH(CH_2)_3$; X = OMe

39, R = R' = CO_2Et
40, R = R' = $CH_2CH{=}CH_2$
41, R—R' = $CH_2CH{=}CHCH_2$
42, R—R' = $(CH_2)_4$
43, R—R' = $(CH_2)_5$
44, R—R' = $CH{=}CH(CH_2)_3$

45, R—R' = $(CH_2)_5$

entry	Meldrum's acid	H(5) chemical shift (ppm)^{a,b}	Δ ppm^c
1	**30**	5.31	0.46 (**30**−**39**)
2	**31**	4.76 (4.93)	1.07 (0.69) (**31**−**40**)
3	**32**	4.16	0.49 (**32**−**41**)
4	**33**	4.19 (4.28)	0.79 (0.15) (**33**−**42**)
5	**34**	3.89 (4.04)	0.45 (0.25) (**34**−**43**)
6	**35**	3.64 (3.85)	0.20 (0.06) (**35**−**43**)
7	**36**	3.61 (3.79)	0.17 (0.00) (**36**−**43**)
8	**37**	5.63 (5.31)	2.19 (1.52) (**37**−**43**)
9	**38**	5.09 (5.06)	1.39 (0.46) (**38**−**44**)
10	**39**	4.85	
11	**40**	3.69 (4.24)	
12	**41**	3.67	
13	**42**	3.40 (4.13)	
14	**43**	3.44 (3.79)	
15	**44**	3.70 (4.60)	
16	**45**	4.08	0.64 (**45**−**43**)

[a] Chemical shifts in $CDCl_3$. [b] ^{1}H NMR chemical shifts in DMSO-d_6 are in parentheses. [c] The compared compounds are in parentheses.

persistent C−H···F bond in solution.[23] On the other hand, by increasing the polarizabitity of the acceptor, the additional steric hindrance imposed by cyclic benzylic substituents was successfully overcome and C−H···X bond formation favored. As depicted in Table 7, thiomethoxy cyclohexyl substrate **37** led to the largest chemical shift difference in this series of Meldrum's acids, with a Δ ppm of 2.19 (entry 8), supporting an intramolecular C−H···S interaction in solution.

In addition, subtle variation in the structure of the *geminal* disubstituent had a profound impact on the Δ ppm as shown with cyclohexane and cyclohexene derivatives **34** and **38** (entries 5 and 9). When one of the sp^3-hybridized methylene substituents on the benzylic carbon center was replaced with a less sterically demanding sp^2-hybridized methine group (Table 7, entry 9), the chemical shift of H(5) substantially increased; Meldrum's acid **38** revealed a H(5) chemical shift of 5.09, in comparison to 3.89 for **34**. The large Δ ppm of 1.39 clearly showed that the deshielding of H(5) was due to C−H···O hydrogen bonding, and not an artifact caused by the electronics of the alkene functional group.

(d) Relative Intramolecular C−H···X (X = O, S, F) Bond Strength in $CDCl_3$ versus DMSO-d_6. At this stage, a persistent intramolecular C−H···X (X = O, S, F) bond in solution had been demonstrated for a variety of benzyl Meldrum's acids. In $CDCl_3$, the chemical shifts of H(5) and related Δ ppm values likely correlate with the relative strength of the intramolecular hydrogen bonds.

TABLE 8. Solvent Data for Meldrum's Acids 7 and 13

		H(5) chemical shift (ppm)		
entry	solvent	for **13**	for **7**	Δ ppm (**13** − **7**)
1	C_6D_6	5.20	3.25	1.95
2	$CDCl_3$	5.21	3.58	1.63
3	CD_3NO_2	5.40	4.06	1.34
4	CD_3CN	5.28	4.05	1.23
5	acetone-d_6	5.37	4.31	1.06
6	DMSO-d_6	5.04	4.56	0.48
	Δ ppm (high − low)	0.36	1.31	

It was envisaged that further information on the relative strength of the intramolecular C−H···X (X = O, S, F) hydrogen bonding would be revealed through solvent effects, which were initially probed by using Meldrum's acid **13** (Table 8). In all solvents examined, including strong hydrogen bond acceptors, H(5) of Meldrum's acid **13** exhibited a similar downfield chemical shift, with a small difference of 0.36 ppm between the highest and lowest values. On the other hand, the chemical shift of H(5) for Meldrum's acid **7**, which does not possess the ability to form an intramolecular hydrogen bond, spanned 1.31 ppm. In DMSO-d_6, the smallest difference (0.48 ppm) of the chemical shift values of H(5) between **7** and **13** was obtained. These results suggest that **13** formed a persistent intramolecular hydrogen bond in solution that was not disrupted by the nature of the medium, except in DMSO-d_6, in which an equilibria of intramolecular and intermolecular hydrogen-bonded species was observed, resulting in a decrease of the chemical shift.

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(21) The origins of the *gem*-dialkyl effect were discussed in thermodynamic terms, see: (a) Allinger, N. L.; Zalkow, V. *J. Org. Chem.* **1960**, *25*, 701–704.

(22) For a study on the *gem*-dialkyl effect on intramolecular bonding in 2-substituted propane-1,3-diols, see: Schleyer, P. v. R. *J. Am. Chem. Soc.* **1961**, *83*, 1368–1373.

(23) These two types of interactions involve different physicochemical factors and the small Δ ppm for **36** may have resulted from a combination of several effects unlike the C−H···C contact in **35**.

The relative strength of the C−H···O bond for Meldrum's acids **2**−**4** was also evaluated. The ^{1}H chemical shifts of H(5) for **2** (4.63 ppm), **3** (4.45 ppm), and **4** (5.18 ppm) in DMSO-d_6 were measured and spanned 0.73 ppm, whereas the ^{1}H chemical shifts of H(5) for **2** (4.13 ppm), **3** (4.29 ppm), and **4** (5.38 ppm) in $CDCl_3$ spanned 1.25 ppm (Table 1, entries 1−3). In DMSO-d_6, comparing **2**−**4** with analogues **5**−**7** and **20**−**22** revealed negligible and negative Δ ppm values for **2** (Δ ppm **2** vs **5** = −0.14 and Δ ppm **2** vs **20** = −0.03) and **3** (Δ ppm **3** vs **6** = −0.27 and Δ ppm **3** vs **21** = −0.02), but significant and positive Δ ppm values for **4** (Δ ppm **4** vs **7** = 0.62 and Δ ppm **4** vs **22** = 0.73). That data suggest that in DMSO-d_6, an equilibrium of intramolecular and intermolecular hydrogen-bonded species was established for **4**, thus lowering the chemical shift of H(5). For compounds **2** and **3**, this equilibrium was entirely displaced toward the intermolecular hydrogen-bonded species, providing consistent increases in H(5) chemical shifts (Table 1, entries 1 and 2), equivalent to the chemical shift values observed for **20** and **21** (Table 4, entries 1 and 2). The H(5) chemical shift increases for **2** and **3** in DMSO-d_6 versus $CDCl_3$ indicated that the intramolecular C−H···O interactions were weaker than the intermolecular C−H···$OS(CH_3)_2$, and accordingly, weaker than the intramolecular hydrogen bond found in Meldrum's acid **4**. A parallel was made with monomethoxy Meldrum's acid **13** and **38**, for which the intramolecular C−H···O interactions were of comparable strength as the one observed for **4**, with Δ ppm values in $CDCl_3$ of 1.63 and 1.39 and DMSO-d_6 of 0.48 and 0.46, respectively (Table 1, entry 12, and Table 7, entry 9). Of note, Meldrum's acid **22** did not show a deshielded H(5) in DMSO-d_6, with relatively similar chemical shifts for **20**−**22** (Table 4). This observation may suggest an alternative conformation for **22** in DMSO-d_6 compared to that in $CDCl_3$, a consequence of intermolecular C−H···O hydrogen bonding of **22** with DMSO-d_6.

Similar solvent effects were observed with other hydrogen bond acceptors. The acquisition of the ^{1}H NMR spectra of **27** and **37** in strong hydrogen bond acceptor solvent DMSO-d_6 further substantiated intramolecular C−H···S bonding in these compounds (Table 5, entry 8 and Table 7, entry 8); the H(5) chemical shifts were insensitive to solvent polarity and remained practically unchanged at a distinctly downfield position compared to **7** and **43**, respectively.

In comparison to $CDCl_3$, the chemical shift of H(5) for Meldrum's acid **24** was unaffected in DMSO-d_6 at 4.57 ppm, the same shift as **7** (Table 5, entries 1 and 5), suggesting that the intramolecular C−H···F bond in **24** is of equal strength to the intermolecular bond C−H···$OS(CH_3)_2$. The chemical shift of H(5) for Meldrum's acid **36** was equal in DMSO-d_6 to the chemical shift of H(5) for acid **43**, with a Δ ppm of zero, which further supported the absence of C−H···F in **36** (Table 7, entries 7 and 14). These data suggested that **36**, like **43**, exclusively formed an intermolecular C−H···$OS(CH_3)_2$ bond in DMSO-d_6.

Solvent effect studies were also carried out with **34** and **43**. As shown in Table 9, the chemical shift of H(5) for Meldrum's acid **43**, which does not possess the ability to form an intramolecular hydrogen bond, spanned 0.60 ppm, and a smaller range of 0.31 ppm was observed for **34**. It is noteworthy that the chemical shift of H(5) for **43** was affected to a lesser extent by the nature of the solvent then Meldrum's acid **7**. Consequently, a smaller range of 0.60 ppm for **43** versus 1.31 ppm for **7** was observed. In DMSO-d_6, the smallest difference (0.25 ppm) in the chemical shift values of H(5) between **34** and **43** was measured. The Δ ppm values discussed above are indicative of a persistent intramolecular hydrogen bond in solution for Meldrum's acid **34**, which overall parallel the observations reported in Table 8 with use of *gem*-dimethyl substrates **7** and **13**. The trend was similar to the one observed with **7** and **13** (Table 8), the smallest Δ ppm values were in DMSO-d_6 and the largest in C_6D_6 (Table 9, entries 6 and 1). Again, these results suggested that DMSO-d_6 displaced the equilibrium of intramolecular hydrogen bonded versus intermolecular hydrogen bonded benzyl Meldrum's acid species toward the latter. The fact that the chemical shift of H(5) increases in DMSO-d_6 compared to $CDCl_3$, despite the disruption of the C−H···O bond, suggests a substantial conformational change, which places H(5) in an entirely different chemical environment. As discussed previously, a Δ ppm of 0.45 in $CDCl_3$ for **34** was indicative of a weak C−H···O bond and the results obtained in DMSO-d_6 corroborated this deduction.

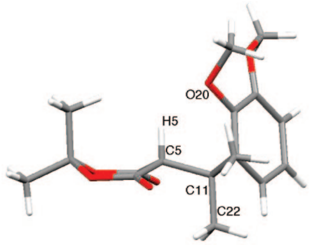
TABLE 9. Solvent Data for Meldrum's Acids 34 and 43

entry	solvent	H(5) chemical shift (ppm) for **34**	H(5) chemical shift (ppm) for **43**	Δ ppm (**34** − **43**)
1	C_6D_6	3.85	3.19	0.66
2	CD_3NO_2	4.16	3.58	0.58
3	CD_3CN	4.08	3.57	0.51
4	acetone-d_6	4.12	3.67	0.45
5	$CDCl_3$	3.89	3.44	0.45
6	DMSO-d_6	4.04	3.79	0.25
	Δ ppm (high − low)	0.31	0.60	

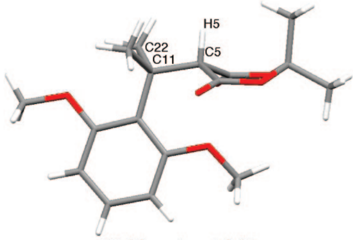
That trend was also noted for compounds **31** and **33** for which the chemical shifts of H(5) in DMSO-d_6 were slightly larger than in $CDCl_3$ (Table 7, entries 2 and 4). Moreover, while the H(5) chemical shifts of **31** in $CDCl_3$ were slightly lower than those in **13**, compound **31** provided Δ ppm values in DMSO-d_6 superior to the one observed for the *gem*-dimethyl analogue **13** (0.69 versus 0.48 ppm) (Table 7, entry 1). The correlation observed for the *gem*-dimethyl compounds regarding the relative intramolecular C−H···X (X = O) bond strength in $CDCl_3$ versus DMSO-d_6, illustrated by the chemical shifts of H(5) and Δ ppm values in both solvents, does not seem to hold for benzyl Meldrum's acids displaying greater steric hindrance at the benzylic position. Therefore, in DMSO-d_6, the chemical shift of H(5) does not correlate exclusively with the strength of the intramolecular C−H···O bond, but also to conformational changes.

In the above sections, we delineated through a series of experiments that 5-benzyl Meldrum's acid derivatives bearing an acceptor group at the *ortho* position of the arene moiety form persistent intramolecular C−H···X (X = O, S, Br, Cl, and F) bonds in solution as characterized by ^{1}H NMR spectroscopy. It was also established that the presence of a *gem*-dimethyl group at the benzylic position is an essential structural requirement in promoting hydrogen bonding, while a larger cyclic substituent weakened the intramolecular interaction in $CDCl_3$. Next, intramolecular C−H···X (X = O, S, F) bonds in solid state will be characterized and correlated with the results obtained in solution.

2. Characterization of Intramolecular C−H···X (X = O, S, F) Bonds in the Solid State by X-ray Crystallography. Further information on the intramolecular hydrogen bonding C−H···X (X = O, S, F) bond in Meldrum's acid derivatives was revealed through X-ray analysis of **2**, **3**, **4**, **10**, **22**, **24**, **27**, **35**, **36**, **38**, **43**, **45**, and **46**. Two criteria are typically



Meldrum's acid **4**



Meldrum's acid **46**

FIGURE 2. X-ray structures of Meldrum's acids **4** and **46**. The dihedral angle H(5)−C(5)−C(11)−C(22) for **4** is 176.1°. Only one molecule of the data set is illustrated. The dihedral angle for the second molecule is 177.9°. The dihedral angle H(5)−C(5)−C(11)−C(22) for **46** is 59.4°.

TABLE 10. Solid Phase Structures

acid	temp (K)	bond length (Å) C(5)−H(5)···X	Δ (sum of the van der Waals radii − obsd X-ray distance) (Å)	bond angle (θ deg) C(5)−H(5)···X
2	180	2.55 (X = O)	0.17	115.9
3	180	2.57 (X = O)	0.15	119.7
4	297[a]	2.15 (X = O)	0.57	130.6
4	180[a]	2.16 (X = O) (2.13)[b] (X = O)	0.56 (0.59)	128.2 (128.0)[b]
10	180			
22	180	2.42 (X = C)	0.48	
24	180	2.13 (X = F)	0.54	132.1
27	180	2.43 (X = S)	0.57	138.2
35	150[c]			
36	150			
38	150	2.11 (X = O)	0.61	125.5
43	150[d]			
45	180	2.12 (X = O)	0.60	134.7
46	180			

[a] A crystal phase change was observed at 291 K so data are reported for both phases. [b] The unit cell contains two molecules, thus two sets of data. [c] The unit cell contains four molecules, thus four sets of data. [d] The unit cell contains eight molecules, thus eight sets of data.

used to judge the presence of the C−H···X hydrogen bond in the solid state, namely bond length and directionality.[2] First, a H···X (X = O, S, F) distance equal to or shorter than the sum of the van der Waals radii of H and X is required. Second, the directionality is characterized by the C−H···X (X = O, S, F) bond angle (θ), a linear bond angle being ideal, and 110° being the minimum requirement.

The X-ray structures of Meldrum's acids **2**, **3**, and **4** were examined to detect the presence of an intramolecular C−H···O bond between H(5) of Meldrum's acid and the oxygen of the *o*-methyl ether of the aromatic moiety (Figure 2). In Meldrum's acid **4**, an obvious H(5)···O(20) contraction was observed (by about 0.4 Å) when compared with analogous compounds **2** and **3** (Table 10). The H···O distance was considerably shorter (2.13 to 2.16 Å) than 2.72 Å, the sum of the van der Waals radii for oxygen (1.52 Å) and hydrogen atoms (1.20 Å), which substantiates an intramolecular C−H···O bond. Since the interatomic distance H(5)···O(20) in the solid-state structures of **4** arises through attractive forces, this correlates with the NMR data in solution—the downfield shift of the acidic proton. Chemical shift variations were much less pronounced for compounds **2** and **3** (Table 1), and accordingly, the interatomic distance H(5)···O(20) in the solid state was significantly longer. A correlation between the C−H···O distance and the tendency of the triad C(5)−H(5)···O(20) to assume a linear configuration (angle (θ)) was also observed. The bond angle (θ) C(5)−H(5)···O(20) (130.6°) found in **4** was larger than the one found in **2** and **3** (Table 10). Despite these structural differences in the solid state, compounds **2** and **3** met the criteria for a C−H···O bond, which parallels the results obtained in solution.[2,24]

In solution, ^{1}H NMR studies supported the presence of a persistent C−H···F bond in Meldrum's acid **24**. In the solid state, bond length and directionality criteria were met (Table 10), with a H···F distance of 2.13 Å, which is much shorter than the sum of the van der Waals radii for H (1.20 Å) and F (1.47 Å) atoms.[25] Similarly, Meldrum's acid **27** containing a thiomethoxy acceptor revealed a C−H···S bond, with a H···S distance of 2.43 Å, which is substantially shorter than the sum of the van der Waals radii for H (1.20 Å) and S (1.80 Å) atoms. The conformation observed in the solid state is in relation with the results obtained in solution, for which Meldrum's acid **27** displayed a large chemical shift variation for H(5), likely a result of the superior polarizability of the sulfur atom. Of note, regardless of the acceptor atom in C−H···X (X = O, S, F), the difference between the sum of the van der Waals radii and the observed H···X distance in the solid state was constant for Meldrum's acids **4**, **24**, and **27**, between 0.54 and 0.57 Å.

The assessment of the X-ray structure of compounds **2**−**4**, **24**, and **27** ascertained a number of conformational similarities. First, in all the structures, the Meldrum's acid moiety was in a boat conformation in which the acidic H(5) hydrogen occupied the pseudoaxial position and the benzylic group the pseudoequatorial one. Second, the substituents on the benzylic carbon and C(5) Meldrum's acid's carbon were staggered. This feature places one of the substituents on the benzylic carbon almost perfectly antiperiplanar to the C(5)−H(5) bond of the Meldrum's acid moiety, and the aryl group gauche to H(5) and one of the carbonyl groups. Third, the conformation adopted by the aromatic group minimizes the $A^{1,3}$-allylic strain; the hydrogen at the unsubstituted ortho position (6-position) of the aromatic eclipses the benzylic substituent, which is antiperiplanar to the C(5)−H(5) bond.

The strong tendency of benzyl Meldrum's acid to adopt that conformation was confirmed by analyzing the X-ray structure of 4-methoxy derivative **10**. The features observed for compounds **2**, **3**, **4**, **24**, and **27** were found in **10**, even in the absence of an intramolecular hydrogen bond.[26] The presence of the benzylic *gem*-dimethyl group then seems to reinforce the positioning of the *ortho* substituent of the aromatic ring in close proximity to H(5). This was further established by examining the X-ray structure of **22**. The conformation of **22** in the solid state was comparable to that of structures **2**, **3**, **4**, **10**, **24**, and

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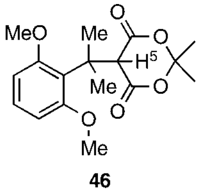
[24] Compounds **2** revealed, through analysis of the crystal packing diagram, an intermolecular C(5)−H(5)···O(10) bond (2.24 Å). Close contacts C(5)−H(5)···O(9) (2.90 Å) and C(5)−H(5)···O(10) (3.25 Å) were observed for Meldrum's acid **3**.

[25] Analysis of the crystal packing diagram showed the formation of an intermolecular C(5)−H(5)···O(10) bond (3.13 Å).

[26] An intermolecular C(5)−H(5)···O(9) bond (2.58 Å) was revealed by analysis of the crystal packing diagram.



46

H(5) chemical shift = 3.76 ppm in $CDCl_3$

FIGURE 3. Meldrum's acid **46**.

27. In solution, NOE studies suggested that the ethyl group was in the vicinity of H(5). In addition, the deshielding of H(5) observed by ^{1}H NMR in solution indicated that van der Waals contacts played a role (Table 4, entry 3). Indeed, in the solid state, the C(5)−H(5)···C(18) distance of 2.42 Å was shorter than 2.90 Å, the sum of the van der Waals radii for the carbon atom (CH_2 group) in the ethyl group (1.70 Å) and hydrogen atoms (1.20 Å).[27] These data enabled us to draw a parallel between the conformations of **22** in solution and in the solid state, and seemed to be matching. The difference of 0.48 Å between the sum of the van der Waals radii and the observed H(5)···C(18) distance in **22** was less important that the ones determined for C−H···X (X = O, S, F), a consequence of the attractive nature of the hydrogen bonding interaction.

The results obtained with **2**−**4**, **10**, **22**, **24**, and **27** suggested that 5-[1-aryl-1-methylethyl] Meldrum's acids have a well-defined three-dimensional structure in solution and in the solid state. In solution, this preferred conformation is constrained and has a very limited degree of freedom as demonstrated by the absence of temperature effect on Meldrum's acids **2**−**4** (Table 3). Even when repulsive van der Waals contacts with H(5) are present, as in **22**, the conformation is preserved. $A^{1,3}$-Allylic strain is a major contributor to the conformation adopted by 5-[1-aryl-1-methylethyl] Meldrum's acids, and when an acceptor (X) group is introduced at the ortho position of the aromatic ring, the formation of a persistent intramolecular C−H···O bond in solution is promoted.[28] The importance of $A^{1,3}$-allylic strain was confirmed with Meldrum's acid **46** (Figure 3). The presence of two *o*-methoxy substituents substantially increased $A^{1,3}$-allylic strain at the expense of hydrogen bonding. As a result, compound **46** adopted a different conformation, in which all eclipsing interactions were minimized (Figure 2). Such conformation clearly explains the chemical shift observed for H(5) in $CDCl_3$ at 3.76 ppm, resulting in a low Δ ppm of 0.18 when compared with **7**.

These data established that the conformational properties of benzyl Meldrum's acid in solution correlate to the conformation in the solid state. The parallel between solution and solid-state three-dimensional structure was further studied with cyclohexyl derivatives **35**, **36**, **38**, **43**, and **45**.

The X-ray structure of Meldrum's acid **45** displayed a short C−H···O of 2.12 Å, and a large C(5)−H(5)−O(20) angle (θ; Table 10). These observations are consistent with our analysis of the presence of intramolecular hydrogen bonding in solution. Similarly, the X-ray structure of Meldrum's acid **38** revealed a short C−H···O distance of 2.11 Å (Table 10). In solution, no nOe signal could be perceived between the hydrogens of the alkene and H(5), suggesting an antiperiplanar orientation of these groups as observed in the solid state. For **38** and **45**, the difference between the sum of the van der Waals radii and the observed H···O distance in the solid state was constant, at 0.61 and 0.60 Å, respectively, and paralleled the differences observed for the dimethyl substrates (Table 10).

The conformation of Meldrum's acid **36** in the solid state, for which no experimental evidence clearly supported a persistent C−H···F bond in solution, was similar to the one observed for compound **46** and revealed the absence of a C−H···F bond (Figure 2). Exceptionally, the Meldrum's acid moiety was in a chair conformation, placing H(5) at the pseudoequatorial position and the large alkyl group at the pseudoaxial position, respectively. The Meldrum's acid moiety was positioned at the equatorial position of the cyclohexane.[29] The conformation of Meldrum's acids **35** and **43** in the solid state was closely related to that of **36**. It was rationalized that the conformation of **35** in solution was likely similar to the one in the solid state, as the chemical shift of H(5) was slightly affected by the presence of the ethyl group (Table 7, entry 6). On the other hand, a substantial chemical shift variation for H(5) in $CDCl_3$ was observed for Meldrum's acid **22**, strongly supporting that the ethyl group was in the close proximity of H(5) in solution (Table 4, entry 3). Indeed, a different conformation was observed for dimethyl analogue **22** in the solid state.

In this section, sound evidence of the ability of the acidic C−H bond to drive the conformational properties of benzyl Meldrum's acids in the solid state through the formation of intramolecular C−H···X (X = O, S, F) bonds was presented. The data obtained by X-ray crystallography were consistent with the ^{1}H NMR studies in solution. However, due to possible packing effects, no direct correlations were found between C−H···X (X = O, S, F) bond distances in the solid state and the chemical shifts and/or the Δ ppm values in solution.

Conclusion

In summary, we established the occurrence and persistence of C−H···X (O, S, Br, Cl, and F) bond in solution using ^{1}H NMR spectroscopy for a large number of benzyl Meldrum's acids. The latter are novel and reliable probes for the evaluation of this type of nonclassical interaction in solution. The persistence of the C−H···X bond in solution was demonstrated to be dependent upon structural features present on the aromatic moiety and the benzylic position of the benzyl Meldrum's acid derivatives. The observations presented in this paper highlight the large potential of Meldrum's acid in developing an understanding of the function and nature of C−H···X interactions.

Experimental Section

General Procedure A: Preparation of Mono-Benzylic Meldrum's Acids via a One-Pot Reductive Alkylation. Meldrum's acid (1.0 equiv) and the appropriate benzaldehyde (0.98 equiv) were dissolved in absolute EtOH (0.5−1.0 M), followed by the addition of catalytic piperidinium acetate (0.1 equiv). The resulting solution was stirred vigorously for 30 min, and then cooled to 0 °C. $NaBH_3CN$ (1.5 equiv) was added portionwise over 1 h,

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[27] Analysis of the crystal packing diagram showed an intermolecular C(5)−H(5)···O(9) bond (2.84 Å).

[28] (a) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860. (b) Wender, P. A.; Ternansky, R. J. *Tetrahedron Lett.* **1985**, *26*, 2625–2628.

[29] A survey of the Cambridge Crystallographic Database revealed a single structure of benzyl Meldrum's acids, namely 5-(4-*tert*-butyl-1-phenylcyclohexyl)-2,2-dimethyl-1,3-dioxane-4,5-dione. In the absence of a hydrogen bond acceptor, 5-(4-*tert*-butyl-1-phenylcyclohexyl)-2,2-dimethyl-1,3-dioxane-4,5-dione displayed a conformation similar to that of compounds **35**, **36**, and **43**, see: Davis, A. P.; Egan, T. J.; Orchard, M. G. *Tetrahedron* **1992**, *48*, 8725–8738.

and the reaction was allowed to warm to room temperature. The reaction was monitored by TLC and upon completion was carefully quenched with 10% HCl (*extreme caution should be exercised due to the evolution of HCN gas*). Vigorous stirring was maintained until gas evolution had ceased, after which time the reaction was concentrated in vacuo to remove EtOH. The residue was resuspended in 10% HCl and extracted four times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The resulting product was generally found to be of good purity by ^1H NMR, but was recrystallized from MeOH or purified by flash chromatography on silica gel.

5-Benzyl-2,2-dimethyl-1,3-dioxane-4,6-dione (5). Compound **5** was prepared by the reductive alkylation of Meldrum's acid with benzaldehyde according to procedure A. Flash chromatography (4:1 hexanes:EtOAc) of the crude reaction mixture provided a white solid in 47% yield; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.31−7.20 (m, 5H), 3.74 (t, $J = 4.8$ Hz, 1H), 3.46 (d, $J = 4.5$ Hz, 2H), 1.70 (s, 3H), 1.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.3, 137.2, 129.7, 128.6, 127.2, 105.2, 48.1, 32.1, 28.4, 27.2.

General Procedure B: Conjugate Addition of Grignard Reagents to Meldrum's Alkylidenes. Meldrum's alkylidene was suspended in dry THF (0.1 M) and cooled to 0 °C with stirring under inert atmosphere. A solution of the appropriate Grignard reagent (2−3 equiv) in THF (or Et_2O) (0.5 to 3 M) was added dropwise, and then the reaction was allowed to warm to room temperature and monitored by TLC. Upon completion, the reaction was quenched with 5% HCl and extracted three times with EtOAc. The combined organic layers were washed with H_2O and brine, then dried over $MgSO_4$ and filtered. Concentration of the organic layers provided the crude product that was purified by either recrystallization or flash chromatography on silica gel.

5-[1-(2,5-Dimethoxyphenyl)-1-methylethyl]-2,2-dimethyl-1,3-dioxane- 4,6-dione (12). Conjugate addition of methylmagnesium bromide to 5-(1-(2,5-dimethoxyphenyl)ethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (prepared by condensation of Meldrum's acid and 2′,5′-dimethoxyacetophenone) according to procedure B provided a 50% yield of a light yellow solid after recrystallization. Mp 117−118 °C (MeOH); ^1H NMR ($CDCl_3$, 300 MHz) 7.21 (d, $J = 8.5$ Hz, 1H), 6.49−6.44 (m, 2H), 5.05 (s, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 1.74 (s, 3H), 1.67 (s, 3H), 1.61 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 164.1, 159.2, 157.4, 127.6, 127.3, 104.1, 103.7, 99.3, 55.1, 55.0, 53.0, 40.0, 28.4, 26.8, 25.5; HRMS(EI) *m/z* calcd for $C_{17}H_{22}O_6$ (M^+) 322.1416, found 322.1423.

General Procedure C: Preparation of Malonates via Acid-Catalyzed Ring Opening of Meldrum's Acid Derivatives. In a typical reaction, Meldrum's acid derivative was dissolved in a 1:1 mixture of Et_2O:MeOH (0.2 M) and concentrated sulfuric acid (1−2 equiv). The reaction mixture was heated to 50 °C for 24 h. After cooling to room temperature, the reaction mixture was diluted with Et_2O, washed with $NaHCO_3$ (aq) and brine, then dried over $MgSO_4$ and filtered. Concentration of the organic layer provided the crude product that was purified by flash chromatography on silica gel.

Dimethyl 2-(2,3-Dimethoxybenzyl)malonate (14). Compound **14** was prepared by ring opening of 5-(2,3-dimethoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2**), using procedure C to provide a 73% yield of a clear oil after purification by flash chromatography (9:1 hexanes:EtOAc); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.91 (t, $J = 7.9$ Hz, 1H), 6.78 (d, $J = 8.1$ Hz, 1H), 6.71 (d, $J = 7.6$ Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.78 (t, $J = 7.8$ Hz, 1H), 3.66 (s, 6H), 3.19 (d, $J = 7.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.4, 152.5, 147.3, 131.3, 123.7, 122.3, 111.4, 60.4, 55.6, 52.4, 52.0, 29.8; HRMS(EI) *m/z* calcd for $C_{14}H_{18}O_6$ (M^+) 282.1103, found 282.1100.

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Supporting Information Available: Experimental procedures, NMR spectra, X-ray structures, and cif files. This material is available free of charge via the Internet at http://pubs.acs.org.

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