Chemical Science

Cite this: *Chem. Sci.*, 2012, **3**, 766

www.rsc.org/chemicalscience

EDGE ARTICLE

Low-temperature ketene formation in materials chemistry through molecular engineering†

Frank A. Leibfarth,[a] Martin Wolffs,[a] Luis M. Campos,[b] Kris Delany,[a] Nicolas Treat,[a] Matthew J. Kade,[a] Bongjin Moon*[c] and Craig J. Hawker*[a]

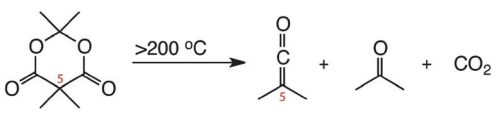
Received 24th October 2011, Accepted 21st November 2011
DOI: 10.1039/c2sc00841f

The thermolysis of Meldrum's acid derivatives has emerged as a powerful methodology to generate ketenes in polymeric structures, but the required high temperatures for ketene formation may reduce its broad applicability. We take a molecular approach toward addressing this limitation by engineering Meldrum's acid derivatives to undergo thermolysis at significantly lower temperatures. Two distinct strategies are presented and a thorough understanding of the molecular interactions governing their reactivity is provided through model compound design and synthesis, crystal structure analysis, and computation of transition structures. The generality of these molecular design principles allows for the generation of ketenes under mild thermal conditions, providing significant opportunities as a comprehensive and wide-ranging tool for controlling reactivity in both chemical and materials science applications.

Introduction

As polymer chemists seek to design materials that move beyond the traditional applications of commodity plastics, particular attention has shifted to the synthesis of functional polymers to address future challenges in health, energy, defense and environmental technologies.[1] Living polymerization strategies have provided unparalleled control over polymer synthesis, but functional polymers for next-generation material applications require marrying precision polymer synthesis with strategies that provide versatile, robust, and orthogonal chemical modification of polymers.[2,3] Recently our group and others have demonstrated the versatility of ketenes[4] in polymer chemistry[5] as an effective functional group for crosslinking and/or functionalization of polymer thin-films.[6] To date, this methodology has provided opportunities in a number of advanced applications, including the patterning of substrates,[6,7] controlled crosslinking of commodity polyolefins[8] and fabrication of mechanically robust, solvent–stable nanostructured materials.[9] Crucial for this methodology has been the use of 5,5-dialkyl Meldrum's acid[10] as a stable and modular ketene precursor that can be incorporated into a variety of polymer backbones. Specifically, upon heating dialkyl derivatives at elevated temperatures (>200 °C), a thermal decomposition of the strained Meldrum's acid ring provides the desired dialkyl ketene along with acetone and carbon dioxide (CO_2) (Scheme 1).[11] Although this thermolysis temperature is well-suited to robust polyolefins, where standard processing conditions require high temperatures,[12] thermally sensitive materials are not amenable to this type of processing.[13] Accordingly, we sought to molecularly engineer Meldrum's acid derivatives in order to develop a family of ketene precursors with lower activation temperatures.

Our observation that spiro-ring strain at the five position of Meldrum's acid lowers the ketene formation temperature (T_{kf})[6] gave us confidence that the structure and energetics of Meldrum's acid derivatives dictates their reactivity. Further, literature reports have noted that interactions of the Meldrum's acid carbonyls with electron withdrawing and/or donating moieties generate ketenes at lower temperatures.[14] For example, neighboring group participation (NGP) has been well established for decades and employs through-space interactions between Lewis bases and carbonyls to accelerate and/or determine the stereochemistry of reactions.[15] Conversely, Fillion and co-workers



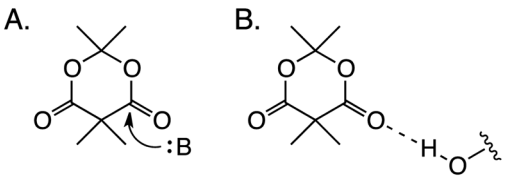
Scheme 1 Thermolysis of Meldrum's acid to ketene, acetone and carbon dioxide.

[a]*Materials Research Laboratory, Materials Department, and Department of Chemistry and Biochemistry, University of California, Santa Barbara, CA, USA. E-mail: hawker@mrl.ucsb.edu*
[b]*Department of Chemistry, Columbia University, New York, New York, USA 10027*
[c]*Department of Chemistry, Sogang University, Seoul, 121-742, Korea. E-mail: bjmoon@sogang.ac.kr*

† Electronic supplementary information (ESI) available: Experimental procedures, synthetic details, complete characterization of molecules and crystal structure details. CCDC reference numbers 850274–850278. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2sc00841f

recently found that Lewis acidic rare-earth triflates and/or Brønsted acids activate the Meldrum's acid carbonyl.[16] They employed these Meldrum's acid derivatives as highly reactive electrophiles in catalytic Friedel–Crafts type chemistry, predicting a ketene intermediate to be formed at moderate temperatures (<150 °C).[16–19]

In our efforts to molecularly engineer Meldrum's acid containing materials for the generation of ketenes at low temperatures, we chose to pursue two distinct mechanisms: the activation the Meldrum's acid carbonyls by (1) intramolecular electron donation of a Lewis base into the carbonyl carbon atom (Scheme 2A) and (2) electron withdrawal by a Brønsted acid (Scheme 2B). Particular attention is given to understanding the mechanism of these distinct approaches through model compound design and synthesis, crystal structure analysis, and computational studies of the transition structures. The molecular design principles, materials synthesis, and further understanding of the thermolytic chemistry described herein will be of broad use to synthetic chemists and material scientists for a variety of applications.



Scheme 2 Pathways to lower the thermolysis temperature of Meldrum's acid derivatives through interactions with (a) Lewis bases or (b) Brønsted acids.

Results and discussion

Lewis base activation

Initially, the intramolecular interaction of Lewis bases with the carbonyl carbons of Meldrum's acid was examined. Specifically, we hypothesized that the presence of an intramolecular heteroatom would lower the energy barrier toward thermolysis (Fig. 1A). Based on previous studies of neighboring group effects,[15,20–22] it is important to carefully select both the nature of the Lewis base and the ring size in transition structure **1** to optimize the interaction. To explore the utility and scope of this chemistry, we designed and synthesized a number of derivatives containing different Lewis bases in various intramolecular relationships with the Meldrum's acid carbonyl (Fig. 1B).

The three molecules (**2**, **3** and **4**) initially employed for screening the validity of the proposed mechanism are structurally similar, varying only with respect to the Lewis basic heteroatom. All three are able to form the proposed five-membered ring transition structures (**1**) and contain Lewis bases that are known to participate in NGP, including ethers,[23] thioethers,[24] and amines.[20,25] The styrenic derivatives of the comparative molecules were selected due to their utility in radical polymerization (Fig. 1C), which will allow these monomers to be incorporated into a range of material platforms.[26–29] Furthermore, examination of the polymers derived from these molecules is advantageous, as these materials are not volatile and allow the thermolysis behaviour to be studied without problems associated with sublimation.

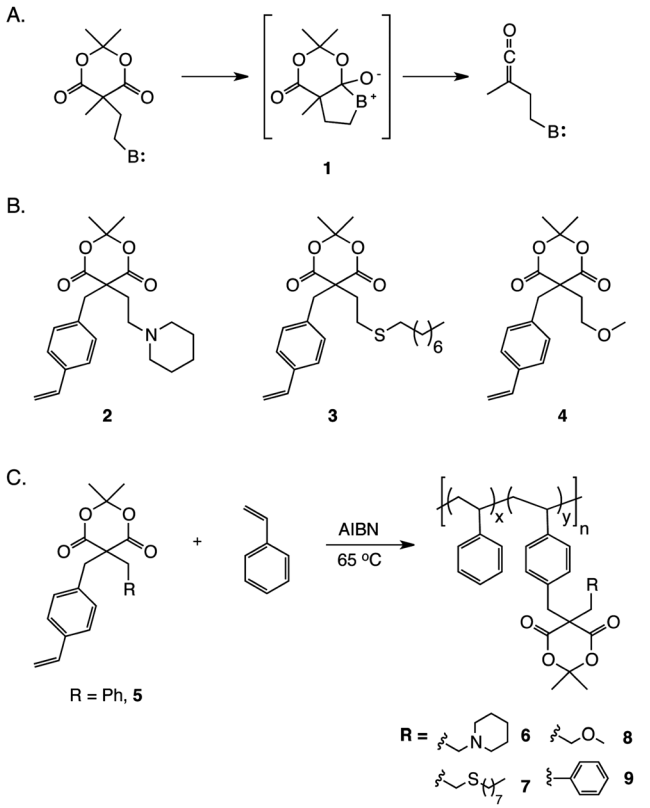
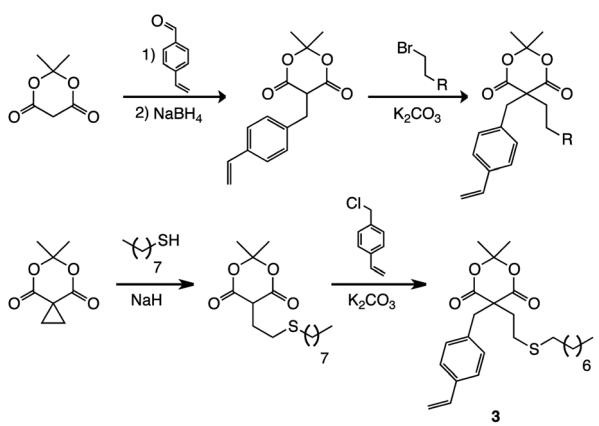


Fig. 1 (A) The proposed mechanism of intramolecular Lewis base activation to lower the thermolysis temperature of Meldrum's acid derivatives. (B) Monomers with different Lewis bases designed and synthesized and (C) subsequent radically polymerized to afford Meldrum's acid containing materials.

Syntheses of the styrenic monomers generally began with a Knoevenagel condensation of 4-vinylbenzaldehyde with Meldrum's acid and *in situ* reduction to yield the 5-(*para*-vinylbenzyl)-substituted Meldrum's acid.[30] Subsequent alkylation at the five position under mildly basic conditions with the appropriate 2-bromoethyl derivative affords the desired β-substituted Meldrum's acid with appropriately placed heteroatoms for NGP (Scheme 3) (see ESI†). Alternatively, monomer **3** could be



Scheme 3 Synthesis of Lewis base-containing Meldrum's acid derivatives.

prepared by ring-opening of the electrophilic cyclopropyl Meldrum's acid[31] with an organic thiol under basic conditions followed by alkylation with *para*-vinylbenzyl chloride. Radical polymerization of these Meldrum's acid derivatives was achieved with the use of azobisisobutyronitrile (AIBN) at 65 °C under oxygen-free conditions (Fig. 1C).

To understand the thermolysis behavior of Meldrum's acid derivatives and determine their T_{kf}, thermal gravimetric analysis (TGA), which measures mass loss as a function of increasing temperature, was employed. TGA has previously been used as a tool to measure the mass loss of acetone and CO_2 accompanying ketene formation from Meldrum's acid derivatives.[6,9] Fig. 2 shows the TGA curves of the polymers made from monomers **2**, **3** and **4**. An initial mass loss is evident for all polymers well below the ceiling temperature of polystyrene and is in close agreement with the theoretical mass loss of acetone and CO_2 to form the desired ketene. Similar results were also observed when the monomers were copolymerized with styrene, with slight differences in % weight loss, due to the different overall molecular weights for the repeat units. This can be seen in Fig. 2 where the TGA curves are normalized and analyzed against the parent polymer **9** of the dibenzyl Meldrum's acid reported previously.[6,9]

As shown in Fig. 2, the thioether (**7**) and ether (**8**) polymers show negligible changes in thermolysis temperature as compared to the parent polymer **9**. In contrast, the polymer bearing a tertiary amine (**6**) shows a considerably lower temperature at which acetone and CO_2 are released. If the temperature at which 5 mol% of acetone and CO_2 has been generated is defined as the T_{kf}, then the thermolysis temperature of **9** is 216 °C, while that of **6** is 158 °C. This significant difference of ~60 °C in thermolysis temperature from the parent Meldrum's acid suggests that the Lewis basic amine plays an important role in activating the Meldrum's acid toward thermolysis. Ketene formation from monomer **2** was confirmed by TGA coupled mass spectroscopy and thermolysis of monomer **2**, which resulted in the characteristic peaks in the ^{13}CNMR spectrum at 214.8 and 215.3 ppm corresponding to the carbonyl carbons of the two isomers (*cis* and *trans*) of the cyclobutanedione dimerization product.

To further investigate the effect of nitrogen-containing Lewis bases, a set of Meldrum's acid derivatives was synthesized to explore the importance of the intramolecular orientation of the neighboring heteroatom as well as the basicity of the nitrogen atom.[32–34] The monomers and the TGA results from their corresponding polymers are shown in Fig. 3. Monomer **10** will lead to an increase in the ring size of the proposed transition state **1** to a six-membered ring, which is known to significantly diminish the rate of reaction in NGP. As shown in Fig. 3B, the thermolysis temperature of the polymer derived from **10** is almost 50 °C higher than for **6**, with an onset temperature of 207 °C. To decouple the intramolecular from intermolecular influence of the tertiary amine, the synthesis of the extended amino monomer **11** was accomplished. Significantly, this derivative actually increases the thermolysis temperature, which can be attributed to a remote electronic effect. Lastly, to probe the influence of nitrogen atoms with varying Lewis basicities, **12** was designed to allow the proper structure for a five-membered ring TS in **1** but with a less Lewis basic nitrogen contained in the aromatic triazole ring. Fig. 3B shows that the thermolysis onset temperature of the polymer derived from **12** is 190 °C, an intermediate value between the thermolysis temperature of **6** and the parent polymer, **9**. Taken together, these results prove that subtle differences in molecular design can dramatically modulate the kinetic barrier to thermolysis over a wide range of temperatures, thereby displaying the generality of this approach to tune T_{kf} of Meldrum's acid derivatives.

In order to rationalize the significant drop in temperature provided by monomer **2**, crystal structures of four relevant molecules were studied. The structures of **2** and **10**‡ are presented in Fig. 4, while the structures of **5** and **12** can be found in ESI†. Interestingly, a sterically unfavorable *gauche* conformation was observed for the two-carbon spacer between the Meldrum's acid ring in **2** and the tertiary amine. This solid-state conformation puts the Lewis basic tertiary amine in close proximity to the

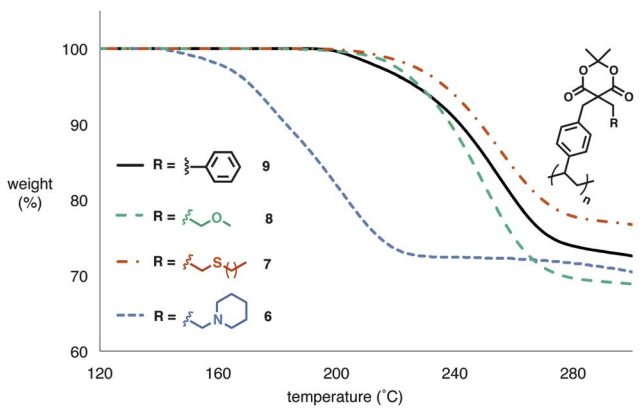


Fig. 2 TGA curves of Meldrum's acid containing polymers. The drop in mass corresponds to the loss of acetone and CO_2, which accompanies ketene formation.

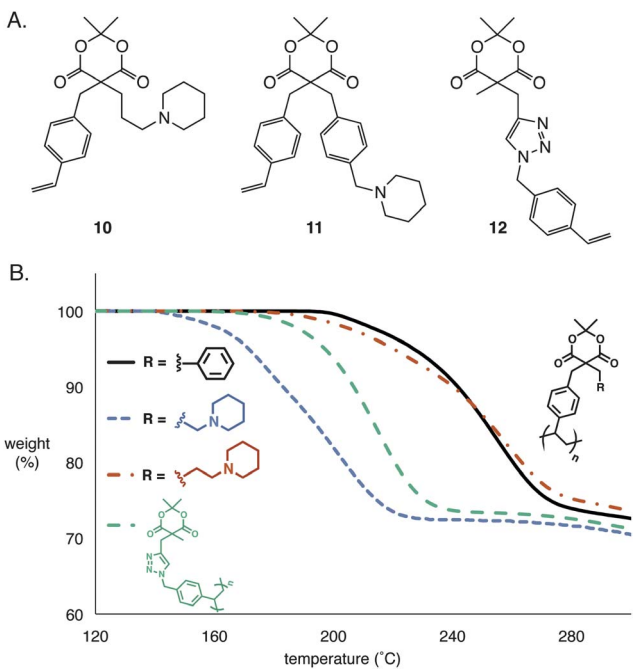


Fig. 3 (A) Nitrogen containing Meldrum's acid derivatives synthesized and (B) the TGA curves of the polymers derived from each derivative.

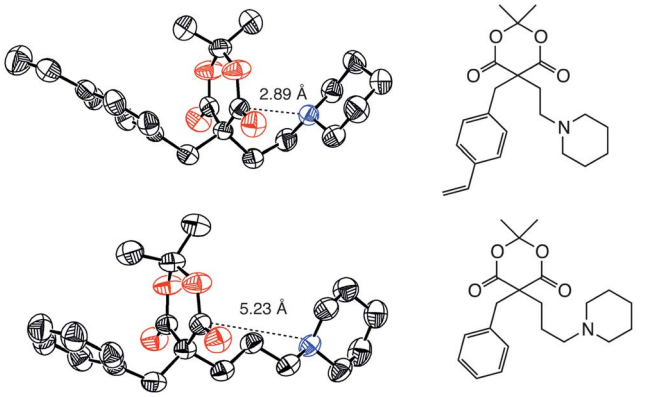


Fig. 4 ORTEP diagrams of tertiary amine containing monomers **2** and **10** with 50% probability ellipsoids. **2** shows a short 2.89 Å distance between the nitrogen and carbonyl carbon, which is in contrast to the long 5.23 Å distance for **10**.

electron deficient carbonyl carbon, a distance measuring only 2.9 Å. This distance is significantly less than the 3.2 Å that the van der Waals radii would predict,[35] and suggest the two atoms in monomer **2** have an interaction which overcomes their inherent steric repulsion. Significantly, the intramolecular phenomenon is similar to that observed by Burgi and Dunitz for amines and ketones,[36] which led to their well-known prediction about the angle of attack on a carbonyl.[37] When comparing the structure of **2** to the crystal structure of monomer **10**, the three-carbon spacer between the Meldrum's acid ring and tertiary amine is in the sterically favorable *anti* conformation, placing the tertiary amine a significant distance from the carbonyl carbon of Meldrum's acid (5.2 Å). The interaction of the amine with the carbonyl carbon in the crystal structure of monomer **2** indicates that this important intramolecular interaction may have implications on the chemistry of **2** and, thus, the polymeric material **5**, as was hypothesized in Fig. 1A.

While we have been able to demonstrate that molecular design of Meldrum's acid derivatives can lead to significant lowering of the thermolysis temperature, the transition state and mechanism is difficult to probe experimentally because of the high temperatures and fast kinetics of thermolysis. For this reason, a range of computational studies was performed in order to understand the mechanism for ketene formation from Meldrum's acid derivatives. To the best of our knowledge, no computational study on the thermolysis of dialkyl Meldrum's acid to dialkyl ketene has been reported, although thermolysis of different Meldrum's acid derivatives and various dioxinones to acylketenes or cumulenones has been studied.[38–41] All computations were carried out using Density Functional Theory (DFT) at the B3LYP/6-31G* level of theory.[42] By computing the thermolysis of 5,5′-dimethyl Meldrum's acid, an analogue of **5**, and using that as a starting point, the energies of the transition structures of a number of derivatives were compared.

For all calculations, the styrene ring was represented as a methyl group to simplify the structural degrees of freedom of the derivatives and minimize computation time. The thermolysis of the analogue of monomer **5** was computed and a concerted mechanism was found with coincident loss of acetone and CO_2 and a relative activation energy ($\Delta E^{\ddagger}$) of 39.7 kcal mol^{-1}. The thermolysis is endothermic by 14.3 kcal mol^{-1}. With the formation of ketene from the analogue of monomer **5** as a benchmark, we calculated the $\Delta E^{\ddagger}$ of the analogues of monomers **2**, **3** and **4** exploring the same concerted mechanism. In all cases the monomers showed a $\Delta E^{\ddagger}$ > 42 kcal mol^{-1}, making the thermolysis unfavorable as compared to the parent system. Although this result was consistent with observations for the ether and thioether systems, it diverged from experimental results for monomer **2**, which displayed a ~60 °C drop in thermolysis temperature. As a result, an alternate, multi-step mechanism for the thermolysis of **2** was considered.

Computation of a multi-step pathway for **13**, the methyl analogue of monomer **2**, provides a $\Delta E^{\ddagger}$ for the initial loss of acetone of 37.2 kcal mol^{-1}, 2.6 kcal mol^{-1} lower in relative energy than the thermolysis of the analogue of monomer **5** (Fig. 5). In this calculated reaction mechanism, initial loss of acetone with a $\Delta E^{\ddagger}$ of 37.2 kcal mol^{-1} from **13** leads to a cyclic structure found in a relatively flat area of the potential energy surface at a $\Delta E^{\ddagger}$ of about 26 kcal mol^{-1} (**14**). Immediate decarboxylation then produces the desired ketene. These results were supported by an intrinsic reaction coordinate (IRC)[43] calculation starting from the zwitterionic energy minimum structure (ESI†). The IRC showed a distinct shallow region of the reaction coordinate owing to the decarboxylation at 25.7 kcal mol^{-1}, but no energy minimum is evident, indicating a barrier-free decarboxylation to form the dialkyl ketene **15**. Analogous studies with other heteroatoms (*i.e.* analogues of **3** and **4**) or a different intramolecular relationship of the amine (analogue of **10**) did not behave similarly, instead preferring to undergo thermolysis in a concerted fashion with $\Delta E^{\ddagger}$ higher than that of **5**. Beyond

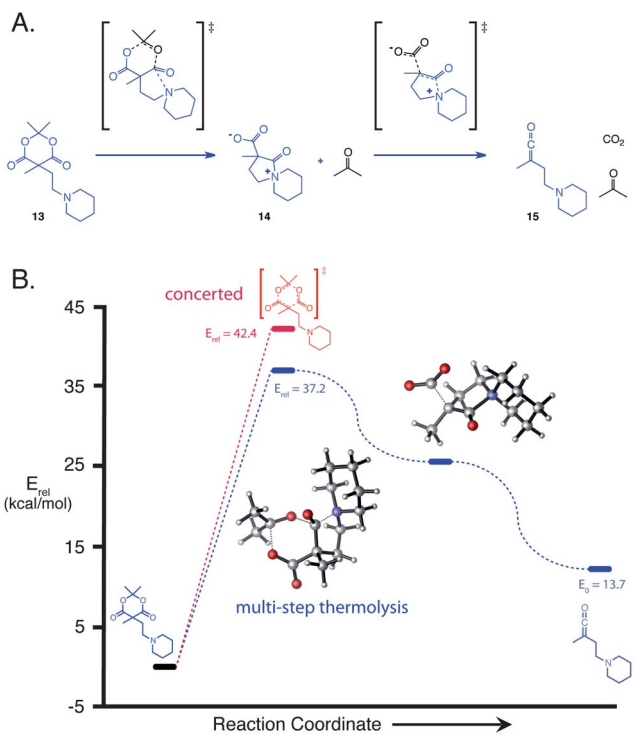


Fig. 5 Computational studies provide a (A) predicted reaction pathway and (B) a reaction coordinate diagram showing transition structures for a stepwise thermolysis of **13** to generate ketene **15**.

rationalizing experimental observations, these computational studies of ketene precursors provide mechanistic insights into the thermolytic events occurring in Meldrum's acid based polymeric materials.

Brønsted-acid activation

In examining other strategies for lowering the thermolysis temperature of dialkyl Meldrum's acid derivatives, we were inspired by an observation of Fillion *et al.* that triflic acid can catalyze the acylation of Meldrum's acid derivatives at reduced temperatures.[16] Brønsted-acid derivatives were therefore designed that would allow the study of both the intramolecular and intermolecular effects of Brønsted-acid activation as well as the relationship between T_{kf} and the magnitude of the Brønsted acidity (Fig. 6A).

With the success of the computational study in understanding Lewis base activated ketene formation, it was employed as a screening tool to rationally design Brønsted-acid derivatives. Initially, ketene formation from molecules **16** and **17** was computed to test the effect of the alcohol as an intramolecular hydrogen bond donor, and multiple plausible mechanisms of thermolysis from Brønsted acid activated systems were considered (Fig. 6B). If thermolysis was to occur along *path a*, the carbonyl participating in hydrogen bonding is that of the resulting CO_2. Conversely, thermolysis by *path b* allows the hydrogen-bound carbonyl to be that of the resulting ketene. Lower activation barriers were found computationally in both cases employing *path a* for **16** and **17**, where the carbonyl participating in hydrogen bonding was that of the resulting CO_2 upon thermolysis. Further, the thermolysis of **17**, with a $\Delta E^{\ddagger}$ of 37.5 kcal mol^{-1}, was calculated to be favorable as compared to both **16** and the analogue of **5**. Unlike in the case of Lewis base activation, which relied on the kinetically favorable intramolecular five-membered ring formation, the favorable nature of the thermolysis of **17** was related to the flexible three-carbon spacer between the Meldrum's acid ring and the hydroxyl. The flexibility of this longer linker afforded more rotational degrees of freedom between the Meldrum's acid ring and the hydroxyl, providing for a short hydrogen bond length of 2.0 Å in the computationally determined minimum energy structure of **17**, compared to a length of 2.4 Å for the analogous structure in **16** (ESI†).

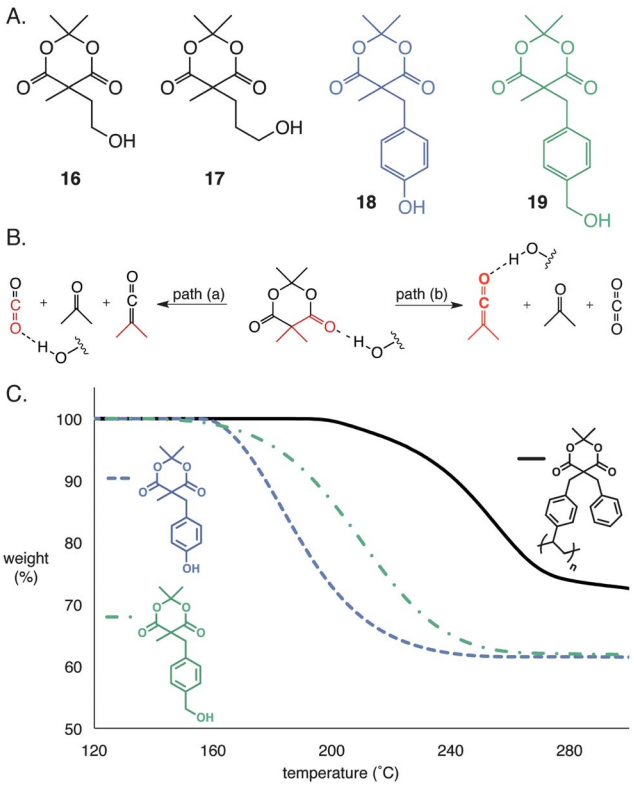


Fig. 6 (A) Brønsted-acid containing Meldrum's acid derivatives studied and (B) the TGA profiles of **18** and **19**.

These computational results allow us to predict that the activation of Meldrum's acid by Brønsted acids was predominately an intermolecular effect, and the translational freedom afforded by intermolecular interactions would lower thermolysis temperature. Removing the restriction of making intramolecular derivatives simplified synthesis considerably, as we chose to evaluate the benzyl derivatives **18** and **19**.[44] TGA results clearly demonstrates the significant lowering of T_{kf} for these molecules, a decrease of ~40 and ~50 °C, respectively. Of particular note is the phenolic derivative **18** shows a lower thermolysis temperature than **19**, displaying the importance of Brønsted acidity on the magnitude of this phenomenon.

Further evidence of Brønsted acids activating the Meldrum's acid carbonyl was obtained from the crystal structure of **18**, where a hydrogen bound dimer was observed in the solid state (Fig. 7A).§ Here, the intermolecular hydrogen bond length from phenol proton to carbonyl oxygen is measured at 2.08 Å (Fig. 7B), much shorter than that predicted by the van der Waals radii of the atoms at 2.7 Å.[35] This hydrogen bonding in the solid state shows the importance of reversible interactions in these systems and provides further evidence for Brønsted-acid activation of Meldrum's acid carbonyl groups.

Again computation of the intermolecular hydrogen bonding was employed to probe its effect on ketene formation. Energy minimization of the dimer of **18**, analogous to that of the crystal structure, was successfully obtained and used for further computation. A calculation of the concerted thermolysis of **18**, assuming no hydrogen-bonding interactions, resulted in a barrier

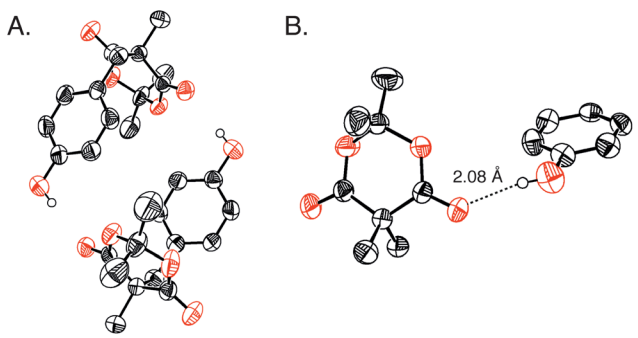


Fig. 7 ORTEP diagrams of **18** with 50% probability ellipsoids showing (A) the hydrogen bond dimer unit cell and (B) a perspective with atoms hidden providing a clear view of the hydrogen bonding interaction between the Brønsted acidic phenol proton and the Meldrum's acid carbonyl.

of 40.8 kcal mol^{-1}, hereafter considered as the reference point for this molecule. The energy-minimized structure of the full dimer was used for calculating the barrier while having hydrogen bond interactions. Again the largest effect occurred when the carbonyl participating in hydrogen bonding was that of the to-be-formed CO_2 fragment upon thermolysis, akin to *path a* in Fig. 6B. In the presence of a fixed hydrogen bond, the calculated energy barrier for thermolysis of **18** is 37.5 kcal mol^{-1}, 3.2 kcal mol^{-1} less than the barrier without a hydrogen bond. Such a result agrees with the experimental findings, which indicate a distinct lowering of T_{kf} for Meldrum's acid derivatives upon formation of intermolecular hydrogen bonding interactions.

Conclusions

Through molecular-scale engineering of Meldrum's acid derivatives, structure/property relationships have been determined that allow for significant lowering of the temperature required for ketene formation. Activation of Meldrum's acid by either neighboring group participation of Lewis bases or the presence of Brønsted acids was shown to lower the thermolysis temperature by ~60 °C. In both strategies, an understanding of the influences on and mechanism of ketene formation was gained through crystal-structure analysis and computation. This study not only affords materials scientists the ability to fine tune the thermolysis temperature of Meldrum's acid derivatives for applications in thermolytic crosslinking or condensation polymer synthesis, but also illustrates the important convergence of polymer property design with physical organic chemistry.

Acknowledgements

F. A. L., M. J. K. and C. J. H. would like to thank the National Science Foundation (MRSEC Program - DMR-1121053, Chemistry Program – CHE-0957492, Graduate Research Fellowship) and the DOD (NDSEG Fellowship) for financial support. Also, we thank Dr Guang Wu for crystal structure analysis. M. W. acknowledges the Netherlands Organization for Research for funding through a Rubicon fellowship. N. T. acknowledges the RISE program of the UCSB MRSEC for a summer research fellowship. B. M. acknowledges the National Research Foundation of Korea (NRF) grant funded by the Korea government (MEST) (No. 2011-0001129).

Notes and references

‡ Monomer **10** was a liquid, but removing the styrene group provided a crystalline material suitable for crystal structure analysis. This small structural variation is not expected to alter the ground state structure of the molecule.

§ **19** could not be obtained as a crystal. It is a liquid at room temperature.

1 C. K. Ober, S. Z. D. Cheng, P. T. Hammond, M. Muthukumar, E. Reichmanis, K. L. Wooley and T. P. Lodge, *Macromolecules*, 2009, **42**, 465–471.
2 C. J. Hawker and K. L. Wooley, *Science*, 2005, **309**, 1200–1205.
3 (*a*) R. K. Iha, K. L. Wooley, A. M. Nyström, D. J. Burke, M. J. Kade and C. J. Hawker, *Chem. Rev.*, 2009, **109**, 5620–5686; (*b*) M. J. Kade, D. J. Burke and C. J. Hawker, *J. Polym. Sci., Part A: Polym. Chem.*, 2010, **48**, 743–750.
4 (*a*) H. Staudiner, *Ber. Dtsch. Chem. Ges.*, 1905, **38**, 1735–1739; (*b*) T. T. Tidwell, *Eur. J. Org. Chem.*, 2006, 563–576.
5 (*a*) A. Sudo, S. Uchino and T. Endo, *Macromolecules*, 1999, **32**, 1711–1713; (*b*) M. Brestaz, N. Desilles, G. Le and C. Bunel, *J. Polym. Sci., Polym. Chem.*, 2011, **49**, 4129–4138; (*c*) J. L. Mynar, A. P. Goodwin, J. A. Cohen, Y. Ma, G. R. Fleming and J. M. J. Fréchet, *Chem. Commun.*, 2007, 2081–2083; (*d*) M. A. Tasdelen, V. Kumbaraci, N. Talinli and Y. Yagci, *Macromolecules*, 2007, **40**, 4406–4410.
6 F. A. Leibfarth, M. Kang, M. Ham, J. Kim, L. M. Campos, N. Gupta, B. Moon and C. J. Hawker, *Nat. Chem.*, 2010, **2**, 207–212.
7 J. M. Spruell, M. Wolffs, F. A. Leibfarth, B. C. Stahl, J. Heo, L. A. Connal, J. Hu and C. J. Hawker, *J. Am. Chem. Soc.*, 2011, **133**, 16698–16706.
8 F. A. Leibfarth, Y. Schneider, N. A. Lynd, A. Schultz, B. Moon, E. J. Kramer, G. C. Bazan and C. J. Hawker, *J. Am. Chem. Soc.*, 2010, **132**, 14706–14709.
9 Y. Miyamura, P. Chiyoung, K. Kinbara, F. A. Leibfarth, C. J. Hawker and T. Aida, *J. Am. Chem. Soc.*, 2011, **133**, 2840–2843.
10 A. N. Meldrum, *J. Chem. Soc.*, 1908, **93**, 598–601.
11 A. E.-A. M. Gaber and H. McNab, *Synthesis*, 2001, 2059–2074.
12 N. K. Boaen and M. A. Hillmyer, *Chem. Soc. Rev.*, 2005, **34**, 267–275.
13 T. Kashiwagi, T. Hirata and J. E. Brown, *Macromolecules*, 1985, **18**, 131–138.
14 B. Rigo, D. Fasseur, P. Cauliez and D. Couturier, *Tetrahedron Lett.*, 1989, **30**, 3073–3076.
15 B. Capon, *Q. Rev. Chem. Soc.*, 1964, **18**, 45–111.
16 E. Fillion and D. Fishlock, *Tetrahedron*, 2009, **65**, 6682–6695.
17 E. Fillion and D. Fishlock, *Org. Lett.*, 2003, **5**, 4653–4656.
18 E. Fillion, D. Fishlock, A. Wilsily and J. M. Goll, *J. Org. Chem.*, 2005, **70**, 1316–1327.
19 A. M. Dumas and E. Fillion, *Acc. Chem. Res.*, 2010, **43**, 440–454.
20 T. C. Bruice and S. J. Benkovic, *J. Am. Chem. Soc.*, 1963, **85**, 1–8.
21 R. B. Martin, R. Hedrick and A. Parcell, *J. Org. Chem.*, 1964, **29**, 158–160.
22 J. J. Morris and M. I. Page, *J. Chem. Soc., Perkin Trans. 2*, 1980, 679–684.
23 S. Winstein, E. Allred, R. Heck and R. Glick, *Tetrahedron*, 1958, **3**, 1–13.
24 H. L. Goering and K. L. Howe, *J. Am. Chem. Soc.*, 1957, **79**, 6542–6546.
25 R. F. Brown and N. M. Van Gulick, *J. Org. Chem.*, 1956, **21**, 1046–1049.
26 K. Matyjaszewski and J. Xia, *Chem. Rev.*, 2001, **101**, 2921–2990.
27 N. V. Tsarevsky and K. Matyjaszewski, *Chem. Rev.*, 2007, **107**, 2270–2299.
28 C. J. Hawker, A. W. Bosman and E. Harth, *Chem. Rev.*, 2001, **101**, 3661–3688.
29 C. Boyer, V. Bulmus, T. P. Davis, V. Ladmiral, J. Liu and S. Perrier, *Chem. Rev.*, 2009, **109**, 5402–5436.
30 S. Yamada, T. Mrozek, T. Rager, J. Owens, J. Rangel, C. G. Willson and J. Byers, *Macromolecules*, 2004, **37**, 377–384.
31 S. Danishefsky and R. K. Singh, *J. Am. Chem. Soc.*, 1975, **97**, 3239–3241.
32 C. Galli, G. Illuminati, L. Mandolini and P. Tamborra, *J. Am. Chem. Soc.*, 1977, **99**, 2591–2597.
33 H. W. Heine, A. D. Miller, W. H. Barton and R. W. Greiner, *J. Am. Chem. Soc.*, 1953, **75**, 4778–4779.
34 F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry Part A: Structure and Mechanisms*, Springer-Verlag, New York, 5th edn, 2007.
35 A. Bondi, *J. Phys. Chem.*, 1964, **68**, 441–451.
36 H. B. Burgi, J. D. Dunitz and E. Shefter, *J. Am. Chem. Soc.*, 1973, **95**, 5065–5067.
37 H. B. Burgi, J. D. Dunitz, J. M. Lehn and G. Wipff, *Tetrahedron*, 1974, **30**, 1563–1572.
38 L. George, M. W. Wong and C. Wentrup, *Org. Biomol. Chem.*, 2007, **5**, 1437–1441.
39 S. W. E. Eisenberg, M. J. Kurth and W. H. Fink, *J. Org. Chem.*, 1995, **60**, 3736–3742.
40 L. George, R. N. Veedu, H. Sheibani, A. A. Taherpour, R. Flammang and C. Wentrup, *J. Org. Chem.*, 2007, **72**, 1399–1404.
41 D. W. J. Moloney, M. W. Wong, R. Flammang and C. Wentrup, *J. Org. Chem.*, 1997, **62**, 4240–4247.
42 T. Ziegler, *Chem. Rev.*, 1991, **91**, 651–667.
43 K. Fukui, *Acc. Chem. Res.*, 1981, **14**, 363–368.
44 M. Wolffs, M. J. Kade and C. J. Hawker, *Chem. Commun.*, 2011, **47**, 10572–10574.