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Differential Scanning Calorimetry (DSC) as a Tool for Probing the Reactivity of Polyynes Relevant to Hexadehydro-Diels–Alder (HDDA) Cascades

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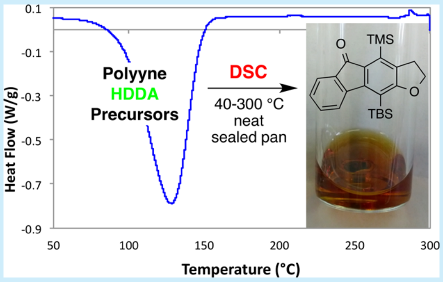
Ⓢ *Supporting Information*

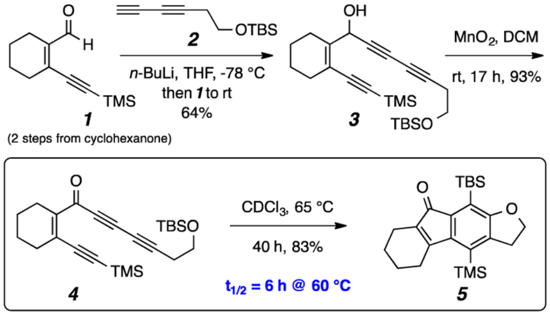
ABSTRACT: The differential scanning calorimetry (DSC) behavior of a number of alkyne-rich compounds is described. The DSC trace for each compound exhibits an exothermic event at a characteristic onset temperature. For the tri- and tetraynes whose [4 + 2] HDDA reactivity in solution has been determined, these onset temperatures show a strong correlation with the cyclization activation energy. The studies reported here exemplify how the data available through this operationally simple analytical technique can give valuable insights into the thermal behavior of small molecules.



Differential scanning calorimetry (DSC) is a commonly available and often-used tool for characterizing the thermal properties (melting and/or glass transition behaviors) of macromolecular assemblies, including both synthetic and biological polymers as well as bulk materials, crystalline solids, nanoparticles, etc. DSC has also been used, although much less frequently, to probe the behavior of small organic molecules. In that regard, one particular application has been as a preliminary screen for safety evaluation of potentially unstable, energetic, small molecules[1] (although more sophisticated thermal assessments are advisible in the course of bona fide process development[1a,2]). The study of other aspects of small molecule reactivity using DSC is less common.[3,4] Although more quantitative calorimetric measurements can give an impressively refined and in-depth understanding of mechanistic aspects of small molecule reactions through, e.g., kinetic profiling,[5] we were surprised, nonetheless, by the variety and nature of the insights that we have been able to extrapolate from a collection of qualitative DSC data.

In the course of establishing the scope and generality of the hexadehydro-Diels–Alder (HDDA) reaction,[6] we have explored the stability and reactivity of various polyynes. Tri- and tetrayne HDDA substrates are synthesized by reaction sequences that involve other polyyne intermediates (e.g., see the synthesis of benzenoid **5** via **1**–**4** shown in Scheme 1[7]). Although there are scattered reports of polyynes showing explosive behavior, these tend to be associated with low molecular weight, unsubstituted members of this functional group class.[8] We have experienced no sign of such extreme reactivity with any of the compounds with which we have worked, as exemplified by those shown in this paper. Much more common are anecdotal comments implying slow decomposition of polyynes, e.g., the inability to obtain a well-defined melting point or change during routine handling in the laboratory.[9]

Scheme 1. Synthesis of HDDA Precursor 4 (via 1–3) and Its Cyclization to Benzenoid 5



Given the large number of polyynes being prepared in our lab, we have often used DSC as a screening tool for evaluation of the potential hazard associated with each new class of intermediates encountered in our work. After accumulating a body of these DSC data, we came to realize that, beyond the comfort level provided from the standpoint of safe handling of these compounds,[10] there was additional instructive information about thermal reactivity embedded in the data, some of which we describe here.[11] We present the DSC behavior of (i) several simple conjugated di- and triynes, (ii) various tri- and tetrayne HDDA substrates, many of whose kinetic behavior in solution we have previously benchmarked, and (iii) a final substrate that undergoes a clean thermal Alder ene reaction. We comment on a number of inferences that can be drawn relating to reactivity

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throughout this set of polyynes. All of the DSC data reported here were collected under identical conditions (single scan from 40−300 °C, 2 deg·min^{-1} ramp rate, sample size of ca. 3−6 mg in a hermetically sealed aluminum pan).

Terminal diyne **2** is a substrate we have used frequently in the synthesis of HDDA-precursor triynes. We have observed that this terminal diyne is susceptible to slow decomposition when stored neat at room temperature. Its DSC behavior (Figure 1) shows an exothermic (downward) curve with an onset temperature of only 92 °C.[12] In contrast, the trimethylsilyl-containing analog **6** was considerably more stable and less prone to decomposition during routine handling. This observation is consistent with its DSC behavior (Figure 1), which showed a remarkably higher onset temperature of 231 °C. The exact pathway for decomposition of substrates such as **2** and **6** is not known. Attempts to elucidate these processes by determination of the structure or physical properties of the products, formed either as a result of the DSC heating process (cf. below) or from the slower decomposition of **2** as handled under ambient conditions, have been unsuccessful. Instead dark-colored, essentially insoluble, soot-like material is formed, which is similar to the outcomes of HDDA cyclizations performed in the absence of an efficient trapping agent.[6a,13] In those instances, we speculate that decomposition is initiated by bimolecular events in which the intermediate benzyne reacts with another molecule of the substrate polyyne.

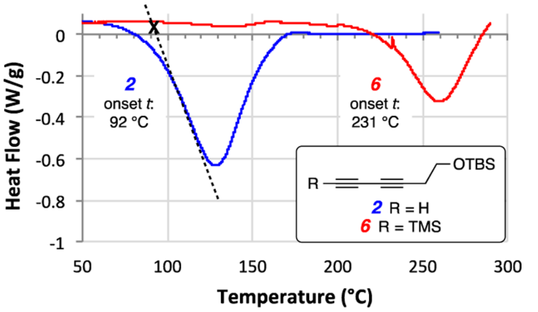

Figure 1. DSC traces for 1,3-diynes **2** and **6**.

The behavior of a second pair of relatively simple diynes **7** and **8** (Figure 2) provides different insights. In each, the butadiyne is capped on both ends with a quaternized substituent that provides considerable steric shielding. The DSC trace of each of these crystalline solids indicates a sharp endotherm characteristic of the melting point for each (**7**: mp 112−113 °C;[14a] **8**: mp 62−64 °C[14b]). Incidentally, the samples of all of the other polyynes for which DSC data are reported in this paper are viscous oils at ambient temperature. No other change was observed for **7** or **8** until well over 200 °C. It is tempting to speculate that the small endotherm at 229 °C might reflect the boiling point of diyne **7**.[15] However, we are reluctant to overinterpret the high temperature DSC behavior in these studies because of potential complications from events such as bulging of the sealed DSC pan and unidentified decomposition and volatilization of low boiling fragments. Such processes can lead to anomalous behavior at those extreme temperatures. In this regard, it is interesting to note that a number of alkynes containing the $Me_2(HO)C-$ moiety, like that present in **8**, are reported to fragment and liberate the terminal alkyne upon thermolysis at high temperatures (175−275 °C).[16] However, it can be concluded with confidence that neither of these bulky diynes shows any significant sign of reactivity below ca. 220 °C.

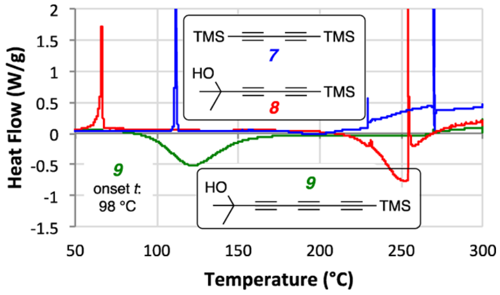

Figure 2. DSC traces for 1,3-diynes **7** and **8** and 1,3,5-triyne **9**.

In contrast, the DSC scan of the conjugated (noncrystalline) triyne **9** showed a broad exotherm characteristic of a reaction and having a relatively low onset temperature (of 98 °C). This presumably reflects the combined greater steric accessibility of the internal alkyne moiety in **9** vis-à-vis that in **7** or **8**, which allows for bimolecular association and reaction, as well as the additional electronic perturbation present in the more highly conjugated triyne **9**. In the course of studying the longest discrete polyyne known to date (a doubly capped docosayne), Tykwinski and co-workers have observed lower DSC onset temperatures with increasing chain length of the polyne.[9b]

The DSC data for four triyne substrates, each known to undergo HDDA cyclization and trapping efficiently in solution,[7] are shown in Figure 3. The measured half-life as well as the energy of activation[17] for cycloisomerization is shown under the structure of each substrate. The relative rates of cyclization of these four triynes span a factor of >10^4.[7] Each gives the tetracyclic product indicated at the bottom right of Figure 3 (and cf. **5**, Scheme 1). The DSC onset

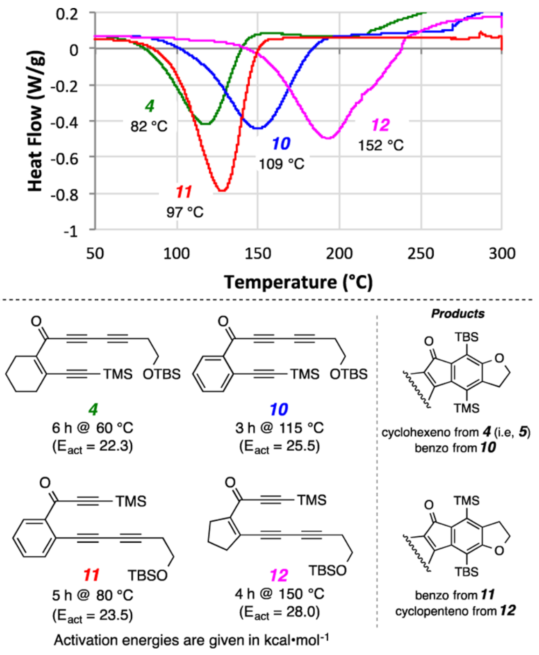

Figure 3. DSC traces for HDDA substrates **4** and **10** (diynones) and **11** and **12** (monoynones).

temperature of each triyne correlates nicely with the experimentally determined half-life for its HDDA cyclization in solution. We take this as evidence to suggest that the DSC exotherm is a result of a (highly exothermic) HDDA cascade reaction in the neat DSC sample. The shape of the DSC traces for these HDDA substrates is not unlike those observed for the alkynes in Figures 1 and 2, none of which is HDDA competent. However, for three of the triynes in Figure 3 (**4**, **10**, and **11**), the tetracyclic, benzofuran-containing product of the HDDA cascade reaction was observed (^{1}H NMR, TLC, GC/MS) when the contents of the sample pan were examined after the DSC run. In the case of triyne **11** we even isolated a 40% yield of the tetracyclic fluorenone product. This is remarkable because in many instances we have found that it is necessary to perform the HDDA cascade under relatively high dilution. This minimizes unwanted reaction between the reactive benzyne intermediate and the alkynes in additional substrate molecules prior to the intervention of a benzyne trapping reaction to complete the HDDA cascade.

The DSC behaviors of four additional polynes are shown in Figure 4. The ketone **13**, which cyclizes to an indanone skeleton, is one of the least reactive HDDA substrates we have successfully cyclized, showing a half-life of 6 h at 180 °C.[7] However, the homologue **14**, which would have produced a tetralone core, is stable even upon being refluxed in *o*-DCB for an extended period. The DSC traces for **13** and **14** are consistent with these observations, the latter not showing an onset temperature for an exothermic event until 220 °C.

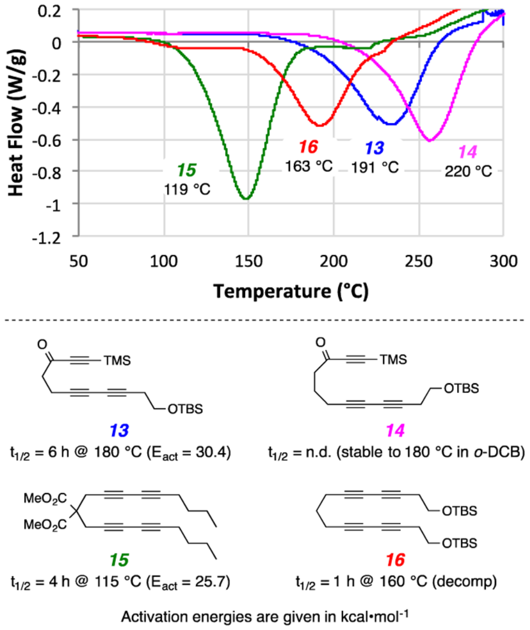

Figure 4. DSC traces for HDDA substrates lacking fully conjugated tethers: Ynones **13** and **14** and tetraynes **15** and **16**.

Tetraynes **15** and **16** were also examined (Figure 4). In solution, the dimethyl malonate **15** shows productive cyclization to the corresponding benzenoid product with a $t_{1/2}$ of 4 h @ 115 °C.[7] However, the all-methylene analogue **16**, which lacks the buttressing effect arising from the geminal ester groups in **15**, showed no ability to participate in HDDA cyclization, decomposing instead to unidentifiable products with a $t_{1/2}$ of ca. 1 h at 160 °C.[7]

We have observed that the DSC onset temperature correlates well with the HDDA activation energy (E_{act}) for all of the substrates whose DSC behavior we have recorded. This is shown in the plot in Figure 5. The E_{act} for each triyne or tetrayne reactant was extrapolated from its half-life data using an Arrhenius treatment (see Supporting Information).[7] This linear correlation (R^2 value of 0.98) suggests that the DSC behavior is reflecting an HDDA process in the neat melt for each of these substrates.

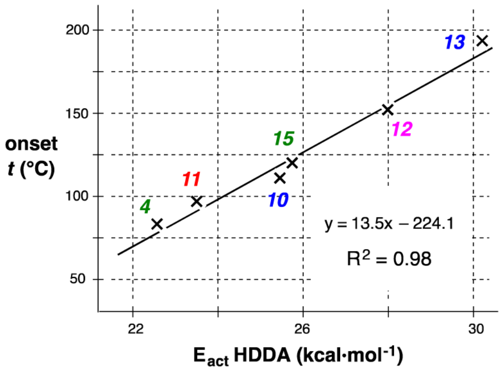

Figure 5. Plot demonstrating linear correlation between DSC onset temperature and E_{act} (*o*-DCB) for **4**, **10**–**13**, and **15**.

Finally, we have used the DSC analysis to probe a different type of reaction process. We observed that the diyne ether **17**, when analyzed by GC/MS, partially underwent a thermal reaction upon introduction into the hot injection port. Heating **17** in *o*-DCB then led to its clean conversion (80% yield) to the intramolecular Alder ene product **18** (Figure 6). Subsequent analysis by DSC showed an onset temperature of 156 °C, a value again consistent with the observed thermal behavior in solution.

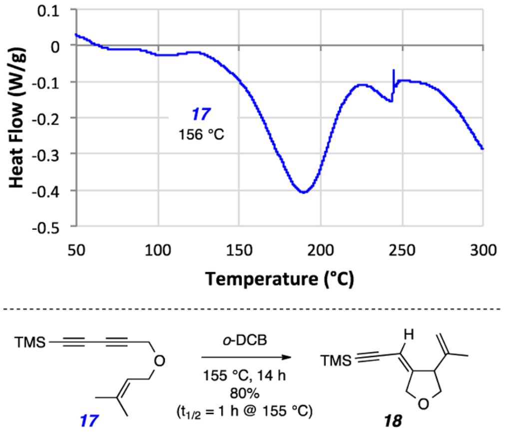

Figure 6. DSC trace of diyne ether **17**.

The studies described here demonstrate that DSC is a useful tool for the study of reactivity and decomposition pathways for HDDA-related polynes. DSC provides a convenient method for preliminary qualitative safety assessment. It can also give an indication of the need (or not) for careful storage (e.g., cold, short-term, or solution) in the laboratory setting. New HDDA substrates can readily be assessed for preliminary insight about the reaction temperature required for their cycloisomerization in solution. DSC investigation of other classes of thermal reactions has the potential to provide new insights and understanding.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization data, copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) See the Supporting Information for a description of the DSC instrumentation and software. The onset temperature is taken from the intersection of the heat capacity baseline and a tangent on the leading edge of the peak (see dashed line in Figure 1).

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(15) Although we were unable to find a reported bp for diyne **7**, extrapolating from the differential of the bp values of 3-hexyne (81 °C) vs 3,5-octadiyne (163 °C) and the bp of bis-trimethylsilyl acetylene (135 °C), one would predict a bp for **7** of ca. 215 °C.

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(17) The energy of activation for each polyyne was estimated by Arrhenius treatment using 1.4×10^{10} s^{-1} as the value of the A factor. This was determined for triyne **11** over a temperature range spanning 40 °C.[7]