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Diels-Alder Reactions of Furans with Itaconic Anhydride: Overcoming Unfavorable Thermodynamics

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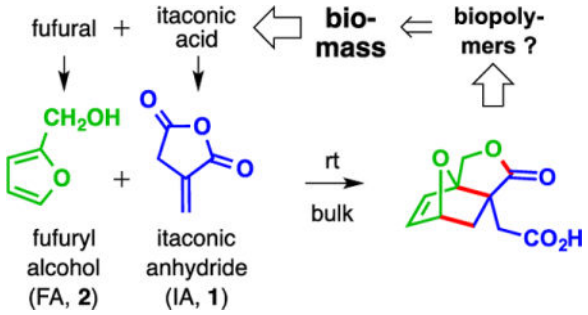
Abstract

Unfavorable thermodynamics often render furans reluctant to engage in high-yielding Diels-Alder (DA) cycloaddition reactions. Here we report the highly efficient conversion of the bio-sourced reactants itaconic anhydride (IA) and furfuryl alcohol (FA) to a single DA adduct. The free energy advantages provided by anhydride ring-opening and crystal lattice energy of the product overcome the loss of aromaticity of the furanoid diene. Detailed ^{1}H NMR studies provided valuable insights about relevant kinetic and thermodynamic features.

Graphical abstract



Itaconic acid[1] and furfural[2] are two chemicals abundantly available from biomass. The first arises by the classical citric acid (or tricarboxylic or Krebs[3]) cycle; the second by acid-catalyzed dehydration of 5-carbon sugars prevalent in, for example, corncobs (see Volume 1 of *Organic Syntheses*[4]). For a century it has been known that each of itaconic anhydride (**1**, IA) and furfuryl alcohol (**2**, FA) is readily available by simple conversions (dehydration[5] and reduction,[6] respectively) of these readily available precursors.

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00276. Experimental procedures and structural characterization data for all new compounds and ^{1}H and ^{13}C NMR spectra (PDF)

Notes

The authors have no competing financial interests to declare.

The ability of IA to function as a dienophile in Diels–Alder (DA) cycloaddition reactions was described even in the first publication by Diels and Alder.[7] The use of furan as a diene was reported one year later in their second paper on the subject of “hydroaromatic synthesis”.[8] Remarkably, we can find no reports of IA (**1**) or itaconic acid (or its esters) ever having been reacted with any furan derivative in the intervening >85 years. This is in spite of the fact that DA adducts of furans with many other types of dienophiles have been appropriated as strategically valuable and enabling intermediates in numerous syntheses of complex molecules.[9]

With an eye toward the preparation of novel reactive monomers from furans for use in sustainable polymer synthesis,[10] we have studied the reactions of IA (**1**) with various furans and report our findings here. A hallmark of furans as participants in DA cycloadditions is the often-unfavorable enthalpic change upon product formation. This frequently results in only low equilibrium conversion to the [4+2] adduct because of loss of heteroaromaticity in the diene and ring strain in the 7-oxanorbornene product.[11] This is all the more true for 1,1-disubstituted dienophiles analogous to **1** (e.g., methacrolein,[12] methacrylates,[12a–c] and methacrylonitrile[12d]), where the equilibrium concentration of product ranges from 7–36% even in the presence of 20-fold excess of furan, at low temperature, and/or under high pressure.

We first describe reactions between IA (**1**) and a variety of simple furans, starting with furan (**3**) itself. In one experiment IA was dissolved in 20 equivalents of furan and held at ambient temperature. Aliquots were periodically withdrawn and dissolved in $CDCl_3$ to monitor reaction progress. It was important in this kind of analysis that the spectral data be recorded soon after sample preparation, because the retro-Diels-Alder reaction was also operative at room temperature, and dilution (here, from neat to NMR sample concentration) shifts the equilibrium composition of this bimolecular-to-unimolecular process toward the starting pair of reactants (here, **1** + **3**). Two diastereomeric products, **4-endo** and **4-exo**, are produced (Figure 1a and Table 1, entry 1). Even at early time points, they formed at nearly identical rates. After 40 hours the system had essentially reached its equilibrium state, which comprises a ratio of 73% of the initial IA (**1**) and 27% of the sum of the two DA adducts. At equilibrium, there was a very slight predominance of **4-endo** over the amount of **4-exo**. These diastereomeric DA adducts were sufficiently stable to be isolable by rapid chromatographic separation on silica gel, even though some retro-DA reaction was occurring as the solutions were being manipulated. Isolated solid-state samples of each isomer were considerably more stable. Upon dissolution in $CDCl_3$ or C_6D_6, each isomer began to slowly revert to **1** and **3** (ca. 50% conversion after 6 h), consistent with the rate of their formation and final equilibrium ratios.

Our assignment of the diastereomeric relationship within each of **4-exo** and **4-endo** was initially based on detailed analyses of NMR data [see Supporting Information (SI)]. This was subsequently confirmed by an X-ray structure of the diacid **5** (Figure 1b) obtained by catalytic hydrogenation of **4-endo** to the derivative **4-endo-h2**, which was then hydrolyzed to the crystalline diacid **5**. Diagnostic features in the ^1H NMR spectral data of each diastereomer of **4** were then useful in assessing the relative configuration of the DA adducts

prepared from additional furan derivatives (cf. **4**, **7, 9**, and **11** in Table 1); details again are provided in the SI.

2,5-Dimethylfuran (**6**) was the next diene studied, again in an experiment where it was used as the reaction solvent and in ca. 20-fold excess over IA (**1**). The results are summarized in Table 1 (entry 2). The reaction of **6** with **1** was notably faster than that of furan ($t_{1/2}$ ~15 min vs. ~8 h at 23 °C); apparently the greater electron density in diene **6** is a more important factor than the increase in its steric bulk. However, the reaction proceeded to a considerably lower equilibrium conversion (ca. 5%) of the sum of DA adducts **7-endo** and **7-exo**, which reflects the greater steric compression between the substituents on the spirocyclic carbon and the adjacent (proximal) bridgehead methyl group present in adducts **7** vis-à-vis adducts **4**. At an intermediate time point (10 min, ca. 3% conversion), the formation of the major isomer had outpaced that of the minor to the extent of ca. 2:1, a ratio that remained essentially constant thereafter.

We next examined the reaction of IA with 2-methylfuran (**8**), a desymmetrized diene that could give rise to four isomeric, NMR-distinguishable DA adducts. These are a pair of endo and exo diastereomers for each of a distal (**9-dist-endo** and **9-dist-exo**) vs. a proximal (**9-prox-endo** and **9-prox-exo**) pair of constitutional isomers. Again, we used an excess of the furan component as the solvent in this ambient temperature experiment and monitored the reaction progress over time. We observed: (i) that the proximal isomers are formed more quickly than the distal, a reasonable event given the electronic polarization imparted by the donor methyl group in **8**, (ii) that the distal isomers eventually predominated over the proximal, again reasonable, now on the basis of minimization of steric compression, and (iii) that the equilibrium amounts of the four products (Table 1, entry 3) are in line with the observed equilibrium ratios of DA adducts **4** and **7**. Finally, the overall extent of conversion was intermediate between that of furan itself and the 2,5-dimethylated derivative **6**.

2-Acetoxymethylfuran (**10**) was another diene substrate that proved informative (Table 1, entry 4). At equilibrium, the four IA DA adducts **11** were formed, again to an extent intermediate between that of **4** vs. **7**. This was observed to be the slowest of all reactions we studied, consistent with the acetoxymethyl substituent having a weakly electron withdrawing character. As was the case for **9**, at equilibrium the distal isomers predominated. The assignments of structure to the distal vs. proximal substitution patterns among the isomers of **9** and **11** were based on the difference in coupling patterns of the resonances for the bridgehead protons (at C4) in each (see SI). HMQC and HMBC NMR analyses also were consistent with the assignments.

We then turned to the reaction between the bio-derived FA (**2**) and IA (**1**). Initially, we monitored the behavior of an equimolar mixture of this diene/dienophile pair in $CDCl_3$ solution (~1.5 M). After being held at 55 °C for 10 minutes, a few percent of total conversion to a mixture of four DA adducts was seen, which is well in line with the behavior (rate and ratio) observed for the reaction between the acetate **10** and **1**. By analogy then, we presumed these four compounds to be a mixture of the four isomeric anhydrides **12** (Figure 2a). When this reaction solution was examined after 7 days, a new, fifth, component was seen to emerge at about 15% relative to the unconsumed IA (**1**). The appearance of (i) a

broad downfield resonance and (ii) a pair of downfield doublets (δ 4.62 and 4.83, J_{ab} = 10.8 Hz) in this new, dominant compound suggested that a carboxylic acid lactone had formed; it is reasonable to anticipate a conversion of one of **12-prox-exo** or **12-prox-endo** to a ring-opened lactone acid by one of the four pathways implied by arrows “a” or “b” in **12-prox-exo** or “a’ ” or “b’ ” in **12-prox-endo** (Figure 2a). The favorable free energy change associated with anhydride opening provides a driving force for DA adduct formation.

The significant breakthrough was achieved when an equimolar mixture of **1** and **2** was allowed to react in the bulk. A suspension of solid **1** (95% grade) in liquid **2** (98% grade) at ambient temperature changed over time in consistency. After about 3.5 h the initial heterogeneous slurry could no longer be magnetically stirred; we could identify in the NMR spectrum of an aliquot the presence of all four isomeric anhydrides **12** (Figure 3), albeit to the total extent of only ca. 5%, along with a significant amount of the same fifth component mentioned above. After 10 h the composition of the bulk mixture was that of a paste and after 18 h it had turned to a solid mass. This material was now comprised of largely a single component, having the same spectral properties as those of the new, fifth component that had appeared after 7 days in the homogenous $CDCl_3$ solution experiment described above. The ^{13}C NMR spectrum of this compound showed a carbonyl resonance at δ 177.8 ppm, suggestive that it contained a 5-membered butyrolactone ring.[13] X-ray diffraction showed the structure to be that of the lactone acid **14**, arising therefore from **12-prox-exo**, presumably by path “a.”

The fact that the rapidly formed, steady-state mixture of the four DA adducts **12** transformed to essentially the single component **14** indicates rapid reversibility of each of **12** back to IA (**1**) and FA (**2**). The ^1H NMR spectrum of an aliquot taken from an equimolar mixture after 2 days is shown in Figure 3. Integration of key resonances indicated that the chemical yield for formation of **14** was 94%. The driving force for the conversion of IA+FA to **14** comes both from (i) the opening of the anhydride as well as (ii) the crystallization of the product from a dynamic, interconverting mixture of multiple components. Crystal lattice energies have been exploited for additional purposes in the arena of furan DA chemistry.[14]

A sample removed from the bulk mixture of **1** and **2** after just 30 minutes was immediately chromatographed on silica gel. The structures of three constituents, each obtained in <1% yield,[15] were deduced. In dilute $CDCl_3$ solution, each of the anhydrides **12-dist-endo** and **12-dist-exo**, assigned as such by comparative NMR analyses with some of the previous DA adducts, was observed to revert to **1** and **2** at room temperature in a matter of minutes. The third sample proved to be an acid lactone isomeric with **14**. It contained ~20% of a second compound whose ^1H NMR resonances suggested it to be the anhydride **12-prox-endo**. Within a day in $CDCl_3$, this anhydride had converted to the same, new acid lactone. By a series of correlation experiments (see below) we concluded the structure of this new lactone to be **13**, arising by the attack indicated by “b’ ” in structure **12-prox-endo** (Figure 2a).

Monitoring the thermal behavior of a $CDCl_3$ solution of the lactone acid **14** was also informative. At 80 °C a 1:4 mixture of the two mono-furfuryl itaconate esters **15a** and **15b** (structure assignment discussed below) was formed. The isomer **15b** cannot arise from direct retro-DA reaction of **14**. Instead **14** apparently reverts to **12-prox-exo** and, in turn **2**

and **1**, which then can repopulate the mixture of **15a** and **15b**. All of these intermediates were detectable (^{1}H NMR, see SI). To probe whether **14** can lead to **15a** directly by a retro-DA reaction, we converted **14** to the methyl ester **14^{Me}**. This compound was very stable at 80 °C in $CDCl_3$ and only upon heating to 140 °C in the melt did it finally and solely revert to the ester **15a^{Me}**. An authentic sample of **15a^{Me}** was prepared by Mitsunobu esterification reaction between FA (**2**) and the commercially available mono-methyl itaconate **16**. The rate of the retro-DA reaction of **14^{Me}** suggests that **14** does not proceed directly to **15a**. A 1:1 mixture of IA and benzyl alcohol, a DA-silent mimic of FA (**2**), at 80 °C produced a mixture of mono-benzyl itaconates in which the major isomer was the analog of **15b**.[16]

We returned to the isomeric lactone acid **13** and converted it to the methyl ester **13^{Me}**. Like its analog **14^{Me}**, this ester also showed clean retro-DA behavior when heated neat at 140 °C (partial reversion after 1 min and complete after 5 min). Only the mixed diester **15b^{Me}** was produced, verifying that **13** embodied a valero- rather than butyrolactone subunit.

In summary, detailed NMR analyses of an array of related Diels-Alder reactions between bio-derivable IA (**1**) and furans has provided an understanding of a number of the underlying kinetic and thermodynamic issues. We have discovered that the metastable lactone acid **14** can be produced in high yield (94%) under trivial reaction conditions [1:1 mixture of IA (**1**) and FA (**2**), neat, ambient temperature]. This opens the way for studying its further conversion into derivatives amenable to polymerization, a topic we are currently exploring.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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15. This example serves as a reminder of the value of the maxim that a 1% yield is infinitely greater than 0%. Importantly, the identification of these trace products revealed significant features about the energetics of several aspects of the reaction manifold.

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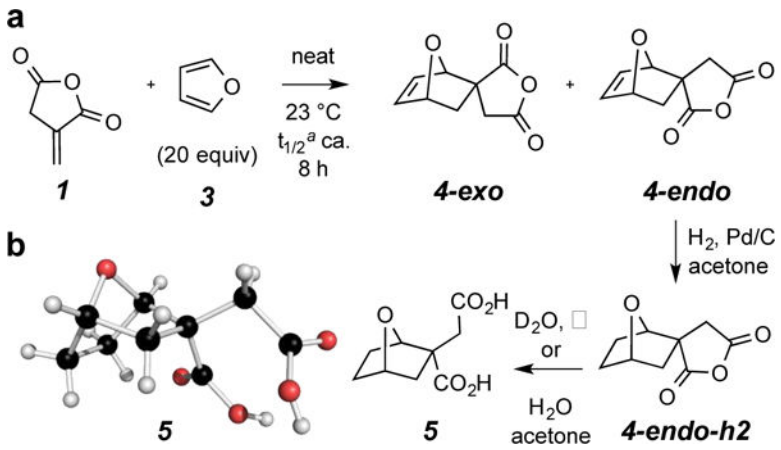

Figure 1.

a. Rate and final equilibrium resting state for the DA reaction between IA (**1**) and furan (**3**).

b. Conversion of **4-endo** to **5** via **4-endo-h2** and 3D structure of **5** from a single crystal X-ray analysis.

[a] This is the half-time for reaching the final equilibrium mixture (this ratio for ***1:4-exo:4-endo*** was 73:13:14).

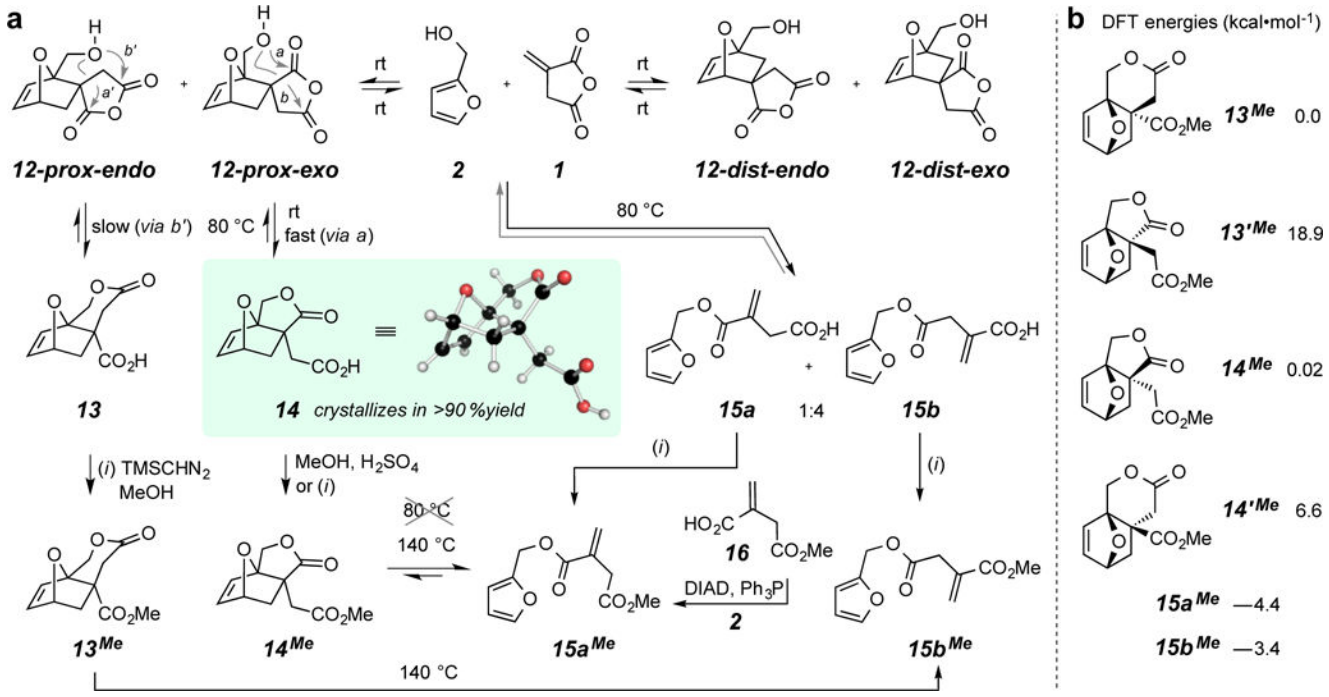

Figure 2.

a. Reaction manifold showing the equilibration among **1** + **2**, four isomeric anhydrides **12**, lactone acids **13** and **14**, and mono-furfuryl itaconates **15**. **b.** DFT [M06-2X/6-31+G(d,p) (SMD:$CHCl_3$), see SI for details] free energies (kcal•mol^{-1}) of the four isomeric lactone esters from ring opening of **12-prox-endo** and **12-prox-exo** and the (more stable) mono-furfuryl itaconate esters **15a** and **15b**.

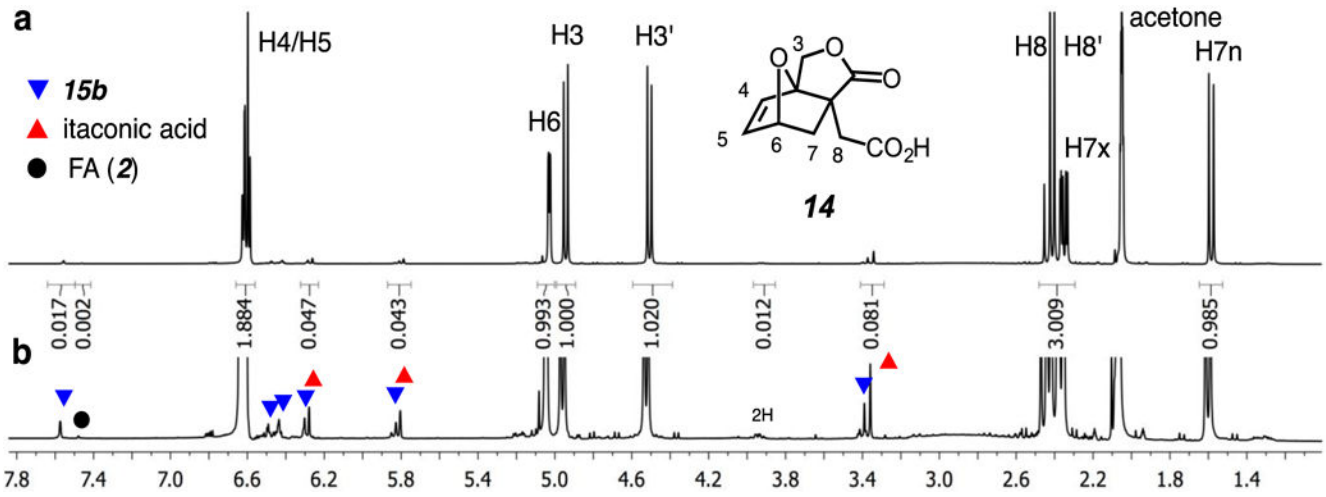

Figure 3.

^{1}H NMR spectrum in acetone-d_6 of an aliquot of the bulk reaction mixture from 1:1 IA (**1**) and FA (**2**). **a.** Resonances from the major product **14** are assigned. **b**. Vertical scale increased 5x; the principal minor components are denoted; integration of all components indicates a 94% yield of **14**. (see SI for full-page version of this graphic).

Table 1

Reactions of itaconic anhydride (1) with furans 3, 6, 8, and 10 (20 equiv) at ambient temperature