Several 5,6-disubstituted-7-oxabicyclo[2.2.1]hepta-2,3-dienoic anhydrides (1) were synthesized on ≥0.1 mol scale. The heat-induced retro Diels–Alder (rDA) decomposition of these derivatives was studied by thermal analysis, and the kinetics of the rDA were measured for 4. First-order rate constants (k = 1.91–14.2 × 10^{-5} s^{-1}), measured at four temperatures between 124 and 150 °C, were used to calculate Arrhenius activation parameters E_a (34.5 ± 0.5 kcal/mol) and ln A (1.77 ± 0.30 × 10^4). The observed activation energy was significantly larger (by 9.5 kcal/mol) than that previously measured for the maleic anhydride adduct 1, and this was attributed to the difference in LUMO energies for the two dienophiles. Modeling of the activation parameters found for 4 with density functional theory (DFT) calculations for similar compounds 5 and 6 gave close quantitative correlations for ΔH‡, ΔG‡, ΔS‡. The rDA reactions studied were found to be entropy-driven.
product was reduced with lithium aluminum hydride to afford crude diol 2. Williamson ether synthesis using carefully dried 2 and stoichiometric NaH in the presence of excess iodomethane produced monoether 3 in up to 69% yield. Product 3 was conveniently separated from byproducts 2 and 4 using an alumina column and a gradient of ethyl acetate and hexanes, which was effective even on a 0.1 mole scale. This represents a significant improvement over previous purification of small amounts of 3 using silica gel. The double Williamson reaction of 2 with excess NaH followed by iodomethane resulted in an 86% yield of diether 4 after purification. A lower yield of 4 was obtained when higher temperatures were used during distillation.

**Thermal Decomposition.** Thermogravimetric Analysis (TGA) of 1–4 under a nitrogen atmosphere showed rapid and complete (>95%) weight losses between ~200 and 260 °C (Figure 1). The lowest temperature for onset of decomposition was observed for 1 (147 °C) and highest for 2 (217 °C). The thermolysis of 4 gave two products which were identified by 1H NMR analysis as furan (7) and cis-1,4-dimethoxy-2-butene (9), the expected products of the retro Diels–Alder reaction. (Scheme 2).

The kinetic behavior of the thermal decomposition of 4 was investigated at four temperatures using solution 1H NMR spectroscopy. As the reaction proceeded, signals at 4.75 ppm in 4 disappeared while peaks consistent with 9 appeared at 3.85 ppm in an otherwise uncomplicated region of the spectrum (Figure 2). Integration of these peaks allowed the calculation of mole ratios of starting material and products. Application of the first-order kinetic formula $k_t = \ln(x+1)$, where $x$ is the mole ratio of 4 to 9 at a given time $t$ and $k$ is the rate constant, resulted in the plots shown in Figure 3. An Arrhenius plot of the kinetic data (included in the Supporting Information) allowed the calculation of activation energy $E_a$ of 35.0 (±0.5 kcal/mol and $\ln A$ of 1.77 (±0.03) $\times 10^4$ from the slope and intercept, respectively. The enthalpy and entropy of activation were calculated to be $\Delta H^\ddagger = 34.5 \pm 0.5$ kcal/mol and $\Delta S^\ddagger = 5.0 \pm 0.1$ cal/mol K. These values are higher than those measured for 1-exo-14 by 9.5 kcal for $\Delta H^\ddagger$ and 4.8 cal/mol K for $\Delta S^\ddagger$ (Table 1).

Unfortunately, independent measurement of the thermodynamic values by differential scanning calorimetry (DSC) was difficult due to the superposition of several peaks. An endotherm (onset at 161 °C), presumably due to the vaporization of the rDA products 7 (bp 32 °C) and 9 (bp 141 °C), obscured the onset of the exotherm due to


The calculated ΔH⁰ of 2.6 kcal/mol lower than the experimental value, while the ΔS¹ is larger by 2.8 cal/ mol K. The resulting ΔG¹ of 3.3 kcal/mol reflects, to some degree, the difference between the environments used for calculations (gas-phase) and experiment (solution) in addition to systematic errors of the quantum-mechanical method.

Although the accurate quantitative reproduction of experimental values was not necessarily expected, the relative energies of the transition states should be modeled well because they are not affected much by solvent. The effect of temperature upon the results was also expected to be small so no attempt was made to correct to experimental temperature.

The tricyclic compound 5, used as a model for dimethyl ether 4, has two conformational minima corresponding to structures with oxygens on either the opposite (5-anti) or same (5-syn) side of the bicyclic ring. The former conformer is the global minimum on the potential energy surface (PES) and is separated from the less stable 5-syn form (ΔG = 0.40 kcal/mol) by an interconversion barrier of 2.1 kcal/mol. The transition state for the rDA reaction was identified as 5TS-syn, and the analogous 5TS-anti could not be located on the PES. The calculated thermodynamic parameters for 5TS-syn differ from those measured experimentally for the diether 4 by about 2.5 kcal/mol, a coincidentally similar margin of error to that found for 1TS-exo.

A comparison of the rDA reactions for the anhydride 1-exo with its di-deoxy analogue 5 shows that both are entropically driven with almost identical overall thermodynamics. The small reaction endotherm (about 3 kcal/mol) is offset by a large entropy gain (about 46 cal/mol K) to give a moderate free-energy gain of about −11 kcal/mol. The most significant difference between the two reactions is their TS energies. When compared to 1TS-exo, the ΔG¹ of 5TS is higher by 8.9 kcal/mol, a value which is very close to the 8.1 kcal/mol difference between the experimental results (Table 1). The two PES's are graphically compared in Figure 5.

The calculated thermodynamic values for the rDA reaction of the parent 7-oxabicyc[2.2.1]hept-2-ene (6) are similar to those for 5, indicating that the perturbation of 6 by the oxymethyl substituents in 2-5 is small, almost negligible.

The observed difference in the TS energies between rDA reactions resulting in a conjugated dienophile (such as 8) and the two with isolated double bonds (10 and 11) are reflected in the geometries of the TS state structures shown in Figure 4. The transition state 1TS-exo is early relative to 5TS (and 6TS), with breaking C−C bonds at 2.117 Å, while in the latter, bond cleavage is further along, with C−C separations of about 2.158 Å (2.150 Å). The same trends are observed in the bond lengths of the furan ring and are consistent with an early transition state for the anhydride 1 decomposition.

These reactivity differences can be traced to the relative energies of the FMO's. For the forward DA reaction, the HOMO of furan (A₂ = −6.11 eV) can be expected to interact with the same symmetry LUMO of the dienophile according to classical FMO theory. According to our calculations, the LUMO (A₂ = 0.50 eV) of the isolated C==C bond in dihydrofuran (10) is significantly higher in energy than that in maleic anhydride (8, A₂ = −3.19 eV). This results in a 3.7 eV difference in the HOMO–LUMO gap for 7 and 8 relative to that

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Table 1. Calculated (B3LYP/6-31G*) and Experimental Thermochemical Parameters for the Retro Diels–Alder Reaction

<table>
<thead>
<tr>
<th>compd R, R'</th>
<th>ΔH kcal/mol</th>
<th>ΔS cal/mol K</th>
<th>ΔG kcal/mol</th>
<th>ΔH* kcal/mol</th>
<th>ΔS* cal/mol K</th>
<th>ΔG* kcal/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-exo -COOCO-</td>
<td>+3.44</td>
<td>+45.9</td>
<td>−10.2</td>
<td>22.4</td>
<td>2.95</td>
<td>21.6</td>
</tr>
<tr>
<td>5-anti -CH₂=OCH₂</td>
<td>+3.07</td>
<td>+48.2</td>
<td>−11.3</td>
<td>31.8</td>
<td>4.11</td>
<td>30.5</td>
</tr>
<tr>
<td>6 H</td>
<td>+5.3</td>
<td>+43.5</td>
<td>−7.6</td>
<td>31.2</td>
<td>3.1</td>
<td>30.3</td>
</tr>
</tbody>
</table>

The thermochemical parameters were calculated using the B3LYP functional with the 6-31G* basis set. The ΔH, ΔS, and ΔG values are reported in kcal/mol, cal/mol K, and kcal/mol, respectively. The ΔH*, ΔS*, and ΔG* values are calculated relative to the reference state.
The better overlap between the FMOs in 7 and 8 lowers the energy of 1TS by 9 kcal/mol below that of 5TS.

The calculated activation parameters for the model rDA reactions of 5 and 6 were almost exactly the same: the two values of $\Delta H^\ddagger$ were within 0.5 kcal/mol of one another, and $\Delta S^\ddagger$ values were within 1.0 cal/mol K, resulting in $\Delta G^\ddagger$ values differing by only 0.2 kcal/mol. Compared to the experimental values for 4, the calculated $\Delta G^\ddagger$ value for 5 was low by 2.5 kcal/mol (a difference of 2.7 kcal/mol for $\Delta H^\ddagger$ and 0.9 cal/mol K for $\Delta S^\ddagger$). These results affirm the validity of using 5, a known compound,\(^{(22)}\) as a model for 4.\(^{(23)}\) Furthermore, the influence of the methoxymethyl substituents at the reaction center in 4 or 5 is minimal when compared to 6.

**Conclusions**

The results for thermolysis of 7-oxabicyclo[2.2.1]-heptenes via the rDA reaction reported here are consistent with expectations from qualitative FMO analysis. Diol 2 and related ethers 3 and 4 underwent the rDA reaction at relatively low temperatures, but higher than that required for the anhydride 1. Kinetic data for the rDA reaction for 4 were closely comparable with calculated thermodynamic and kinetic parameters and experimental data on 1 from the literature. Generally, for the solution reactions described here, the kinetic and thermodynamic data compared unusually well quantitatively to the calculated (gas phase) data. Computational analysis of the transition states at the B3LYP/6-31G* level confirmed that the $E_a$ in 1 is lowered by 9.5 kcal/mol relative to that of model compound 5, a value almost identical to the difference in the experimental $\Delta H^\ddagger$ for 1-exo and 4. The faster rate of the rDA in 1 as compared to 4 is likely due to the energetic differences in the LUMO's of 8 and 9.

Large entropic contributions to the rDA resulted in a favorable $\Delta G$ for the reactions of 1, 5, and 6, overcoming a slightly unfavorable enthalpic term.

**Experimental Section**

**Kinetics.** Rates of retro Diels–Alder reactions were measured by following the decomposition of 4 by solution $^1H$ NMR. For each data point, a 20 $\mu$L sample was transferred with an Eppendorf pipet to an NMR tube and 0.6 mL of 1,2-dichlorobenzene-$d_4$ added. The solution was freeze–thaw degassed twice, and the NMR tube sealed under vacuum (~50 Torr). Samples were immersed in a Fisher Isotemp 800 constant-temperature bath heated to 124 °C, 130 °C, 140 °C, or 150 °C ± 0.5 °C for at least six different time intervals corresponding to between 5 and 95% decomposition. Each decomposition was taken to at least three half-lives to determine whether the process was first order. The sample was periodically cooled to room temperature and the ratio of one product [NMR $\delta$ 3.14–3.20 (m, max at 3.17, 6H), 3.84–3.87 (m, center at 3.85, 4H), 5.58–5.62 (m, max at 5.60, 2H)] to the starting material 4 [NMR $\delta$ 1.73–1.80 (m, 2H), 3.07–3.21 (m, max at 3.17, 6H), 3.22–3.35 (m, 2H), 4.72–4.75 (m, max at 4.75, 4H), 6.13 (m, max at 6.13, 2H)] was monitored by $^1H$ NMR (200 MHz).
The assignment of structures of the products was confirmed by comparison to a published 1H NMR spectrum of 9 and NMR of pure 7 in 1,2-dichlorobenzene-d$_6$ (1H NMR δ 6.22 (t, J = 1.3 Hz, 2H), 7.27 (t, J = 1.2 Hz, 2H)). The enthalpies and entropies of activation were calculated using standard formulas: ΔH$_f$ = -E$_a$ - RT and AS$_f$ = R[ln A - ln(e/kT/h)].

**Computational Methods.** Quantum-mechanical calculations were carried out using the Gaussian 98 package on an SGI Power Challenge workstation, and the resulting energies are listed in the Supporting Information. Geometry optimizations were undertaken using appropriate symmetry constraints at the B3LYP/6-31G* level of theory. Transition states were located using the QTS2 procedure. Vibrational frequencies were used to characterize the nature of the stationary points and to obtain thermodynamic parameters. Zero-point energy corrections (ZPEC) were calculated using a 0.9804 scaling factor. The thermodynamic properties were calculated at 298 K and 1 atm.

**Synthesis.** Boiling and melting points are uncorrected. 1H NMR and 13C NMR spectra were run at 200 and 50 MHz, respectively. Samples were dissolved in deuteriochloroform and referenced to CHCl$_3$ unless noted otherwise. IR spectra were measured as neat samples. Commercial reagents were used as received. Tetrahydrofuran were dried over benzophenone ketyl and distilled before use. Differential scanning calorimetry measurements were run on a Perkin-Elmer DSC-7 under nitrogen calibrated to an indium standard. Aluminum pans (50 μL) with a pinhole and sample sizes of 2–5 mg were used and the heating rate was 20 °C/min. Thermal gravimetric analysis measurements were done using a Perkin-Elmer TGA-7 under nitrogen. Samples with weights ranging from 15 to 20 mg were heated from 40 to 350 °C at a rate of 20 °C/min. Compound 1 was synthesized according to a modification of the method of Furdić.

**exo,exo-7-Oxabicyclo[2.2.1]hept-5-ene-2,3-dimethanol (2).** Following a modification of the method of Novak, a dry 2 L three-necked round-bottomed flask was charged with LiAlH$_4$ and added dropwise to the stirred slurry. The resulting white suspension was filtered through Celite, the solid washed with THF (0.5 mL/1 mmol), and the solvent removed. The product was purified by column chromatography on neutral alumina (80–200 mesh) packed in hexanes using 1.4 ethyl acetate/hexanes eluent, gradually changing the gradient to 1:1 ethyl acetate/hexanes as products eluted. The chromatography was followed using 1.1 ethyl acetate:hexanes: hexanes (R$_f$ = 0; R$_f$ = 0.5; R$_f$ = 1.0). A single column could be loaded heavily and used repeatedly without hindering separation. After separation and solvent removal, 3 was obtained as a pale yellow oil, but yield varied from 35 to 69%. 1H NMR δ 1.83–2.04 (m, max at 1.97, 2H), 3.26 (bs, 1H), 3.26–3.78 (m, 4H), 3.35 (3H, 4.66 (m, 1H), 4.70 (m, 1H), 6.32–6.39 (m, center at 6.38, 2H); 13C NMR δ 40.2, 42.9, 59.1, 62.7, 73.3, 81.2, 81.5, 135.7, 136.3.

**exo,exo,exo-6-Dimethoxymethyl-7-oxabicyclo[2.2.1]hept-2-ene (4).** Sodium hydride (10.0 g, 60% in oil, 0.25 mol) was added to form a slurry. The mixture was stirred for 30 min and then allowed to warm to room temperature and stir for 3 h. The mixture was filtered through Celite, the solid washed with THF (0.5 mL/1 mmol, 3), and the solvent removed. The product was purified by column chromatography on neutral alumina (80–200 mesh) packed in hexanes using 1.4 ethyl acetate/hexanes eluent, gradually changing the gradient to 1:1 ethyl acetate/hexanes as products eluted. The chromatography was followed using 1.1 ethyl acetate:hexanes:hexanes (R$_f$ = 0; R$_f$ = 0.5; R$_f$ = 1.0). A single column could be loaded heavily and used repeatedly without hindering separation. After separation and solvent removal, 4 was obtained as a pale yellow oil, but yield varied from 35 to 69%. 1H NMR δ 1.83–2.04 (m, max at 1.97, 2H), 3.26 (bs, 1H), 3.26–3.78 (m, 4H), 3.35 (3H, 4.66 (m, 1H), 4.70 (m, 1H), 6.32–6.39 (m, center at 6.38, 2H); 13C NMR δ 40.2, 42.9, 59.1, 62.7, 73.3, 81.2, 81.5, 135.7, 136.3.

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**Supporting Information Available:** Tables of computed energies for structures discussed in the text, calculated rates, and puckering angles, a DSC thermogram, NMR spectra relevant to the thermal decomposition of 4, an 1H NMR spectrum of the 2 exo and endo isomer mixture, an Arrhenius plot, and some experimental descriptions are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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