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The Preparation of 7-Substituted Norbornadiene-2,3-dicarboxylic Anhydrides and a Theoretical and Experimental Study of their Thermolysis to 5-Membered Carbocyclic or Heterocyclic Anhydrides

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Abstract. New substituted methano-bridged or heteroatom-bridged norbornadienomaleic anhydrides have been prepared and converted to sesquinorbornadiene anhydrides by reaction with cyclic 1,3-dienes. The versatility of parity reversal, in conjuction with *N*-substituent steric effects, has been used to produce stereoisomers of the *N*,*O*-sesquinorbornadiene anhydrides in separate, stereoselective cycloadditions. The anhydrides have been synthesized by cyclisation of their diacids (*in situ* production) or by flash vacuum pyrolysis of their furan adducts (yielding crystalline products); further fragmentation occurs at these or higher temperatures to produce five-membered carbocyclic or heterocyclic anhydrides. Activation energies have been evaluated for the two fragmentation processes and Diels-Alder reactions using DFT calculations (B3LYP/6-31G*) and these calculations correctly predict which reactions can be intercepted at the norbornadienomaleic anhydride stage.

Introduction. Alkene systems formed by sharing a common p-bond between two dienophiles have been found to yield a class of highly reactive dienophiles and this was particularly evident in those which included maleic anhydride as one component, *e.g*. maleic anhydride with itself to give **1**,[1] maleic anhydride with *p*-benzoquinone to give **2**,[2] and maleic anhydride with norbornadiene or 7-oxanorbornadiene to give **3**,[3,4] or **4**, respectively[5,6] (Figure 1). In fact, the last mentioned compound **4** has been described in our previous paper where it is shown to be the most powerful C=C dienophile capable of isolation.[5,7] The ease with which **4** adds cyclic 1,3-dienes (cyclopentadiene, fulvenes) or 5-membered heterocycles (furan and pyrrole) at room temperature has allowed rapid entry to a vide range of bridge-substituted oxasesquinorbornadienes, many for the first time. The fact that reaction of anhydride **4** can be achieved with thiophene under high pressure at room temperature has allowed production of the first sulfur-bridged sesquinorbornadiene.[8]

Figure 1 Superdienophiles **1-4**, formed by the formal fusion of two dienophiles at the p-bond

In this study, we discuss approaches to the synthesis of norbornadiene-2,3-dicarboxylic anhydrides **7a-f** modified at the 7-position (aza, oxa, thia, isopropylidene, adamantylidene), report on a high level computational and FVP study of the propensity of norbornadienes **7a-f** to undergo retro Diels-Alder fragmentation to form carbocyclic and heterocyclic anhydrides **8a-f** and demonstrate the power of parity reversal and steric substituent control to form *N*,*O*-bridged sesquinorbornadiene anhydrides covering all geometrical types via individual, stereoselective cycloaddition reactions.

Scheme 1

Our approach to the synthesis of norbornadiene-2,3-dicarbocyclic anhydrides **7a-f** was based on the flash vacuum pyrolysis (FVP)[9] of their respective furan adducts **5a-f** (Scheme 1). Retro Diels-Alder reaction[10] led to the production of the parent anhydride **7a**, mp 85-85 ^{o}C (lit[1] mp 88-89 ^{o}C) in 85% isolated yield by FVP (325 ^{o}C, 0.005 mbar) of the furan adduct **5a** in only the second method reported for the preparation and isolation of this compound. Given the simplicity of the process and the ready availability of the starting materials, this now constitutes the preferred route to **7a**. The ^{1}H NMR spectrum of **7a** (vinylic d 7.14, bridgehead d 4.08, and methylene d 2.77) corresponded with that published,[1] while the ^{13}C NMR (not reported previously) exhibited five resonances (d 47.7, 78.0, 142.6, 159.3, and 170.6) in accord with its C$_2$-symmetry. Reaction of **7a** with furan **6** regenerated the adduct **5a**, together with its isomers,[2] in the same ratio as that observed in the *in situ* method (*vide supra*).

Similar FVP of the furan adduct **5e** at 375 ^{o}C yielded 7-isopropylidene-norbornadiene-2,3-dicarboxylic anhydride **7e**[11], mp 127-128 ^{o}C, in 57% isolated yield. The ^{1}H NMR of **7e** contained three proton resonances (vinylic d 7.06, bridgehead d 4.49, and methyl d 1.52) which is completely consistent with the assigned structure, and further supported by the seven-line ^{13}C NMR (19.5, 48,2, 103.5, 142.6, 159.1, 164.1, and 168.3). FVP pyrolysis of the extended-frame[12] furan adduct **5f**[13] in the adamantylidene series at 380 ^{o}C produced the corresponding anhydride **7f**, in quantitative yield. The ^{1}H NMR of **7f** contained five sets of proton resonances (vinylic d 7.06, bridgehead d 4.50 and adamantyl resonances: allylic d 2.47, saturated d 1.59-1.67 and 1.79-1.91). Similarly, FVP of *exo,endo*-furan adduct **9f** (X-ray Figure 2) produced anhydride **7f**. These experiments confirm that the stereochemistry of the adduct, *e.g.* *exo,endo*- adduct **9f** or *exo,exo*- adduct **5f**, is not critical for successful thermolysis.

Figure 2. Crystal structure of **9f** with 30% of anisotropic thermal probability.[14]

The 7-oxa derivative **7b** was prepared by FVP of **5b** as outlined in the previous paper[5] and the oily product so obtained was used immediately for cycloadditions with the 1,3-diene trapping agent. Attempts to prepare the *7-N-Z*-derivative **7c** by FVP of the adduct **5c** were unsuccessful and led only to the *N-Z*-derivative of pyrrole-3,4-dicarboxylic anhydride **8c** and acetylene. In the case of the *S*-bridged system **7d**, pyrolysis of adduct **9d**[8] (370 ^{o}C, 0.005 mbar) gave no spectral support for the production of 7-thianorbornadiene anhydride **7d** in the crude pyrolysate, however circumstantial evidence for its formation came from the isolation of phthalic anhydride **10** and spectral identification of furan from the cold trap. It is clear from this result that loss of sulfur from the 7-thianorbornadiene anhydride **7d** is preferred to retro-Diels-Alder ejection of acetylene.

In seeking an explanation for these varied FVP results, we have conducted quantum-chemical study with a full optimization of the transition states (TS1) involved in the production of the norbornadiene-2,3-dicarboxylic anhydrides **7a-c** from their furan adducts **5a-c** and the related transition states (TS2) for the fragmentation of **7a-c** to their 5-membered-ring anhydrides **8a-c** using high level DFT calculations (B3LYP/6-31G*).[15] It is found that the activation energy for the retro Diels-Alder loss of furan (Ea1) remains very similar (29.2-33.2 kcalmol^{-1}) for all three substrates **5a-c** (see Table 1). In contrast, the activation energy (Ea2) for the loss of acetylene from the norbornadiene-anhydrides drops from 52.2 kcalmol^{-1} for the parent **7a** to 37.9 kcalmol^{-1} for the oxa-system **7b**, and further to 32.3 kcalmol^{-1} for the aza-system **7c**. As this activation energy (Ea2) for the aza-system is less than the activation (Ea1) for its formation from the *exo,exo*-fused stereoisomer **5c** by 1 kcalmol^{-1}, then the failure to intercept the intermediate anhydride **7c** is fully supported by the calculated energetics of the two sequential reactions.

Table 1. Activation energies for the retro-Diels-Alder fragmentation reactions **5a-c** to **7a-c** (Ea1) and **7a-c** to **8a-c** (Ea2) calculated using B3LYP/6-31G* method

An alternative route to adducts of norbornadiene anhydride, *e.g.* furan **5a** and **9a**, was reported by Williams *et al.*,[16] in which the related norbornadiene dicarboxylic acid was dehydrated to produce **7a** *in situ* and trapped by warming in acetic anhydride in the presence of cyclopentadiene. We have now used this technique to form adducts of 7-(N-bezyoxycarbonyl)norbornadienomaleic anhydride **7c** and 7-adamantylidene norbornadienomaleic anhydride **7f**. The required dicarboxylic acids were prepared from the addition of acetylene dicarboxylic acid to N-Z pyrrole (diethyl ether, sealed tube, 65 ^{o}C, 40%) to form **13** or hydrolysis of the adduct of DMAD with 6,6-adamantylidenefulvene to access **14**. A selection of new azasesquinorbornadiene anhydrides formed by the generation and trapping of various pentacyclic dienes with norbornadienomaleic anhydride **7c** is presented in Scheme 2. All reactions are stereospecific giving a single product at the anhydride olefinic bond.

Dienophile **7c** reacted with excess cyclopentadiene at 60 ˚C to produce exclusive 2:1 adduct **19**. Formation of intermediate anhydride

9c could be deduced from the structure of the final bis-adduct. The *exo,endo-* geometry on the unsubstituted part of **19** is revealed by the observation of the coupling between *endo-* and bridgehead protons but not between on the anhydride side of molecule. The *exo,endo*-structure of the anhydride side of **19** can be envisaged by similar chemical shifts of the olefinic signals on the both sides of adduct and the lack of steric compression effects of nitrogen[17]. Owing to the steric hindrance on both sides, the rotation of the central carbamate N-CO bone is locked even at 60˚C, causing the loss of symmetry and the duplication of the ^{1}H and ^{13}C NMR signals. This NMR analysis is further confirmed by determination of crystal structure (Figure 3).

Reaction of **7c** with excess of furan gives three adducts: *exo,endo-* 1:1 adduct **9c**, together with 2.1 *exo,endo;exo,exo*-bis-adduct **17** and *exo,endo;exo,endo*-bis-adduct **18**. At 30 ^{o}C, the olefinic proton resonances of pyrrole side in the ^{1}H NMR spectrum of 1:1-adduct **9c** are broad and separated by 0.30 ppm; while on furan side by 0.06 ppm. This reflects their relative position in regard to the N-CO bond, which is undergoing slow rotation at this temperature. The coalescence of olefinic signals at pyrrole side occurs at 63 ^{o}C, and the activation energy DG‡ for the N-CO bond rotation has been calculated to be 67.8 kJ mol^{-1}. Structure **9c** was unequivocally confirmed by X-ray crystallography (Figure 3), while structures of adducts **17** and **18** are assigned by 1D and 2D NMR spectroscopy.

Scheme 2 Azasesquinorbornadiene anhydrides formed by the generation and trapping of azanorbornadienomaleic anhydride **7c**

High stereospecificity was observed in the reaction of **7c** with 6,6-dimethyl fulvene, where *exo,endo*-adduct **21** was formed as the single product in moderate yield (15%). Structure of **21** was deduced by NMR analysis and supported by similarity of its ^{1}H NMR spectrum to that of **9c**. The most indicative feature is the separation of olefinic protons of pyrrole and fulvene sides (0.26 and 0.07 ppm, respectively). This reaction also indicated that 6,6-dimethylfulvene is less reactive than CPD and furan, presumably due to conjugated 6p-system or steric interaction or both.

The opposite stereochemistry was obtained in reaction of *N*-Z pyrrole **11** and diene **7c**. In this case, the *exo,exo-* product **20**, was formed exclusively (Scheme 2). The simplicity of the ^{1}H NMR spectra of **20** at 60 ˚C is indicative, possessing three non-benzenoid resonances, is in full agreement with its C_{2v} symmetry. At room temperature, the system suffers slow rotation about the bridge N-CO bond causing signal broadening. Again, the crystal analysis confirms the geometry of **20** (Figure 4).

Figure 3. Crystal structures of **19** and **9c** with 30% of anisotropic thermal probability.

Figure 4. Crystal structure of **20** with 30% of anisotropic thermal probability.

This difference and stereochemical outcomes could be easily predicted by DFT calculations at B3LYP/6-31G* level. Transition state calculations of Diels-Alder reactions of pentacyclic dienes with dienophile **7c** are illustrated in Figure 5. Calculated activation energies (Table 2) are in good agreement with experiment: *exo,endo-* addition is favored for CPD, furan and 6,6-dimethylfulvene, while *exo,exo-* addition is predicted for NZ-pyrrole reaction.

Table 2. Activation energies for Diels-Alder reactions of **7c** with CPD, furan, NZ-pyrrole and 6,6-dimethylfulvene calculated using B3LYP/6-31G* method (in kcalmol^{-1})

Figure 5. Transition state for a) *exo,exo-* Diels-Alder reaction of **7c** with furan, b) *exo,endo-* Diels-Alder reaction of **7c** with 6,6-dimethylfulvene, calculated using B3LYP/6-31G* method

The ability to access adducts of formal *endo-* cycloaddition origin (adducts **9c** and **21**), a cycloaddition selectivity seldom observed in norbornene chemistry, makes the present methodology a powerful synthetic strategy.

Experimental details. Flash vacuum pyrolyses were conducted (100 mg scale) under very high vacuum (0.005 mbar)[18] in an unpacked 600x6 mm Pyrex tube heated by a horizontally-mounted ‘Termolyne’ model 21100 tube furnace (300-400). The optimum pyrolysis temperature (calibrated using a thermocouple externally attached to the glass pyrolysis tube) was determined separately for each substrate. All new compounds are fully characterized by NMR spectroscopy and mass spectrometry.

NMR spectra were recorded on a Bruker AMX-300 or a Bruker Advance DPX 400 NMR spectrometers. Spectra were measured in $CDCl_3$ with tetramethylsilane as internal reference at 30 ˚C unless indicated otherwise. Mass spectra were conducted by Central

Queensland University Analytical Laboratories using a Shimadzu QP200 mass spectrometer or a Micromass Autospec instrument. Melting point were determined on a Gallenkamp melting point apparatus and are uncorrected. Microanalyses were performed by CQUAL using a Fisons GSE EA 1108 microanalyser. Column chromatography was carried out on Merck silica gel 60 (180-230 mesh). Radial chromatography was performed on the Chromatotron model 7924T with Merck silica gel 60 PF_{254} as absorbent.

Calculations were performed using Spartan program on a Silicon Graphics R5000 workstation. For all structures, harmonic vibration frequency calculations were performed to confirm whether the obtained geometry represents a transition or minimum energy structure.

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7. RHF/6-31*G//B3LYP/6-31G* FMO-furan gaps of **1-4** and TCNE are 11.89, 10.63, 9.46, 9.10 and 10.16 eV respectively, indicating that **4** is the most reactive dienophile. This is further supported by activation energies are 6.65, 14.28, 16.22, 12.09 and 18.99 kcalmol^{-1}, respectively, indicating that **1** is the most reactive and **4** is the second. Reactivity of **4** is the consequence of combination of p-bond pyramidalization, ring strain and stereoelectronic effects (Margetić, D.; Warrener, R. N.; Butler, D. N., *Sixth electronic computational chemistry conference (ECCC-6)*, paper 39, H. H. Homeier ed., November 1-30, **1999**. http://www.chemie.uni-regensburg.de/ECCC6/).

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12. This *exo*- stereochemical assignments is based on the chemical shift of the vinylic protons (d 6.58), which is similar to those observed for the corresponding vinylic protons in other cyclic diene adducts. Initial attack from the *endo*- face would form adduct which positions the vinylic protons proximate to each other would result in a significant upfield shift.

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18. We find that conducting the FVP at higher pressures also increases the proportion of secondary fragmentation, a factor we attribute to increased residence time of the initially formed norbornadiene anhydride in the pyrolysis tube.