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COMPUTATIONAL ANALYSIS OF THE NUCLEOPHILIC ELIMINATIVE RING FISSION OF BRIDGEHEAD SUBSTITUTED 1,3-BISHOMOCUBYL ACETATES

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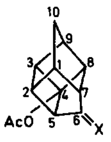
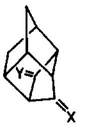
Abstract—Molecular mechanics (MM2) calculations on the conceivable seco-cage structures by homoketonization of two types of bridgehead substituted 1,3-bishomocubyl acetates, *viz.* type **A**: 4-acetoxypentacyclo[$5.3.0.0^{2,5}.0^{3,9}.0^{4,8}$]decan-6-one and its ethylene ketal, and type **B**: 8-acetoxypentacyclo[$5.3.0.0^{2,5}.0^{3,9}.0^{4,8}$]decan-6-one, its ethylene ketal and 8-acetoxypentacyclo[$5.3.0.0^{2,5}.0^{3,9}.0^{4,8}$]decane were performed.

The chemistry of rigid polycyclic systems provides an ideal opportunity for a comparison of results obtained by experimental and computational techniques. This paper deals with a computational analysis of the base induced cage fission of bridgehead substituted 1,3-bishomocubyl acetates of which the experimental results have been described in the preceding paper.[1]

The regiochemistry of the base induced homoketonization of bridgehead 1,3-bishomocubyl acetates **A** and **B** is strongly affected by the nature of the β-substituent X. While treatment of **A** (X = OCH_2CH_2O) with NaOMe in MeOH leads exclusively to halfcage ketone **A1** (X = OCH_2CH_2O, Y = O), cage fission of **A** (X = O) produces only dione **A3** (X = O, Y = O) under comparable conditions.[1] A similar situation is encountered for acetates of type **B**. Here, for X = OCH_2CH_2O and X = H_2, acetate **B** produces halfcage ketones **B1** (X = OCH_2CH_2O, Y = O and X = H_2, Y = O), whereas for X = O, a very fast cage opening is observed leading to a mixture of cage fragmentation products probably arising from initially formed dione **B3** (X = O, Y = O).[1]

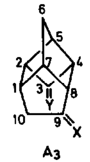


A

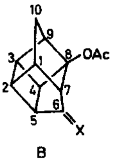


A1

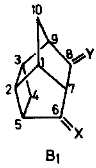
A2



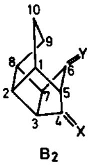
A3



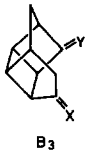
B



B1



B2



B3

Based on a previous computational analysis of ring fission reactions in related cage molecules[2] and molecular modeling, we reasoned that in those cases in which X is a functionality which does not stabilize the intermediate carbanionic species involved in these C—C fission reactions, the regiochemistry of cage opening is governed by the thermodynamic stabilities of the conceivable cage opening products. However, in the case X is a carbonyl function, the decrease in activation energy for C—C bond cleavage leading to a stabilized enolate anion is apparently large enough to override this thermodynamic control and a 'contra-thermodynamic' product is formed.[1] In order to verify this rationale, molecular mechanics (MM2)[3] was applied to calculate the heats of formation and strain energies of two series of tetracyclodecanes **A1**–**A3** and **B1**–**B3**, which basic structures are directly related to the three conceivable modes of C—C bond fission in acetates **A** and **B**, respectively.

Type **A** *compounds*

According to MM2, **A1** (X = OCH_2CH_2O, Y = O, see Table 1) is significantly less strained than the other keto-acetals **A2** and **A3**. The stability order, **A1** > **A2** > **A3**, is the same in the diketone (X = Y = O), monoketone (X = H_2, Y = O) and hydrocarbon (X = Y = H_2) series, although the energy differences are affected by the pattern of X, Y-substituents.

Interestingly, the 'contra-thermodynamic' product **A3** (X = Y = O) resulting from the homoketonization of keto-acetate **A** (X = O) is calculated to be the most strained among the three possible diketo products (**A1**–**A3**). According to these calculations, the β-carbonyl group of starting keto-acetate **A** decreases the activation energy of central C_4—C_5 bond scission by at least 7 kcal/mol.

The optimized structure of diketone **A3** (X = Y = O) furnishes additional aids for the interpretation of some experimental observations. In this structure, the dihedral angles between H_1 (bridgehead proton at C_1) and H_n (*endo*-proton at C_{10}) and between H_1 and H_x (*exo*-proton at C_{10}) are 85.4° and −37.3°, for which Altona's empirically generalized Karplus equation[4,5] gives 1.0 and 6.6 Hz, respectively, for the corresponding vicinal coupling constants.[6] These values agree well with those experimentally observed (0 and 6 Hz).[1]

The inside proton H_n in this calculated structure is located 3.01 Å from the C_3-carbonyl oxygen atom, a distance considerably smaller than the sum of the empirical van der Waals radii[3b] of hydrogen (1.50 Å) and carbonyl oxygen (1.74 Å). This result supports our

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Table 1. Results of MM2 calculations on tetracyclodecanes and derivatives. Heat of formation/(strain energy), both in kcal/mol

		Type A			Type B		
X	Y	**A1**	**A2**	**A3**	**B1**	**B2**	**B3**
H_2	H_2	8.16 (43.54)	14.60 (49.98)	16.99 (52.37)	14.60 (49.98)	14.37 (49.75)	31.81 (67.19)
H_2	O	−17.84 (43.59)	−11.24 (50.19)	−6.25 (55.18)	−11.52 (49.91)	−10.88 (50.55)	5.57 (67.00)
Ek[a]	O	−83.93 (48.02)	−77.94 (54.00)	−73.27 (58.67)	−78.23 (53.71)	−77.50 (54.44)	−61.21 (70.73)
O	O	−37.96 (49.80)	−34.86 (52.90)	−31.01 (56.75)	−35.04 (52.72)	−31.10 (56.67)	−20.54 (67.22)

[a] Ethylene ketal function OCH_2CH_2O.

explanation for the much faster exchange of inside proton H_n in comparison with proton H_x upon treatment of **A3** (X = Y = O) with NaOMe in MeOD. This unexpected phenomenon has been attributed to through-space interaction of the cyclobutanone C=O function with this *endo*-proton.[1]

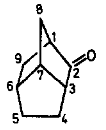
*Type-*B *compounds*

The products of homoketonization of acetates **B** ($X = OCH_2CH_2O$; $X = H_2$) *viz.* tetracyclodecanones **B1** ($X = OCH_2CH_2O$, Y = O and $X = H_2$, Y = O, respectively), are calculated to be less strained than the other possible products, marginal for the **B2** series and convincing for the **B3** compounds. In the case of the hydrocarbon series ($X = Y = H_2$), the stability order even reverts (**B2** > **B1** ≫ **B3**). The exclusive formation of the **B1**-type tetracyclodecanones in the homoketonization of **B** ($X = OCH_2CH_2O$ and $X = H_2$) can be justified by assuming that the calculated stabilities of the **B2**-tetracyclodecanones do not accurately reflect the difference in activation energy for the formation of **B1** and **B2**-structures from **B** ($X = OCH_2CH_2O$ and $X = H_2$). The geometry optimization changes the unnatural twist at the C_9—C_{10} ethano bridge in the **B2**-type structures. However, this twist features the structure of the actual transition state of the cage opening process. Hence the actual difference in activation energy is likely to be somewhat higher than calculated, disfavouring the **B2**-type tetracyclodecanones. The cage opening for **B** (X = O) experimentally leads to **B3** (X = Y = O). Thus, in spite of the fact that an extra strain energy of 14.5 kcal/mol needs to be overcome, the reaction takes the contra-thermodynamic course. The calculated strains of the **B3**-series are by far the highest among the tetracyclodecanes listed in Table 1, their strain energy being more than 67 kcal/mol. This strain effect is in accordance with the chemical behaviour of the **B3**-diketone (X = Y = O) which under the mild conditions needed for its formation from acetate **B** (X = O) is not stable but rapidly undergoes further cage degradation.[1] It should be mentioned that the marginal difference in strain energies for **B1** and **B2** ($X = OCH_2CH_2O$ and $X = H_2$) has no reliable *predictive* value for the preferential cage opening reaction.

The interesting observation of H/D exchange at the bridgehead C_7-position in the **B1**-type tetracyclodecanone ($X = H_2$; Y = O) upon treatment with NaOMe in MeOD,[1] prompted us to calculate Schleyer's olefinic strain (OS)[7] of a model anti-Bredt olefin **C**. Olefinic strain is the difference between the total strain energy of an olefin and that of the parent hydrocarbon.[8] For **C**, the OS value is 23.1 kcal/mol,[10] which categorizes **C** as an *unstable bridgehead olefin.*[7]

C

D



E

This is in accord with the severe conditions that had to applied to effect the H/D exchange in **B1** ($X = H_2$; Y = O), and with Wiseman's rule which states that the *trans*-double bond accommodated in an eight-membered ring produces highly strained anti-Bredt olefins.[11] The OS value of a tricyclic homologue **D** which geometrically closely resembles **C** but lacks the four-membered ring is calculated to be about 3 kcal/mol less strained than **C** (OS 20.0 kcal/mol).[10] This result is consistent with the observed, more facile H/D exchange at the bridgehead C_3-position in the corresponding ketone **E** as observed by Nickon.[12] In contrast to previous OS studies where almost exclusively bicyclic olefins and diolefins[13] have been discussed, tri- and higher polycyclic bridgehead olefins are advantageous in that the structures are generally rigid and conformationally less ambiguous.

In conclusion, MM2-calculations are valuable in understanding our experimental results on the base induced homoketonization of bridgehead substituted 1,3-bishomocubyl acetates.[1] The observed consistency of experimental and computational results for these strained cage compounds suggests that molecular mechanics is a profitable aid in synthetically designing polycyclic structures.[14]

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[10] MM2-strain energy of **C** is 73.06 kcal/mol. For the parent hydrocarbon, see Table 1 (**A2**, **B1**, $X = Y = H_2$). MM2-strain energies of **D** and its parent hydrocarbon are 45.70 and 25.66 kcal/mol, respectively.

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