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Supplementary Material Available: 1D and 2D NMR spectra for **1** and **2** (13 pages). Ordering information is given on any current masthead page.

Automerization of Naphthalene. New Evidence Consistent with the Intermediacy of Benzofulvene[1]

Lawrence T. Scott,* Mohammed M. Hashemi,† Thomas H. Schultz, and Michael B. Wallace‡

Department of Chemistry and Center for Advanced Study University of Nevada, Reno, Nevada 89557-0020

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We first reported the thermal interconversion of [α-^{13}C]-naphthalene (**1**α) and [β-^{13}C]naphthalene (**1**β) in 1977[2] and have subsequently observed the 1,2-scrambling of carbon atoms at high temperatures in a variety of other aromatic hydrocarbons,[3-8] as well as in benzene-$^{13}C_2$.[9] Considerable evidence suggests that the mechanism of these "automerization" reactions and related thermal rearrangements of benzenoid hydrocarbons involves reversible contraction of a benzene nucleus to a five-membered-ring intermediate.[7,10,11] Herein we present new evidence that deposes the previously proposed carbene **2** as a candidate for that intermediate in favor of benzofulvene (**3**); Scheme I depicts plausible pathways to **3** via ring contractions of carbenes **4** and **5**.

R. F. C. Brown et al. have reported that flash vacuum pyrolysis (FVP) of benzofulvene gives naphthalene as the exclusive product.[12] We have now repeated this reaction using isotopically labeled benzofulvene, enriched to 99% ^{13}C in the methylene group (**3**).[13] At 900 °C/10^{-3} Torr, labeled benzofulvene **3** yields [α-^{13}C]naphthalene (**1**α) and [β-^{13}C]naphthalene (**1**β) in a ratio of 21:79 ± 3.[14,15] Control experiments (repyrolysis of the labeled naphthalene mixture) confirm that **1**α and **1**β do not interconvert (≤3%) under these conditions.[16]

We believe that the disparate product distribution in this experiment argues strongly against carbene **2** as an intermediate *on the pathway from benzofulvene to naphthalene.* Our reasoning is as follows: At 900 °C, a kinetically controlled product ratio of 21:79 requires a difference in free energy of activation ($\Delta\Delta G^{\ddagger}$) of ca. 3.1 kcal/mol between two competing pathways.[15] If carbene **2** were the intermediate in the aromatization of benzofulvene (Scheme I), then these two competing pathways would be the aryl shift (**2** → **1**α) and the vinyl shift (**2** → **1**β).[17] Such rearrangements of carbenes, however, are extremely exothermic reactions with very low energy barriers (Figure 1A)[18] and should be characterized by quite early (carbene-like) transition states.[19] Given two equally exothermic pathways (**2** → **1**α vs **1**β),[20] both with very low energy barriers, it seems highly unlikely that they could differ in $\Delta G^{\ddagger}$ by as much as 3.1 kcal/mol. Thus, carbene **2** appears improbable as an intermediate *on the pathway from benzofulvene to naphthalene.*

Brown et al. originally proposed an alternate pathway for the aromatization of benzofulvene via carbene **4** (Scheme 1).[12] This mechanism would certainly account for the minor product (**1**α) we obtain from labeled benzofulvene **3**, and the major product (**1**β) could presumably arise by an analogous pathway via carbene **5**. It would be reasonable to assume that the initial ring expansions, rather than the subsequent hydrogen shifts, represent the rate-limiting steps on these two competing pathways.

This proposal has the virtue that the product-determining branch point in the mechanism involves highly endothermic reactions with very high energy barriers (Figure 1B) that should be characterized by quite late (carbene-like) transition states.[19] These two competing pathways, which lead to different carbenes, could more easily differ in $\Delta G^{\ddagger}$ by 3.1 kcal/mol. Indeed, Dewar and Merz place carbene **5** lower in energy than carbene **4** by 3.4 kcal/mol on the basis of MNDO calculations.[21] This calculated difference in energy not only qualitatively predicts the preferential formation of **1**β from **3** via carbene **5** but even agrees quantitatively with the product ratio we observe.

If benzofulvene isomerizes to naphthalene via the six-membered-ring carbenes **4** and **5**, as we now propose, rather than via the indenyl carbene **2**, then a strong case can be made that the automerization of naphthalene is also more likely to proceed via **4**, **5**, and benzofulvene rather than via simple ring contraction to **2**. A crucial element of this argument is the postulate that the transition state between **2** and **3** lie lower in energy than the transition states separating **2** from either **1**α or **1**β. This seems reasonable, since 1,2-hydrogen shifts in carbenes almost always occur more readily than 1,2-carbon shifts.[18] Furthermore, Kjell and Sheridan have actually observed that carbene **2**, when generated in a frozen matrix at low temperatures, rearranges exclusively to benzofulvene and gives no naphthalene.[22] Conse-

† Visiting scholar from Sharif University of Technology, Tehran, Iran.
‡ Undergraduate summer research student from Northwestern University.

(1) Thermal Rearrangements of Aromatic Compounds. 15. For precedng papers in this series, see: Scott, L. T.; Hashemi, M. M.; Meyer, D. T.; Warren, H. B. *J. Am. Chem. Soc.* **1991**, *113*, 7082.
(2) Scott, L. T.; Agopian, G. K. *J. Am. Chem. Soc.* **1977**, *99*, 4506.
(3) Scott, L. T.; Highsmith, J. R. *Tetrahedron Lett.* **1980**, *21*, 4703.
(4) Scott, L. T.; Kirms, M. A. *J. Am. Chem. Soc.* **1981**, *103*, 5875.
(5) Scott, L. T. *Acc. Chem. Res.* **1982**, *15*, 52.
(6) Scott, L. T.; Kirms, M. A.; Berg, A.; Hansen, P. E. *Tetrahedron Lett.* **1982**, *23*, 1859.
(7) Scott, L. T.; Tsang, T.-H.; Levy, L. A. *Tetrahedron Lett.* **1984**, *25*, 1661.
(8) Scott, L. T. *Chem. Aust.* **1987**, *54*, 298.
(9) Scott, L. T.; Roelofs, N. H.; Tsang, T.-H. *J. Am. Chem. Soc.* **1987**, *109*, 5456.
(10) Scott, L. T.; Roelofs, N. H. *J. Am. Chem. Soc.* **1987**, *109*, 5461.
(11) Scott, L. T.; Roelofs, N. H. *Tetrahedron Lett.* **1988**, *29*, 6857.
(12) Brown, R. F. C.; Gream, G. E.; Peters, D. E.; Solly, R. K. *Aust. J. Chem.* **1968**, *21*, 2223-2236.
(13) Benzofulvene enriched to 99% ^{13}C in the methylene group (**3**) was synthesized by (a) quenching the lithium salt of indene in ether with $^{13}CO_2$ generated from 99%-^{13}C-enriched $BaCO_3$, (b) esterification of the resulting indenecarboxylic acid ($SOCl_2/CHCl_3$, then EtOH/THF), (c) reduction of the ester with $LiAlH_4/AlCl_3/Et_2O$, and (d) dehydration of the indenylmethanol in benzene at 10 °C with methanesulfonyl chloride (1.0 equiv) and triethylamine (9 equiv). The indene derivatives in this synthetic sequence are known compounds in their unlabeled form: see ref 12 and citations therein.
(14) Flash vacuum pyrolyses were conducted in a commercially available Trahanovsky pyrolysis apparatus purchased from Kontes, Inc., Vineland, NJ 08360. Polymerization of **3** in the sample chamber was suppressed by matrix-isolating the material in frozen benzene at 0 °C; a portion of the benzene dimerizes to biphenyl in the pyrolysis tube. The pyrolysate was doubly sublimed prior to quantitative ^{13}C NMR analysis; the appropriate correction was made for unequal α and β ^{13}C signal intensities in the NMR spectrum of unenriched naphthalene.
(15) The 900 °C temperature we report here is the thermocouple reading inside the oven at the midpoint of, but external to, the pyrolysis tube.
(16) The automerization of naphthalene has a half-life of approximately 2 s at 1035 °C in a nitrogen flow system.[2]
(17) Cyclization of carbene **2** to naphthvalene would not account for formation of **1**α.
(18) Tomioka, H.; Ueda, H.; Kondo, S.; Izawa, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7817-7818. Stevens, I. D. R.; Liu, M. T. H.; Soundararajan, N.; Paike, N. *Tetrahedron Lett.* **1989**, *30*, 481-484. Moss, R. A.; Ho, G.-J. *Tetrahedron Lett.* **1990**, *31*, 1225-1228. Moss, R. A.; Ho, G.-J. *J. Am. Chem. Soc.* **1990**, *112*, 5642-5644. Evanseck, J. D.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 9148-9156 and references cited therein.
(19) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334. For a modern discussion of the Hammond postulate, see: Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 3rd ed., Plenum Press: New York, 1990; Part A, pp 211-215.
(20) The thermodynamic product ratio **1**α:**1**β is essentially 50:50.[2]
(21) Dewar, M. J. S.; Merz, K. M., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 5146-5153. The tricyclic tetraenes proposed by these authors as intermediates separating benzofulvene from carbenes **4** and **5** not only are superfluous but also are incompatible with the experimental observation that naphthalene (with a greater total resonance energy) automerizes significantly more readily than does benzene.[9]

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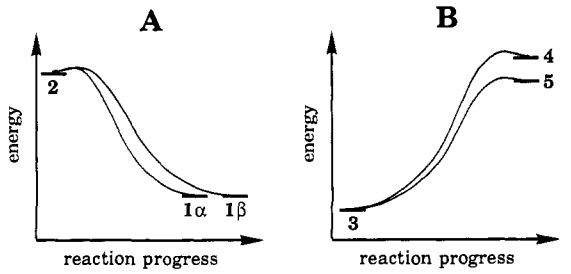
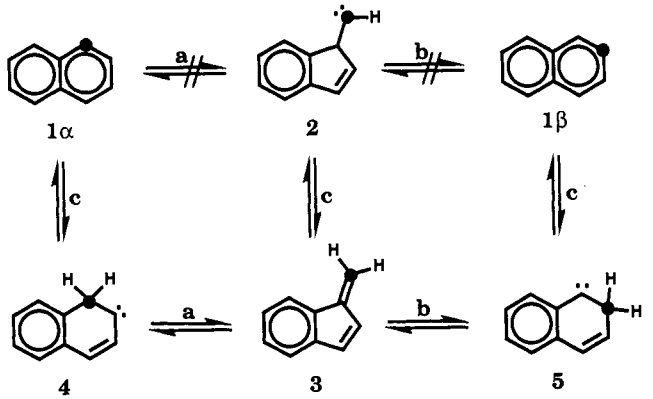


Figure 1. (A) Early transition states of similar energy for competing exothermic reactions. (B) Late transition states of different energies for competing endothermic reactions.

Scheme I[a]



[a] ● = ^{13}C; a = aryl shift, b = vinyl shift, c = hydrogen shift.

quently, since benzofulvene appears to aromatize via the six-membered-ring carbenes **4** and **5**, rather than via the indenyl carbene **2** (vida supra), it follows that all four of the other transition states in Scheme I must likewise lie lower in energy than the transition states separating **2** from either **1α** or **1β**. The lowest energy pathway between **1α** and **1β** in Scheme I, therefore, is **1α** ⇌ **4** ⇌ **3** ⇌ **5** ⇌ **1β**.

All the experimental and theoretical evidence to date is consistent with (but does not "prove") this pathway for the automerization of naphthalene. One cannot exclude the direct "dyotropic" rearrangement[23] of naphthalene to benzofulvene (simultaneous carbon and hydrogen shifts), bypassing carbene intermediates entirely, but in either case, benzofulvene would be an obligatory intermediate in the naphthalene automerization. Alternative pathways involving reversible isomerization of naphthalene to azulene or to isonaphthvalene have already been disproven.[5,7] We conclude, therefore, that the thermal automerization of naphthalene probably occurs by reversible formation of benzofulvene, either via carbenes **4** and **5** or by direct dyotropic rearrangements.

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Registry No. **1α**, 20526-83-4; **1β**, 29571-13-9; **3**, 137175-13-4; naphthalene, 91-20-3; benzofulvene, 2471-84-3.

(22) Kjell, D. P.; Sheridan, R. S. *J. Am. Chem. Soc.* **1986**, *108*, 4111-4114. Extrapolation to high temperatures could lead to a reversal of the observed preference for hydrogen shift over carbon shift only if the hydrogen shift were to have a significantly more negative $\Delta S^{\ddagger}$, which we deem unlikely.

(23) Reetz, M. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 129-130. Reetz, M. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 130-131. Brook, A. G.; Bassindale, A. R. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 2, Chapter 9.

Total Synthesis of Onnamide A

Chang Yong Hong and Yoshito Kishi*

Department of Chemistry, Harvard University
12 Oxford Street, Cambridge, Massachusetts 02138
Received September 17, 1991

Antiviral and antitumor natural products mycalamides A (**1**) and B (**2**) and onnamide A (**3**) were isolated from marine sponges.[1,2] Structurally, they strikingly resemble pederin.[3] We recently reported an enantioselective total synthesis of mycalamides A and B, which unambiguously established their absolute stereochemistry and structural link to pederin.[4] In this context, we turned our attention to onnamide A, whose structure has been elucidated primarily by spectroscopic methods. However, its relative stereochemistry at the C-11 and C-21 positions and absolute stereochemistry except at the C-2′ position still remain unknown.[5] In the synthetic studies leading to mycalamides A and B, we recognized that the diol **10** might be a useful substance to establish not only the stereochemistry of onnamide A but also the structural link between these three classes of natural products. However, we also realized that its synthesis, particularly the synthesis of **9**, needed to be improved for this purpose, and we first studied an alternative synthesis of **9**.

Sodium triacetoxyborohydride reduction [$NaBH(OAc)_3$/$CeCl_3$/MeOH/0 °C] of the ketone **4**,[6] followed by methylation (MeI/NaH/THF/room temperature), yielded the desired methyl ether **5** in 78% overall yield (stereoselectivity = 12:1). It is notable that this reduction did not proceed in the absence of $CeCl_3$. Furthermore, various reduction conditions, including $NaBH_4$ (desired/undesired = 0/1), LAH (0/1), L-Selectride (0/1), BH_3·THF (0/1), $Zn(BH_4)_2$ (1/3), $NaBH_3CN$ (1/5), $NaBH_4$–$CeCl_3$ (1/1), and $NaBH_3CN$–$CeCl_3$ (3/2), neither yielded the desired diastereomer nor gave a satisfactory level of stereoselectivity. The required protecting group manipulation at the C-16 and C-18 positions, i.e. **5** → **6**, was possible in two steps [(1) LAH/$AlCl_3$/Et_2O–CH_2Cl_2/reflux and (2) Ac_2O/BF_3·Et_2O/room temperature]. However, for large-scale preparation, this transformation was carried out in four steps [(1) H_2/$Pd(OH)_2$ on C/MeOH/room temperature, (2) MMTrCl/(*i*-Pr)$_2$EtN/CH_2Cl_2/room temperature, (3) BnBr/NaH/DMF/room temperature, and (4) Ac_2O/BF_3·Et_2O/0 °C → room temperature] in 75–80% overall yield because of its better reproducibility. C-Glycosidation of **6** (CH_2=$CHCH_2TMS$/TMSOTf/BF_3·Et_2O/MeCN/0 °C)[7] gave exclusively the expected, axially substituted product **7** in 93% yield. Corey asymmetric osmylation of **7** [OsO_4/*S*,*S* Corey ligand/CH_2Cl_2/−90 °C],[8,9] followed by carbonate formation (Im_2CO/C_6H_6/reflux) and separation by silica gel chromatography, afforded the desired diastereomer **8**

(1) (a) Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Pannell, L. K. *J. Am. Chem. Soc.* **1988**, *110*, 4850. (b) Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Thompson, A. M. *J. Org. Chem.* **1990**, *55*, 223.

(2) Sakemi, S.; Ichiba, T.; Kohmoto, S.; Saucy, G.; Higa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4851.

(3) (a) Cardani, C.; Ghirinhelli, D.; Mondelli, R.; Quilico, A. *Tetrahedron Lett.* **1965**, 2537. (b) Matumoto, T.; Yanagiya, M.; Maeno, S.; Yasuda, S. *Tetrahedron Lett.* **1968**, 6298. (c) Furusaki, A.; Watanabe, T.; Matsumoto, T.; Yanagiya, M. *Tetrahedron Lett.* **1968**, 6301.

(4) Hong, C. Y.; Kishi, Y. *J. Org. Chem.* **1990**, *55*, 4242.

(5) The numbering of compounds used in this paper corresponds to that of onnamide A: see structure **3**. Satisfactory spectroscopic data (^1H and ^{13}C NMR, HRMS, MS, IR, UV, α_D) were obtained for all the new compounds reported.

(6) Rocherolle, V.; Lopez, J. C.; Olesker, A.; Lukacs, G. *J. Chem. Soc., Chem. Commun.* **1988**, 513.

(7) For the stereochemical outcome of this type of C-glycosidation, see: Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.

(8) Corey, E. J.; Jardine, P. D.; Virgil, S.; Yuen, P.-W.; Connell, R. D. *J. Am. Chem. Soc.* **1989**, *111*, 9243. For recent papers on asymmetric osmylation, see references cited in ref 4.

(9) We are indebted to Professor Sharpless for a sample of new ligands prior to publication (Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585). The stereoselectivity with the DHQD-MEQ ligand was approximately 2:1, favoring the desired diastereomer.

0002-7863/91/1513-9693$02.50/0