mM (L form) which is less than the absolute Michaelis constant of L-aspartate (4.4 mM). L-Aspartate at a concentration of 2.0 mM provides only modest protection[18] against inactivation by 1.8 mM β-methylene-DL-aspartate.

Vinylglycine is a good substrate of L-amino acid oxidase[19,20] and D-amino acid oxidase[20] and a poorer one of beef heart glutamate-alanine transaminase.[20] β-Methylene-DL-aspartate is not a substrate of these enzymes. γ-Cystathionase and L-threonine deaminase catalyze rapid double-bond migration, resulting in conversion of vinylglycine to α-ketobutyrate and ammonia.[20] Rat organ homogenates do not catalyze α-keto acid formation from β-methylene-DL-aspartate under conditions which result in rapid conversion of L-homoserine (the commonly used substrate of γ-cystathionase) to α-ketobutyrate and ammonia.[21]

Vinylglycine irreversibly inactivates snake venom L-amino acid oxidase.[19,20] No inactivation of D-amino acid oxidase, L-amino acid oxidase, pig heart glutamate-alanine transaminase, soluble rat kidney glutamine transaminase, *E. coli* glutamate decarboxylase, *P. fluorescens* GABA transaminase, and rat brain GABA transaminase (homogenates) was observed with β-methylene-DL-aspartate.[22,23]

In vivo experiments were carried out as follows: Six hours following an intraperitoneal injection of 100 mM β-methylene-DL-aspartate in 0.9% saline into six mice (5 mmol/kg),[24] kidney glutamate-aspartate transaminase activity was decreased by 40% ($P < 0.0005$) and the liver enzyme activity was decreased by 23% ($P < 0.01$) compared to six saline injected controls.[25-27]

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(18) Incubation at 25 °C in 100 mM potassium phosphate buffer (pH 7.2) with 1.8 mM β-methylene-DL-aspartate led to 50% inactivation after 7 min. In the presence of 2 mM L-aspartate and 1.8 mM β-methylene-DL-aspartate, the time required to reach 50% inactivation was 19 min.

(19) Cooper, A. J. L.; Stephani, R. A.; Meister, A. *J. Biol. Chem.* **1976**, *251*, 6674.

(20) Marcotte, P.; Walsh, C. *Biochemistry* **1976**, *15*, 3070.

(21) Tissue extracts were prepared and γ-cystathionase was assayed with L-homoserine as substrate according to the methods of: Greenberg, D. M. *Methods Enzymol.* **1962**, *5*, 936. In a separate experiment L-homoserine was replaced by β-methylene-DL-aspartate. No α-keto acid formation from β-methylene-DL-aspartate was detected in rat brain, liver, and kidney homogenates. Conditions were such that a rate of α-keto acid formation from β-methylene-DL-aspartate as low as 0.0001% the rate of α-ketobutyrate formation from DL-homoserine would have been detectable in rat liver homogenates. One qualification is required. The enamine derived from β-methyleneaspartate may be more stable than that derived from homoserine; hydrolysis to the α-keto acid or attack at the α carbon by 2,4-dinitrophenylhydrazine may be slow reactions. If so, the negative 2,4-DNP result would not rule out the possibility of interaction of β-methyleneaspartate with γ-cystathionase.

(22) β-Methylene-DL-aspartate is neither a substrate nor an inhibitor of bacterial D-amino acid transaminase: Soper, T. S.; Manning, J. M., personal communication.

(23) Glutamate-alanine transaminase in rat liver homogenates and glutamate decarboxylase in rat brain homogenates are, however, slowly inactivated when incubated with 5 mM β-methylene-DL-aspartate in 100 mM potassium phosphate buffer, pH 7.2, 25 °C.

(24) No obvious behavioral difference between mice injected with β-methylene-DL-aspartate and controls was discernible.

(25) No inactivation of brain enzyme was noted; L-aspartate is known to cross the blood-brain barrier only poorly: Oldendorf, W. H. *Am. J. Physiol.* **1971**, *221*, 1629. The skeletal muscle enzyme and the heart muscle enzyme were also not affected.

(26) Further evidence that β-methylene-DL-aspartate is active in vivo is provided by the findings that 1 h after intraperitoneal administration of β-methylene-DL-aspartate into mice (2.5 mmol/kg), the initial rate of exhaled $^{14}CO_2$ (derived from L-[1-^{14}C]aspartate) is diminished significantly. Owen W. Griffith, personal communication.

(27) In experiments in which the blood-brain barrier is circumvented, i.e., in tissue slices, cerebral glutamate-aspartate transaminase is strongly inhibited by β-methylene-DL-aspartate. The inhibition of enzyme activity is accompanied by a marked reduction in oxygen consumption. Fitzpatrick, S. M.; Cooper, A. J. L.; Duffy, T. E. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1981**, *40*, 1843.

Bimolecular Thermal Reactions of 5-Methylene-1,3-cyclohexadiene (*o*-Isotoluene) and 3-Methylene-1,4-cyclohexadiene (*p*-Isotoluene)

Joseph J. Gajewski* and Andrea M. Gortva

Department of Chemistry, Indiana University
Bloomington, Indiana 47405
Received August 17, 1981

Despite intensive study of the pyrolysis of C_7H_8 compounds, the methylenecyclohexadienes, *o*- and *p*-isotoluenes, **1** and **2**, respectively, have received little attention.[1] Both **1** and **2** are ca. 23 kcal/mol less stable than toluene,[2] and so their pathways for isomerization are of concern. Further, these species may be involved in retro-ene reactions occurring in coal liquefaction.[3]

While both **1** and **2** have been prepared,[4,5] their sensitivity to acid and base have precluded or obscured efforts to observe their thermal behavior. We report here the benzene solution second-order pyrolytic reactions of these materials which are preparatory to our efforts to examine their dilute gas-phase isomerization.

o-Isotoluene has been prepared in different ways by Bailey,[4a] Kopecky,[4b] and Pryor[4c] who also reported that it disappears in a second-order process; all previous workers have reported that toluene is formed.[4d] *p*-Isotoluene was prepared by Plieninger and Maier-Borst who pyrolyzed (1,4-dihydrobenzyl)trimethylammonium hydroxide,[5] but the oxide of (1,4-dihydrobenzyl)dimethylamine has been found to eliminate smoothly to **2** (and toluene) at 60 °C under vacuum. *o*-Isotoluene could not be purified by GC without ca. 20% conversion to toluene under conditions which allowed purification of the para isomer, but **1** is remarkably pure upon pyrolytic generation from 5-methylenecicyclo[2.2.1]hept-2-en-7-one,[4c] and so it was used directly after vacuum line transfers.

In degassed benzene-d_6 solution in NMR tubes sealed under vacuum both **1** and **2** disappear with second-order kinetics: $\log k_1$ (L/mol·s) = $(4.6 \pm 1.0 - 11\,800 \pm 2000)/(2.3RT)$ and $\log k_2$ (L/mol·s) = $(8.1 \pm 0.2 - 21\,800 \pm 300)/(2.3RT)$.[6] Thus at 56 °C **1** reacts ca. 1500 times faster than **2** at equivalent concentrations. The activation parameters, especially the *A* factor for reaction of **1**, suggest a concerted reaction for **1** but not for **2**. The cyclopentadiene dimerization has a log *A* factor between 3.5 and 6.8.[7] The *A* factor for loss of **2** suggests little orientational demand by the transition state.

The product distribution from each material reinforces the kinetic observations. *o*-Isotoluene gives 75% of ene products **3** and **4** in a 2:1 ratio along with 12% of two preparative GC inseparable unknowns with the residual material apparently being trimeric;[8] however, little, if any, toluene is formed in contrast to

(1) For a review, see: Gajewski, J. J. "Hydrocarbon Thermal Isomerizations"; Academic Press: New York, September 1981.

(2) Bartmess, J. E. *J. Am. Chem. Soc.*, following communication in this issue.

(3) This is particularly true with **1**: Virk, P. S. *Fuel* **1979**, *58*, 149.

(4) (a) Bailey, W. J.; Baylouny, R. A. *J. Org. Chem.* **1962**, *27*, 3476. (b) Kopecky, K. R.; Lau, M. P. *Ibid.* **1978**, *43*, 524. (c) Graham, W. D.; Green, J. G.; Pryor, W. A. *Ibid.* **1979**, *44*, 907 and references contained therein. (d) *o*-Isotoluene is apparently extremely sensitive to acids giving toluene.

(5) Pleininger, H.; Maier-Borst, W. *Chem. Ber.* **1965**, *98*, 2504. *o*-Isotoluene is the thermal isomerization product of 5-methylenebicyclo[2.2.0]-hex-2-ene. Hasselmann, D.; Loosen, K. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 606.

(6) The average deviation reported is that for two separate runs of a sample of **1** or **2** which was divided into separate tubes and examined over a 40–42° range of temperatures. E_a is reported in kcal/mol.

(7) Benson, S. W. "Foundations of Chemical Kinetics"; McGraw-Hill: New York, 1960; p 302. Benson, S. W.; O'Neal, H. E. "Kinetic Data on Gas-Phase Unimolecular Reactions; National Bureau of Standards, Washington, DC, 1970; NBS-21, p 342.

(8) The major products were identified after GC separation on SE-30 column. 220-MHz NMR of **3**: δ 7.2 (m, 5 H), 6.07 (d, J = 10 Hz, 1 H), 5.42 (d, J = 10 Hz, 1 H), 4.72 (s, 1 H), 4.69 (s, 1 H), 2.7–2.0 (m, 5 H), 1.77 (sym m, 1 H, 1.36 (sym m, 1 H). 220-MHz NMR of **4**: δ 7.2 (m, 5 H), 5.8 (m, 3 H), 5.46 (d, J = 10 Hz, 1 H), 2.57 (ABq, J = 13 Hz, 2 H), 2.07 (ABq, J = 17 Hz, 2 H) (the downfield lines are doubled with J = 5 Hz and the upfield lines are doublets of doublets with J = 4, 2 Hz), 0.93 (s, 3 H). One of the unknowns appears to be 1-methyl-5-benzyl-1,3-cyclohexadiene, a 10-electron ene product.

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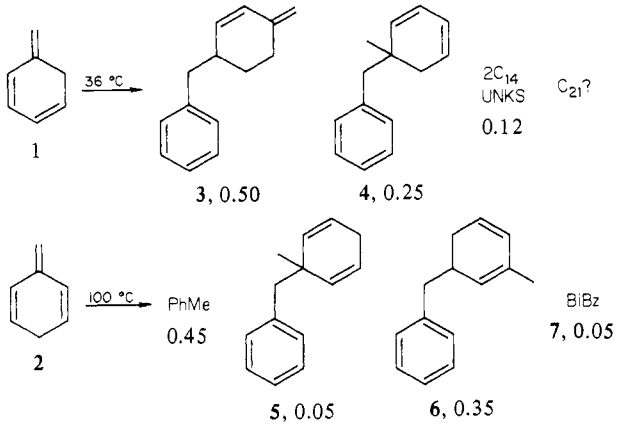
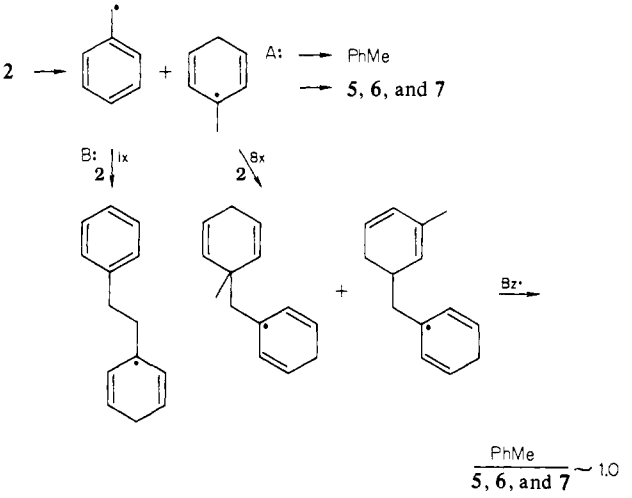
previous reports. On the other hand, *p*-isotoluene gives ca. 50% toluene as well as a 1:7:1 ratio of two dimeric products, **5** and **6**, and bibenzyl, **7**, respectively, along with small amounts of apparently trimeric material.[9] This product distribution is relatively independent of concentration of starting material.



The difference between the two isomers would appear to be their relative ability to undergo an ene reaction. Only **1** can give an aromatic nucleus directly in this concerted reaction. Thus the reaction exothermicity appears to control the relative ene reactivity of **1** and **2**. *p*-Isotoluene apparently slowly transfers its reactive hydrogen to a second molecule to give a benzyl radical and a 3-methylcyclohexadienyl radical which can either (A) disproportionate to toluene and combine to give C_{14} products in a 1:1 ratio or (B) add to more triene which disproportionates with benzyl radical. In path B the product distribution suggests that methylcyclohexadienyl radical adds to **2** roughly eight times faster than the benzyl radical, and so mostly benzyl radical is left to undergo disproportionation. Interestingly, path B *requires* a near 1:1 ratio of toluene to **5**, **6**, and **7** which is in accord with the experimental facts.



There are a number of significant observations regarding the reaction of **2**. Benzyl radicals are being generated by a retro radical-radical disproportionation (molecule assisted homolysis[4c]); yet they do not induce a long-chain isomerization of **2** to toluene. The formation of such a high proportion of potential termination products, **5-7**, excludes a long radical chain isomerization. Significantly, the presence of dimethylhydroxylamine, a good hydrogen donor,[10] had no effect on the reaction nor did changing the solvent to cyclohexane-d_{12}. Further, equimolar amounts of AIBN gave little if any toluene in the presence of **2** in benzene at 80 °C for 1 h; most of the *p*-isotoluene was unaffected and roughly 50% of the AIBN was converted to tetramethylsuccinonitrile.[11] It appears that the E_a for the hydrogen atom transfer path from **2** is too high to be traversed relative to recombination and disproportionation if path A is followed or relative to addition to **2** is path B is utilized.

Using thermochemical group additivity and relative heats of formation of **2** and toluene,[2] the first step of either path A or B can be calculated to be uphill 18 kcal/mol enthalpically which is only 4 kcal/mol less than the observed E_a. Interestingly, this same retrodisproportionation for *o*-isotoluene also has a calculated endothermicity of 18 kcal/mol. Significantly, it is precisely this hydrogen transfer that occurs in **1**, but it is coupled with C-C bond making and generation of an aromatic system.[12]

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Registry No. **1**, 20679-59-8; **2**, 3217-87-6; **3**, 80106-13-4; **4**, 80106-14-5; **5**, 80106-15-6; **6**, 80106-16-7; **7**, 101-81-5; PhMe, 108-88-3; 1-methyl-5-benzyl-1,3-cyclohexadiene, 80106-17-8.

(9) The major dimer product **6** rearranged on the GC column, so it was identified by NMR spectrum of the nonvolatile product after the resonances of **5**, which could be purified, and bibenzyl were subtracted. 220-MHz NMR of **5**: δ 7.2 (m, 5 H), 5.57 (d, J = 10 Hz, 2 H), 5.43 (d, J = 10 Hz, 2 H), 2.55 (s, 2 H), 2.40 (m, partly obscured by the δ 2.55 resonance, 2 H), 1.03 (s, 3 H). 220-MHz NMR of **6**: δ 7.2 (m, 5 H), 5.70 (brs, 3 H), 5.30 (brs, 1 H), 2.7-2.2 (m, 3 H), 1.98 (ABq, J = 17 Hz, 2 H) (the downfield lines are doublets of doublets, J = 8, 4 Hz and the upfield lines are doubled, J = 3 Hz); 1.68 (s, 3 H).

(10) Cáceres, T.; Lissi, E. A.; Sanhueza, E. *Int. J. Chem. Kinet.* **1978**, *10*, 1167.

(11) The half-life of AIBN in benzene at 80 °C is ca. 1 h, and the major product is tetramethylsuccinonitrile: Wu, C.-H.S.; Hammond, G. S.; Wright, J. M. *J. Am. Chem. Soc.* **1960**, *82*, 5386. The half-life for loss of **2** in this experiment is ca. 20 h.

(12) For early work on 1,2,4,5,6,6-hexamethyl-3-methylene-1,4-cyclohexadiene, see: Hart, H.; DeVrieze, J. D. *Tetrahedron Lett.* **1968**, 4257. *Chem. Commun.* **1968**, 1651. For related work on 6-allyl and 6-benzyl substituted materials, see: Miller, B.; Lai, K.-H. *Tetrahedron Lett.* **1971**, 1617.

Gas-Phase Ion Chemistry of 5-Methylene-1,3-cyclohexadiene (*o*-Isotoluene) and 3-Methylene-1,4-cyclohexadiene (*p*-Isotoluene)

John E. Bartmess

Department of Chemistry, Indiana University
Bloomington, Indiana 47405

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The structures of the $C_7H_8^+$ and $C_7H_7^+$ ions produced by ionization of various C_7H_8 and C_7H_7X compounds in mass spectrometers have been the subject of numerous investigations.[1-5] Studies involving photodissociation and ion-molecule reactions indicate that the long-lived radical cations formed by ionization of the various C_7H_8 isomers, such as toluene, cycloheptatriene, and norbornadiene, do not interconvert.[2,3] The $C_7H_7^+$ ions arising from

(1) Rylander, P. N.; Meyerson, S.; Grubb, H. M. *J. Am. Chem. Soc.* **1957**, *79*, 842-846. Meyerson, S. *Ibid.* **1963**, *85*, 3340-3344. Rinehart, K. L., Jr.; Buchholz, A. C.; Van Lear, G. E.; Cantrill, H. L. *Ibid.* **1968**, *90*, 2983-2985. Siegel, A. S. *Ibid.* **1970**, *92*, 5277-5278. Howe, I.; McLafferty, F. W. *Ibid.* **1971**, *93*, 99-105.

(2) Hoffman, M. K.; Bursey, M. M. *Tetrahedron Lett.* **1971**, 2539-2542. Bursey, M. M.; Hoffman, M. K.; Benezra, S. A. *J. Chem. Soc., Chem. Commun.* **1971**, 1417-1418. However, see: Ausloos, P.; Lias, S. G. *Chem. Phys. Lett.* **1977**, *47*, 495.

(3) Dunbar, R. C.; Fu, E. W. *J. Am. Chem. Soc.* **1973**, *95*, 2716-2718. Fu, E. W.; Dymerski, P. P.; Dunbar, R. C. *Ibid.* **1976**, *98*, 337-343. Dunbar, R. C.; Klein, R. *Ibid.* **1977**, *99*, 3744-3746.

(4) Dunbar, R. C. *J. Am. Chem. Soc.* **1975**, *97*, 1382-1384. Shen, J.; Dunbar, R. C.; Olah, G. A. *Ibid.* **1974**, *96*, 6227-6229.

(5) Jackson, J.; Lias, S. A.; Ausloos, P. *J. Am. Chem. Soc.* **1977**, *99*, 7515-7521.

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