selenide in the manner described by Kang and Kice.[2c] Once prepared **1a** was dissolved in 50% acetonitrile and the solution (10^{-2} M in **1a**) was stored in the refrigerator until used, but in no event for longer than 1 day. Methyl *o*-nitrobenzeneselenenate (**2a**) was prepared from **1a** by the procedure outlined in the same paper[2c] and was purified by recrystallization from methanol, mp 52–53 °C. Hydrogen peroxide (Mallinckrodt, 30% aqueous solution) was used without further purification. Acetonitrile (Aldrich, spectrophotometric grade) was redistilled before use. All water used in the kinetic runs was doubly distilled from glass.

Procedure for Kinetic Runs. An aqueous solution (3.5 mL) containing the desired concentration of buffer (or sodium hydroxide) was placed in a 1-cm cell in the thermostated cell compartment of a Beckmann Model DU-50 spectrophotometer. To this solution was then first added 35 μL of a 10^{-2} M solution of **1a** in 50% acetonitrile. This was followed by the addition via a second microsyringe of the desired amount (10–20 μL) of a 1.5 M solution of hydrogen peroxide in water. The progress of the oxidation was then monitored by following the decrease in the absorbance of the solution at either 420 nm (for runs at pH $\leq$10.0) or 550 nm (for runs at pH $\geq$10.5).

The procedure for the kinetic runs in 50% acetonitrile was similar. With **2a** a 10^{-2} M stock solution in *anhydrous* acetonitrile was used. The progress of the oxidation of the ester was followed at 410 nm, that of **1a** at 422 nm.

Products of the Oxidation of 1a in Alkaline Solution. To confirm that *o*-nitrobenzeneseleninic acid is the product formed when **1a** is oxidized by H_2O_2 in alkaline solution, 0.037 g (0.17 mmol) of **1a** was dissolved in 5 mL of purified tetrahydrofuran and 1 mL of aqueous 0.1 M sodium hydroxide was added, followed by 0.10 mL of aqueous 30% hydrogen peroxide. The solution was allowed to stand at room temperature for 2 h and then acidified by the addition of 1.5 mL of 0.1 M perchloric acid. Most of the solvent was removed under reduced pressure at room temperature and the precipitate that separated was filtered off, washed with cold water followed by a little cold ether, and dried under vacuum, yielding 0.032 g (79%) of *o*-nitrobenzeneseleninic acid, mp 179–182 °C, identical in all respects with a known sample prepared by the procedure of Behaghel and Seibert.[8]

Registry No. **1a**, 56790-59-1; **1a** (anion), 108366-29-6; **1a** (methyl ester), 108366-30-9; H_2O_2, 7722-84-1; KH_2PO_4, 7778-77-0; $NaHCO_3$, 144-55-8; Na_2HPO_4, 7558-79-4; NaOH, 1310-73-2.

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(8) Behaghel, O.; Seibert, H. *Chem. Ber.* **1933**, *66*, 708.

On the Existence of *trans*-Cyclohexene

J. Verbeek and J. H. van Lenthe*

Theoretical Chemistry Group, University of Utrecht, Utrecht, The Netherlands

P. J. J. A. Timmermans[1] and A. Mackor

Institute of Applied Chemistry, TNO, Utrecht, The Netherlands

P. H. M. Budzelaar

Eindhoven University of Technology, Eindhoven, The Netherlands

Received January 13, 1987

Cis $\rightleftharpoons$ trans isomerization is a commonly observed reaction of photochemically excited olefins. In the case of small-ring cycloolefins, the trans isomer is more strained than the cis isomer, and this higher ring strain may lead to enhanced chemical reactivity.

The smallest stable cyclic trans olefin is *trans*-cyclooctene.[2] *trans*-Cycloheptene has also been prepared, but at 1 °C it reverts to the cis isomer with a half-life of ca. 10 min.[3] From the lifetimes at various temperatures Inoue et al.[3] estimated a $\Delta H^{\ddagger}$ of ca. 17 kcal/mol for the isomerization. The intermediacy of *trans*-cyclohexene (**1**) in reactions of *cis*-cyclohexene (**2**) has frequently been postulated.[4] However, no indications for the existence of *trans*-cyclohexene as a discrete chemical species have been reported to date, although Joussot-Dubien et al. obtained evidence for the formation of 1-phenyl-*trans*-cyclohexene upon flash pyrolysis of the cis isomer.[5] Because experimental detection of **1** is bound to be difficult, we decided to address this problem from a theoretical point of view.

From molecular mechanics calculations, Allinger and Sprague predicted **1** to be 42 kcal/mol less stable than **2**. They did not carry out a full optimization of the transition state for the trans → cis isomerization, but a reaction path calculation produced an estimated barrier of ca. 13 kcal/mol.[6] Maier and Schleyer concluded that **1** does not exist on the basis of MNDO calculations including a limited CI.[7] It has been noted before that MNDO adventitiously produces correct cis $\rightleftharpoons$ trans isomerization barriers *without* the use of CI.[8] Inclusion of CI will thus result in an artificially low barrier or no barrier at all.[9] However, **1** does correspond to a local minimum at the closed-shell RHF/MNDO level.[7,10] We now report ab initio calculations on **1**, **2**, and the transition-state **3** for the isomerization **1** → **2**, which we believe provide a definitive answer to the question of the existence of **1**.

trans-Cyclohexene will have a large amount of torsion strain at the C_1C_2 double bond. Both it and its cis isomer will presumably have C_2 symmetry, but the isomerization **1** → **2** is forbidden in this symmetry. Thus, a correct zeroth-order description requires at least a two-configuration wave function; in this work we have employed an equivalent GVB formalism,[11] using one pair function for the C_1C_2 π-bond. The geometries of **1**–**3** were optimized[12]

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(1) Part of the forthcoming Ph.D. Thesis of P. J. J. A. Timmermans, Utrecht.

(2) See, e.g.: Cope, A. C.; Pike, R. A.; Spencer, C. F. *J. Am. Chem. Soc.* **1953**, *75*, 3212. See also ref 16.

(3) Inoue, Y.; Ueoka, T.; Kuroda, T.; Hakushi, T. *J. Chem. Soc., Perkin Trans. 2* **1983**, 983 and references cited therein.

(4) Salomon, R. G.; Folting, K.; Streib, W. E.; Kochi, J. K. *J. Am. Chem. Soc.* **1974**, *96*, 1145. Timmermans, P. J. J. A.; de Ruiter, G. M. J.; Tinnemans, A. H. A.; Mackor, A. *Tetrahedron Lett.* **1983**, *24*, 1419 and references cited therein.

(5) Bonneau, R.; Joussot-Dubien, J.; Salem, L.; Yarwood, A. J. *J. Am. Chem. Soc.* **1976**, *98*, 4329. Dauben, W. G.; v. Riel, H. C. H. A.; Leroy, F.; Joussot-Dubien, J.; Bonneau, R. *J. Am. Chem. Soc.* **1980**, *101*, 1901.

(6) Allinger, N. L.; Sprague, J. T. *J. Am. Chem. Soc.* **1972**, *94*, 5734.

(7) Maier, W. F.; Schleyer, P. v. R. Presented at the 5th IUPAC Conference on Physical Organic Chemistry, Santa Cruz, CA, Aug. 17–22, 1980.

(8) Dewar, M. J. S.; Merz, K. M., Jr. *J. Chem. Soc., Chem. Commun.* **1985**, 343.

(9) In C_2 symmetry, the ground-state of 1 correlates with an excited state of 2. This means that a realistic closed-shell description of the isomerization process is impossible. In MNDO calculations, a "minimal CI" is frequently used to avoid this problem. This minimal CI is just a way to arrive at a (more or less) correct zeroth-order wave function within the MNDO formalism (in our ab initio calculations we have used a two-configuration wave function for the same purpose). The minimal CI avoids the unrealistically sharp peaking of the energy associated with the closed-shell description of a forbidden process; since the minimal-CI contribution is large near the transition state but much smaller for reactant and product, it will *always* lower the calculated activation energy. In contrast, the *subsequent* application of a *large-scale CI* to a *correct* (*two-configuration*) *zeroth-order wave function* can improve the description of reactant, transition state and product equally well and can therefore *increase or decrease* the activation energy.

(10) Budzelaar, P. H. M., unpublished results.

(11) Goddard, W. A., III; Dunning, T. H., Jr.; Hunt, W. J.; Hay, P. J. *Acc. Chem. Res.* **1973**, *6*, 368.

0022-3263/87/1952-2955$01.50/0

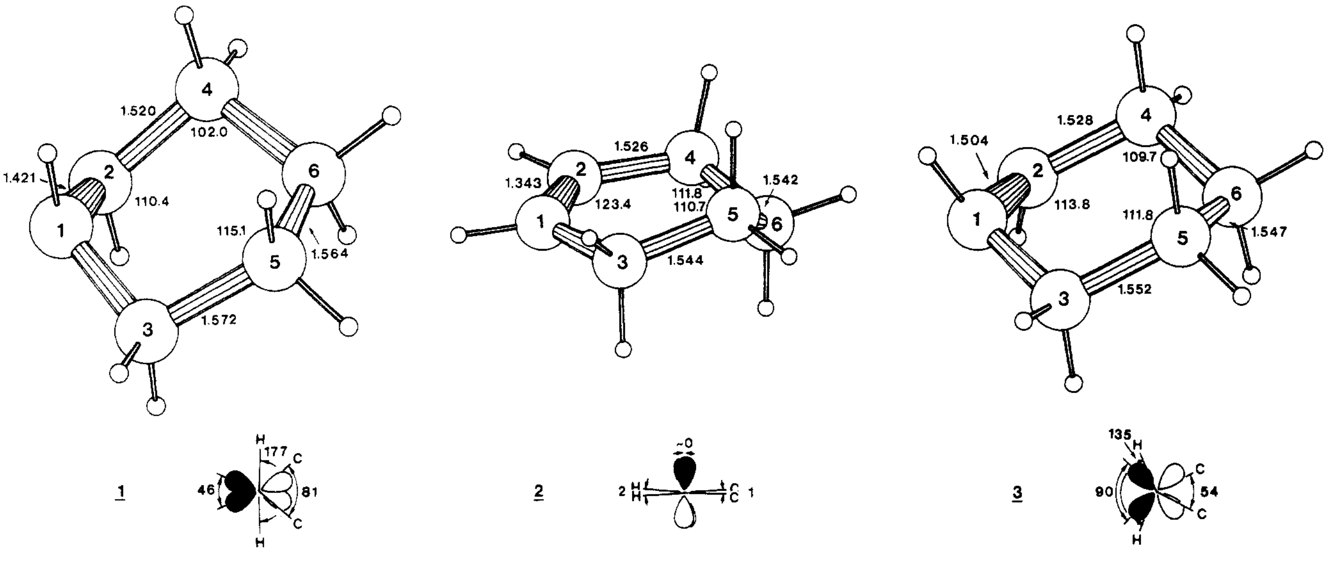

Figure 1. Drawings of 1–3, showing important bond lengths (Å) and angles (deg). Below, Newman projections along the C_1C_2 bonds, showing the arrangements of the C–C and C–H single bonds and schematic representations of the carbon "p_π" atomic orbitals forming the π and π^* molecular orbitals.

Table I. Total and Relative Energies of 1–3[a]

	E_{tot}, au			E_{rel}, kcal/mol		
method	1	2	3	1	2	3
GVB/STO-3G	-230.20797	-230.30241	-230.19625	0	-59.3	7.4
GVB/6-31G	-232.86376	-232.95558	-232.84600	0	-57.6	11.1
GVB/6-31G*	-232.95696	-233.04606	-232.93698	0	-55.9	12.5
MRDCI/6-31G	-233.34672	-233.43657	-233.32557	0	-56.4	13.3
MRDCI/6-31G*$_{est}$[b]				0	-56.0	15.4

[a] At GVB/STO-3G optimized geometries. [b] Assuming additivity of the GVB → MRDCI and 6-31G → 6-31G* corrections. A Davidson correction for size consistency[20] was also included, in which C_0 was obtained from the projection of the GVB function onto the CI space.[21]

at the GVB level with a minimal (STO-3G[13]) basis set, assuming C_2 symmetry throughout; important bond lengths and bond angles are shown in Figure 1. Single-point GVB calculations at these optimized geometries were then carried out in the split-valence 6-31G basis set.[14] The effect of adding polarization functions to the carbon basis was checked by using Pople's 6-31G* basis set.[15] Electron correlation corrections were estimated separately from CI calculations involving all single and double substitutions with respect to the two configurations of the zeroth-order wave function (using the 6-31G basis).[9] The results are summarized in Table I. Assuming additivity of the two corrections, we obtain an estimated barrier of 15 kcal/mol for the reaction 1 → 2[16] and a difference in energy of 56 kcal/mol in favor of the cis isomer.

Table II. Occupation Numbers of the C_1C_2 π and π^* Natural Orbitals

	1		2		3	
method	13*a*	11*b*	13*a*	11*b*	13*a*	11*b*
GVB/STO-3G	1.64	0.36	0.12	1.88	1.05	0.95
GVB/6-31G	1.72	0.28	0.09	1.91	1.10	0.90
GVB/6-31G*	1.73	0.27	0.09	1.91	1.10	0.90

trans-Cyclohexene is indeed a highly strained molecule. The distortion resides mainly in the C_1C_2 "double" bond: the CC_1C_2C torsion angle is less than 90°! The long C–C single bonds in 1 also testify to its highly strained nature. The HC_1C_2H torsion angle, however, is normal, and the hydrogen atoms are bent a little toward the ring, as observed for various *trans*-cyclooctene complexes and derivatives.[17] The Newman projection (Figure 1) shows the arrangements of the C–C and C–H single bonds and the π-orbitals around the C_1C_2 bond. Clearly, the π-overlap is poor, and this is reflected in the large amount of biradical character of 1 (ca. 30%) compared to 2 (ca. 10%) (see Table II). Not unexpectedly, the C_1C_2 bond in 1 is much longer than in 2.

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[12] The GAMESS package (Dupuis, M.; Spangler, D.; Wendoloski, J. J. "National Resource for Computation in Chemistry Program QC01", 1980; extended by Guest, M. F.; Kendrick, J.; Pope, S.) was used for all calculations. The geometries of 1–3 were *fully* optimized *within* the constraint of overall C_2 molecular symmetry. *Within* this symmetry, they correspond to stationary points with *zero* (1, 2: local minima) or *one* (3: saddle point) negative eigenvalues of the force constant matrix. In principle, it is possible that a lower energy path for the reaction 1 → 2 exists which has a lower symmetry (C_1). In the present case, however, this is very unlikely since any deviation from C_2 symmetry will only *increase* the ring strain of 3.

[13] Hehre, W. J.; Stewart, R. F.; Pople, J. A. *J. Chem. Phys.* **1969**, *51*, 2657. There have been some reports of cases where STO-3G predicts reaction paths differing from those obtained with better basis sets (see, e.g.: Bernardi, F.; Bottoni, A.; Robb, M. A.; Field, M. J.; Hillier, I. H.; Guest, M. F. *J. Chem. Soc., Chem. Commun.* **1985**, 1051. Bernardi, F.; Bottoni, A.; Robb, M. A.; Schlegel, H. B.; Tonachini, G. *J. Am. Chem. Soc.* **1985**, *107*, 2260). In those cases, however, the system is loose and the potential energy surface is very flat. In the present case, the system is constrained by strong σ-bonds and has little freedom, so the possibility of a substantially different reaction path with better basis sets is extremely remote.

[14] Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257. Gordon, M. S.; Binkley, J. S.; Pople, J. A.; Pietro, W. J.; Hehre, W. J. *J. Am. Chem. Soc.* **1982**, *104*, 2797.

[15] Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213.

[16] The most important error sources in these numbers will be (a) neglect of zero-point energy corrections and (b) use of minimal-basis geometries for all calculations. These errors are expected to be in the order of a few kcal/mol and will therefore not affect our conclusion concerning the marginal stability of 1.

[17] Ganis, P.; Lepore, U.; Paiaro, G. *J. Chem. Soc., Chem. Commun.* **1969**, 1054. Ganis, P.; Lepore, U.; Martuscelli, E. *J. Phys. Chem.* **1970**, *74*, 2439. Ermer, O. *Angew. Chem.* **1974**, *86*, 672. (For MM calculations on *trans*-cycloheptene and *trans*-cyclooctene, see ref 6.)

The transition state **3** is nearly a pure biradical (ca. 90%, see Table II). The CC_1C_2C and HC_1C_2H torsion angles have decreased with respect to **1**; the C_1C_2 distance corresponds to a normal single bond. The other ring bonds in **3** show the relief of strain already achieved in the transition state.

Our results essentially confirm the predictions of Allinger and Sprague[6] and clearly indicate that *trans*-cyclohexene corresponds to a local minimum, although the activation energy for its isomerization is not very large. Thus, it might be possible to generate and observe it in an inert matrix. The stabilization of highly strained olefins by coordination to a transition metal has enabled the isolation of stable copper(I)–*trans*-cycloheptene complexes.[18] Similarly, we expect that coordination of **1** to a transition metal may result in a considerable stabilization, though probably not enough to produce isolable complexes of **1**. Nevertheless, coordinated **1** may well be an intermediate in metal-catalyzed photochemical reactions of **2**.[19]

Acknowledgment. This work was supported in part (P.J.J.A.T.) by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for the Advancement of Pure research (ZWO).

Registry No. Cyclohexene, 110-83-8.

Supplementary Material Available: Complete geometry specifications (*Z* matrices, Cartesian coordinates, and important geometric parameters) of **1**–**3** (4 pages). Ordering information is given on any current masthead page.

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[18] Evers, J. T. M.; Mackor, A. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 423. Evers, J. T. M. Ph.D. Thesis, Utrecht, 1979. Mackor, A., umpublished results.

[19] Timmermans, P. J. J. A.; et al., manuscript in preparation.

[20] Langhoff, S. R.; Davidson, E. R. *Int. J. Quantum Chem.* **1974**, *8*, 61.

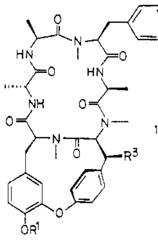
[21] Ahlrichs, R., private communication.

Communications

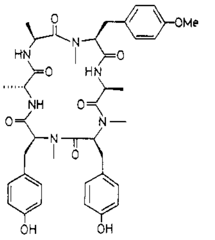
The First Total Synthesis of Deoxybouvardin and RA-VII, Novel Antitumor Cyclic Hexapeptides

Summary: Intramolecular oxidative coupling of two phenolic parts of protected (2,6-dibromotyrosyl)-2,6-dichlorotyrosine with thallium trinitrate afforded a highly strained 14-membered ring system, from which deoxybouvardin and RA-VII were synthesized.

Sir: Recently, unique hexapeptides, which show potent antitumor activity, were isolated from *Bouvardia termifolia*[2] (Rubiaceae) and *Rubia Coldifolia* L.[3] (Rubiaceae). They are represented by general formula **1** (**1a** = RA-VII; **1b** = deoxybouvardin or RA-V; **1c** = bouvardin; **1d** = RA-II). Their unusual structural feature is a highly strained 14-membered ring including a cis-peptide grouping as well as a paracyclophane and a metacyclophane ring system. The 14-membered ring, derived presumably by oxidative coupling of the phenolic parts of two adjacent tyrosines in plants, as shown to be indispensable to their antitumor activity since a ring-opened analogue (**2**) of deoxybouvardin (**1b**) lacks the activity.[4] In this paper we report the first total synthesis of RA-VII (**1a**) and deoxybouvardin (RA-V, **1b**).



1a ; $R^1=R^2=Me$, $R^3=H$
b ; $R^1=R^3=H$, $R^2=Me$
c ; $R^1=H$, $R^2=Me$, $R^3=OH$
d ; $R^1=Me$, $R^2=R^3=H$
e ; $R^1=R^2=R^3=H$



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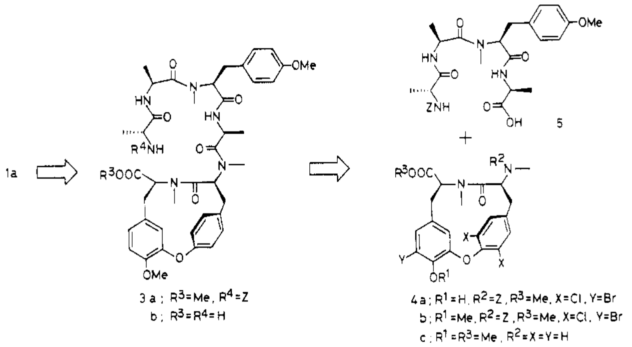
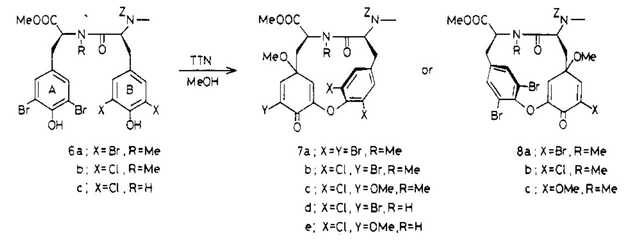
Scheme I



Scheme II



Scheme I shows our strategy for the synthesis of **1a**, which comprises construction of the 14-membered ring unit

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[1] (a) Tobishi Pharmaceutical Co., Ltd. (b) Tokyo College of Pharmacy. (c) Chiba University.

[2] (a) Jolad, S. D.; Hoffmann, J. J.; Torrance, S. J.; Wiedhopf, R. M.; Cole, J. R.; Arora, S. K.; Bates, R. B.; Gargiulo, R. L.; Kriek, G. R. *J. Am. Chem. Soc.* **1977**, *99*, 8040. (b) Bates, R. B.; Cole, J. R.; Hoffmann, J. J.; Kriek, G. R.; Linz, G. S.; Torrance, S. J. *Ibid.* **1983**, *105*, 1343.

[3] (a) Itokawa, H.; Takeya, K.; Mihara, K.; Mori, N.; Hamanaka, T.; Sonobe, T.; Iitaka, Y. *Chem. Pharm. Bull.* **1983**, *31*, 1424. (b) Itokawa, H.; Takeya, K.; Mori, N.; Hamanaka, T.; Sonobe, T.; Mihara, K. *Ibid.* **1984**, *32*, 284. (c) Itokawa, H.; Takeya, K.; Mori, N.; Sonobe, T.; Serisawa, N.; Hamanaka, T.; Mihashi, S. *Ibid.* **1984**, *32*, 3216. (d) Itokawa, H.; Takeya, K.; Mori, N.; Kidokoro, S.; Yamamoto, H. *Planta Med.* **1984**, 313. (e) Itokawa, H.; Takeya, K.; Mori, N.; Takanashi, M.; Yamamoto, H.; Sonobe, T.; Kidokoro, S. *Gann* **1984**, *75*, 929. (f) Itokawa, H.; Takeya, K.; Mori, N.; Sonobe, T.; Mihashi, S.; Hamanaka, T. *Chem. Pharm. Bull.* **1986**, *34*, 3762.

[4] Bates, R. B.; Gin, S. L.; Hassen, M. A.; Hruby, V. J.; Janda, K. D.; Kriek, G. R.; Michaud, J. P.; Vine, D. B. *Heterocycles* **1984**, *22*, 785.

0022-3263/87/1952-2957$01.50/0