179–180 °C, and 390 mg of a mixture of *o*- and *p*-chloroacetanilide, containing mostly the ortho isomer. The mixture was dechlorinated by heating overnight in ethanol (40 mL) solution with 0.5 mL of hydrazine hydrate and 100 mg of 10% Pd/C and gave 270 mg of acetanilide. The recovered acetanilide was rechlorinated, giving 170 mg of *p*-chloroacetanilide, mp 179–180 °C. The total conversion of acetanilide into *p*-chloroacetanilide was, thus, 70.5%. The *p*-chloroacetanilide was hydrolyzed to 488 mg (95%) of *p*-chloroaniline, mp 66–69 °C, and this was oxidized by MnO_2 into [2,2′,6,6′-$^{13}C_4$]-**3**, giving 412 mg (86%) of product, mp 187–188 °C after column chromatography on silica gel. The [$^{13}C_4$]-**3** (400 mg) was recrystallized with 7.6 g of unenriched **3** for use in preparing **1** for KIE studies.

KIE Measurements. The trifluoroacetyl derivatives **7–9** were used for measurements of relative abundances of the M and (M + 2) ions in **7** and the M and (M + 4) ions in **8** and **9**. Whole-molecule-ion abundances were measured with a Hewlett-Packard mass spectrometer, Model 5995, in the SIM mode, and KIE were calculated as described earlier.[1] The number of scans in each of the 25 blocks of scans was approximately 60 for **7**, approximately 140 for **8**, and approximately 100 for **9**. Each ratio of abundances was measured three or four times and then averaged. The KIE results are given in Table II.

Acknowledgment. We thank the Robert A. Welch Foundation (Grant No. D-028) and the National Science Foundation (Grant No. CHE 86-12031) for generous support.

A New Method for Predicting Isomerization Barriers in Sterically Congested Alkenes from the First Correct Barrier Measurement in Solution: (*Z*)-2,2,3,4,5,5-Hexamethyl-3-hexene

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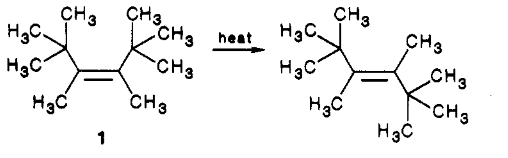
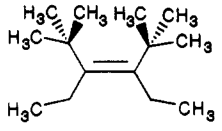
Although considerable effort has been expended to determine thermal isomerization barriers in simple alkenes,[1] investigations in solution were fraught with difficulties. All reported values have eventually been found to be erroneous. Although steric congestion should lower such barriers, little is known regarding the magnitude of those effects. The development of the low valent titanium coupling reaction of ketones, such as the McMurry reagent,[2] has made available a large variety of sterically congested alkenes.[3,4] The first, correct, solution phase measurement of a thermal, *Z*/*E* isomerization barrier in a sterically congested alkene, (*Z*)-2,2,3,4,5,5-hexamethyl-3-hexene (**1**) is reported below along with a method for predicting the quantitative effects of steric congestion on such barriers. Predictions of barriers are made for **3** and **4**.

Results

A mixture of alkenes **1** and **2** was prepared by the low valent titanium induced coupling of pinacolone.[5] Pure samples of **1** (93.6%) and **2** (98.7%) were obtained by GLC fractionation of the mixture. In the absence of vinylic hydrogens, the distinction between **1** and **2** was not trivial. The published procedures assumed that the intensity of the Raman scatterings from **1** and **2** were identical or that



1 **2**



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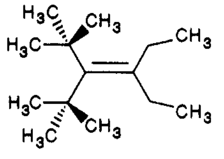

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2 was formed because it was the *E* isomer. Since twisting of the double bond can dramatically attenuate the Raman intensity, the first assumption was questionable. As might have been expected, neither IR spectrum showed a recognizable C=C stretching band. The NOE enhancement, which should have been greater for **2**, was essentially the same for both **1** and **2**. This surprising result was understood by inspection of models. Apparently, the nonbonded repulsions in **1** pushed the *tert*-butyl groups sufficiently close to the methyl groups to create a significant NOE effect. Likewise, the highest frequency C–H stretching vibrations in the IR spectrum of **1** showed abnormally high bands, 3040–3050 cm^{-1}, for both isomers rather than just for **1**.[6] Eventually, the stereochemical assignment had to rely upon the observation that **1** isomerized to **2** upon heating. Force field calculations (vida infra) and many other examples of *Z*/*E* isomerizations demonstrated that **1** should be significantly more strained than **2**. The only impurities detected in **1** were its isomer

1 **5**

2 (1.7%) and an unidentified material (4.7%), which remained unchanged (vida infra) during the reaction. A preliminary pyrolysis experiment revealed **1** readily isomerized at temperatures below 165 °C in nitrobenzene-d_5. Careful NMR analysis, however, demonstrated that the isomerization product was not **2** but rather 2-*tert*-butyl-3,4,4-trimethyl-1-pentene (**5**). Since this isomerization was known to occur under conditions of Lewis acid catalysis,[7a] all traces of polar, acidic substances were avoided (vide infra). Under those conditions and in the absence of exposure to air, pyrolysis of **1** in tetradecane lead to reluctant isomerization to **2**. The reverse reaction, **2** to **1**, was not observable at 225 °C. The presence of varying concen-

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(1) For a general review of alkene isomerizations, see: Saltiel, J.; Charlton, J. L. *Rearrangements in the Ground and Excited States*; DeMayo, P., Ed.; Academic: New York, 1980; p 25.

(2) (a) For a review, see: Lai, Y.-H. *Org. Prep. Proced. Int.* **1980**, *12*, 361. (b) McMurry, J. E. *Acc. Chem. Res.* **1983**, *16*,405.

(3) See the series of papers Sterically Congested Olefins, I–XI; Part XI: Lenoir, D.; Malwitz, D.; Meyer, B. *Tetrahedron Lett.* **1984**, *25*, 2965.

(4) (a) Lenoir, D.; Gano, J. E.; McTague, J. *Tetrahedron Lett.* **1986**, *27*, 5339. (b) Michalczyk, M. J.; West, R.; Michl, J. *Organometallics* **1985**, *4*, 826.

(5) Pure **1** has not been reported, but the isomeric mixture has been prepared: Rice, J. E.; Okamoto, Y. *J. Org. Chem.* **1982**, *47*, 4189. See also: Lenoir, D. *Chem. Ber.* **1978**, *111*, 411 for preparation of **2**.

(6) Ermer, O.; Lifson, S. *Tetrahedron* **1974**, *30*, 2425.

(7) (a) This isomerization was instantaneous in the presence of iodine in pentane. (b) Fieser, M.; Fieser, L. *Reagents for Organic Synthesis*; Wiley-Interscience: New York, 1974; Vol. 4, p 503.

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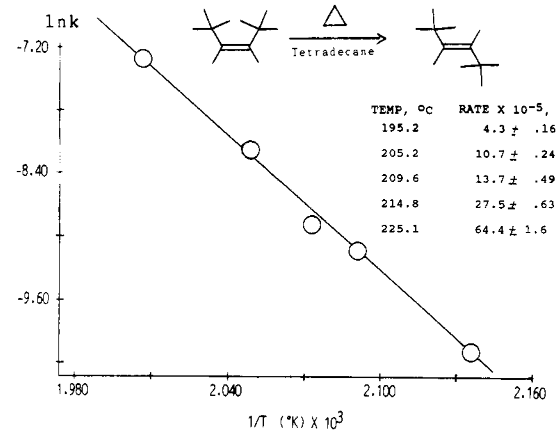

TEMP, °C	RATE X 10⁻⁵, SEC⁻¹
195.2	4.3 ± .16
205.2	10.7 ± .24
209.6	13.7 ± .49
214.8	27.5 ± .63
225.1	64.4 ± 1.6

Figure 1. Arrhenius plot of the rates of isomerization of **1** to **2** in tetradecane.

trations of 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide, a free radical trapping agent,[7b] did not affect the reaction rate. An Arrhenius plot of the reaction rates measured between 195 and 225 °C, Figure 1, gave a straight line. Regression analysis gave E_a = 40.4 + 1.7 kcal/mol and $A = 3 \times 10^{14}$. This compared to gas-phase values reported for ethene (E_a = 65 kcal/mol and $A = 10^{13}$) and 2-butene (E_a = 62.4 kcal/mol and $A = 10^{14}$).[1]

Discussion

Once all catalytic isomerization pathways were prevented, the mechanism of reaction was best viewed as a simple, uncatalyzed, unimolecular rotation about the carbon–carbon double bond along the ground-state-energy surface. This was supported by the reasonable preexponential factor,[8] lack of rate change with free radical trapping agent, lack of the typical product associated wiih Lewis acid catalysis, and linear Arrhenius plot.

Force field (MMI) calculations for **1** and **2** gave heats of formation (−29.74 and −38.11 kcal/mol, respectively) and strain energies(33.74 and 25.40 kcal/mol, respectively). Thus, the enthalpy of isomerization should be −8.4 kcal/mol.[9] This was in agreement with the experimental limit, $\Delta G > -3.7$ kcal/mol, put on the free energy of reaction by the absence of observable reverse isomerization at 225 °C. An energy diagram of steric effects in these systems is shown in Figure 2. The plotted energies of *Z* and *E* isomers are calculated strain energies.[9c] The transition-state energies are the sums of the measured isomerization barriers and the calculated strain energies for the *Z* isomers.[10]

The diagram in Figure 2 provided a means for comparison of strain energies in transition states.

Inspection of Figure 2 shows the introduction of *tert*-butyl substituents increased the strain *in both the Z and E isomers*. The greatest effect occurred in the *Z* isomers, as expected. Although introduction of two *tert*-butyl groups raised the energy of **1** by 32.55 kcal/mol, compared to 2-butene, this only lowered the barrier to isomerization in **1** by 22.0 kcal/mol. Although one might have guessed there would be no strain in the twisted transition state, that result demonstrated the transition state for isomerization of **1** still retained at least 9 kcal/mol of strain energy, compared to 2-butene.

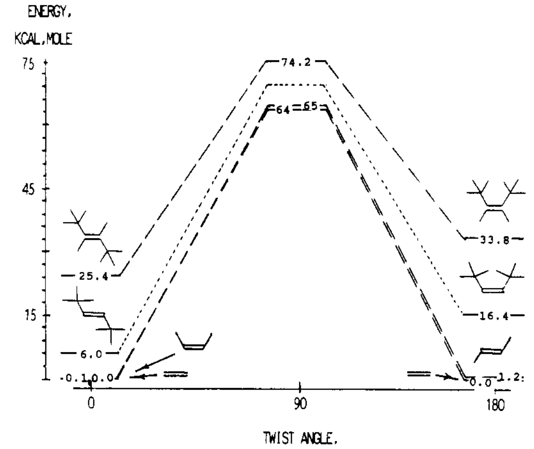

Figure 2. Strain energies of reactants and transition states in alkene isomerizations. Alkene strain energies are calculated (MMI). Transition-state strain energies are the sums of calculated strain energies for the *Z* isomers and measured barriers to isomerization.

Prediction of isomerization barriers with theoretical methods is difficult because such methods are designed to find energy minima rather than energy maxima. Since the observed range of transition-state energies was small, 10 kcal/mol, it should be possible to use Figure 2 and strain energies calculated for reactants to predict unknown isomerization barriers. By use of that approach, the isomerization barrier in (*Z*)-2,2,5,5-tetramethyl-3-hexene was predicted, from a calculated strain energy of 16.4 kcal/mol, to be 53 kcal/mol. Subsequent to this prediction it was learned this barrier has just recently been measured in the gas phase.[11a] The measured barrier, E_a = 54.4 ± 0.7 kcal/mol, was in excellant agreement with the predicted value. Similar considerations predict the isomerization barriers in **3**, strain energy = 40.4 kcal/mol, and **4**, strain energy = 44.2 kcal/mol, to be 35 and 33 kcal/mol, respectively.

Experimental Section

(*Z*)-2,2,3,4,5,5-Hexamethyl-3-hexene. A mixture of (*Z*)-2,2,3,4,5,5-hexamethyl-3-hexene and (*E*)-2,2,3,4,5,5-hexamethyl-3-hexene was synthesized as follows.[3] $LiAlH_4$ (1.67 g, 44 mmol) was added slowly to a 1-L, three-necked flask that contained a slurry of $TiCl_3$ (12.35 g, 80 mmol) in THF (500 mL) blanketed under a strong flow of nitrogen at −78 °C. While the mixture warmed to 0 °C, pinacolone (7.40 g, 74 mmol) was added dropwise. The solution was refluxed for 24 h, cooled, and neutralized (until bubbling stopped) with 10% Na_2CO_3 to decompose remaining unreacted low-valent Ti. The solution was extracted with hexane several times. The combined organic layers were dried ($MgSO_4$) and eluted (hexane) through a silica gel column to remove polar by products, giving a hexane solution of approximately equal amounts of (*Z*)- and (*E*)-2,2,3,4,5,5-hexamethyl-3-hexene in 62% yield. The (*E*)- and (*Z*)-2,2,3,4,5,5-hexametyl-3-hexene were separated from the *Z*/*E* mixture by semipreparative GLC on a 2-m, 4-mm i.d., 20%, Apiezon-L column at 180 °C. Analysis of the product by capillary GLC (25 m, 0.32-mm i.d., 5.0 μm, methyl silicone) on an FTIR/GC (Nicolet SX60) was necessary to reveal the true composition. This showed **1**, its isomer **2** (1.7%), and an unidentified material (4.7%). The concentration of the unidentified material was the same before and after the pyrolysis reaction. (*Z*)-2,2,3,4,5,5-Hexamethyl-3-hexene ^{13}C NMR (cyclohexane-d_{12}) δ 138.1 (C═C), 37.8 (C), 32.3 [$C(CH_3)_3$], 22.6 (CH_3); ^1H NMR (cyclohexane-d_{12}) δ 1.22 [s, 18,

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[8] Kalinowski, H.-O.; Kessler, H. *Top. Stereochem.* **1973**, *7*, 295.

[9] (a) For the first calculations of this kind on a series of alkenes, see: ref 6. (b) Lenoir, D.; Dauner, H.; Frank, R. M. *Chem. Ber.* **1980**, *113*, 2636. (c) These give *Z*/*E* energy differences which agree, within experimental error, with measured values.

[10] Ground-state energies and geometrics were calculated by MMI. (a) Allinger, N. L.; Sprague, T. T. *J. Am. Chem. Soc.* **1972**, 94, 5734. (b) See also ref 9b.

[11] (a) Roth, W. R., Ruhr-Universität Bochum, personal communication, 1987.

$C(CH_3)_3]$, 1.64 (s, 6, CH_3); IR (CCl_4) 2956 (s), 2919 (s), 1477 (m), 1444 (m), 1394 (m), 1363 (m), 1192 (m), 1141 (m), 1073 (m); MS *m/e* 168 (M^+), 111, 97, 84, 69, 57, 41 (base).

(*E*)-2,2,3,4,5,5-Hexamethyl-3-hexene from above showed spectral properties comparable to those already reported.[5]

Pyrolysis. Samples of a solution containing 5 μL of **1**, 5 μL of tridecane, and 0.5 mL of tetradecane (prefiltered through a small column of basic alumina) were sealed in washed (1% ammonia water) and dried melting point capillaries. Samples were heated in a stirred, constant-temperature bath filled with silicone oil, heated with a quartz heater, and controlled (cycled, ± 0.4 °C, about an accurately (±0.02 °C) measured temperature) with an Omega 2001 regulator. After pyrolysis, each sample was removed from the bath, immediately quenched in ice water, and analyzed by GLC. Peak areas were determined by triangulation. Integration against tridecane showed the total amount of **1** and **2** remained essentially constant throughout the pyrolysis period. Correction was made for the small impurity by subtracting a constant amount from each area for **1**. In order to minimize the significance of this 4.7% correction, data points beyond 90% conversion to **2** were excluded from the analysis.

Data Treatment. Rate constants and Arrhenius parameters were determined by using the least-squares procedure available with Mintab.[12] The Arrhenius parameters were calculated by using a weighted regression that took into consideration the errors in the rate constants.[13] All error limits are statistical standard deviations calculated during the data treatment.

Effect of Free Radical Trap. Varying concentrations, up to a saturated solution, of 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide[7b] were added to the reaction solution, and the samples were heated for 40 min at 220 °C. GLC analysis showed no detectable difference in results between the samples.

Reversibility of Isomerization. A sample of **2** containing 98.7% **2** and 1.7% **1** in tetradecane was heated at the highest temperature available, 225 °C, for 90 min. This lead to no further conversion to **1**. This result, which was limited by the purity of **2**, showed no further formation of **1** from **2**. At one extreme they could be at equilibrium. At the other extreme, **1** could be slowly going to **2**. This sets a limit on the value of $\Delta G > -3.7$ kcal/mol at 225 °C.

Acknowledgment. Partial financial support from the University of Toledo Faculty Research Awards and Fellowship Program, the technical assistance of Scott Roberts, Jackie Inman, and Allen Neyland, and helpful discussions with W. R. Roth are gratefully acknowledged.

Registry No. **1**, 54429-93-5; **2**, 54290-40-3; **3**, 75245-22-6; **4**, 75245-13-5; **5**, 105903-60-4; (E)-$(CH_3)_3CCH{=}C(CH_3)_3$, 692-48-8; (Z)-$(CH_3)_3CCH{=}CHC(CH_3)_3$, 692-47-7; ($Z$)-$CH_3CH_2{=}CH_2CH_3$, 590-18-1; ($E$)-$CH_3CH_2{=}CH_2CH_3$, 624-64-6; $CH_2{=}CH_2$, 74-85-1; pinacolone, 75-97-8.

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(12) Ryan, T. A., Jr.; Joiner, B. L.; Ryan, B. F. *Mintab Student* Handbook; Duxbury: North Scituate, Massachusetts, 1976; pp 148–193.

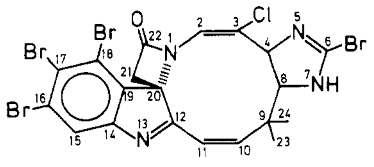
(13) Young, H. D. *Statistical Treatment of Experimental* Data, McGraw: New York, 1962; p 108.

Communications

Chartellamide A and B, Halogenated β-Lactam Indole–Imidazole Alkaloids from the Marine Bryozoan *Chartella papyracea*[1a]

Summary: Two structurally unusual β-lactam indole–imidazole alkaloids have been isolated from the marine bryozoan *Chartella papyracea*.

Sir: Investigations of the marine bryozoan *Chartella papyracea* (Ellis and Solander) (also known as *Flustra papyracea*) have resulted in the identification of unique alkaloids[1a,2] exemplified by (*S*)-chartelline A (**1**).[3] These alkaloids possess the β-lactam ring and may equally well be classified as indole or imidazole alkaloids. This report deals with the isolation and structure elucidation of two novel alkaloids, chartellamide A (**2**) and B (**3**), originating with the same organism.



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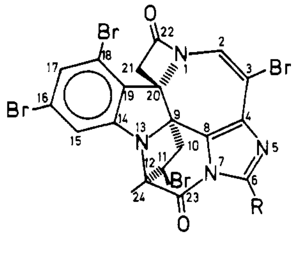

2 R=H
3 R=Br

The bryozoans collected from Roscoff Marine Biological Station in the autumn of 1985 were lyophilized to give 801 g of dry material. After the material was defatted with petroleum ether, extraction with twice-distilled ethyl acetate gave 5.7 g of soluble material. Cellulose column chromatography served, after elution with hexane, to yield a raw alkaloid mixture (4.1 g) on elution with methylene chloride. Recrystallization of this fraction from methylene chloride gave almost pure chartelline A (**1**).[1a] Evaporation of the mother liquor followed by silica chromatography (Merck, kiesel gel, ethyl acetate) gave the chartellamides. Preparative HPLC (RP-8 Merck; MeOH/H_2O, 80/20) gave pure chartellamide A (**2**) (28 mg, 3.5×10^{-3}% of dry weight) and chartellamide B (**3**) (36 mg, 4.5×10^{-3}% of dry weight).

The elemental compositions were determined from MS (**2**, calcd for $C_{20}H_{12}N_4{}^{79}Br_4O_2$, 655.76, found 655.81 with

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(1) (a) Contribution 13 of the series "Marine Alkaloids". For part 12, see: Anthoni, U.; Chevolot, L.; Larsen, C.; Nielsen, P. H.; Christophersen, C. *J. Org. Chem.* in press. (b) Department of Organic Chemistry, The Technical University of Denmark, DK-2800 Lyngby, Denmark. (c) UA CNRS 322, Université de Bretagne Occidentale, 29287 Brest, France.

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