(5*S*)-1-Azabicyclo[3.1.0]hexane

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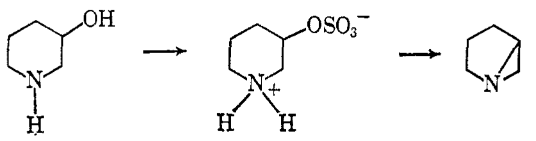
Procedures have been developed for the synthesis of (5*S*)-1-azabicyclo[3.1.0]hexane (1), $[\alpha]^{28}\mathrm{D}$ −19°. Catalytic hydrogenation of 1 gave 2-methylpyrrolidine and piperidine. The mass spectral cracking pattern of 1 is discussed.

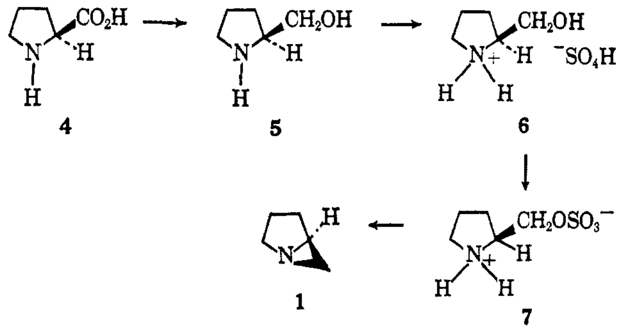
As part of our continuing interest[2,3] in the synthesis and reactions of azabicyclics, we have prepared (5*S*)-1-azabicyclo[3.1.0]hexane (**1**) and subsequently we have investigated some of its reactions. Although 1-azabicyclo[3.1.0]hexane[4,5] and substituted variants[4,6-8] had been reported previously in the literature, the published synthetic routes did not lend themselves to the preparation of pure material in research quantities. In addition, we were interested in obtaining optically active **1**.

Our initial attempt to prepare 1-azabicyclo[3.1.0]hexane (**1**) employed 3-hydroxypiperidine (**2**) as the starting material. Conversion of **2** to (±) **1** formally involves loss of water and formation of the 1–5 bond of **1**. The actual method used to accomplish this transformation was that of Wenker[9] as modified by Leighton[10] and Reeves.[11] Thus, **2** was converted to its sulfuric acid salt which on pyrolysis underwent dehydration to yield the sulfuric acid ester **3**. When the ester was treated with sodium hydroxide solution followed by steam distillation, (±) **1** was obtained in low yield.



2 **3** **1**

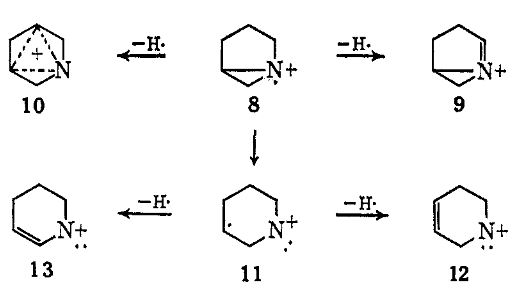
Since the simultaneous formation of the three- and five-membered rings failed to occur in good yield, it seemed advisable to attempt to close the three-membered ring onto a preformed five-membered ring. L-Proline (**4**) was reduced with lithium aluminum hydride in tetrahydrofuran to give the known[12] L-prolinol (**5**) in 65% yield. This prolinol was neutralized with sulfuric acid and the resulting salt, **6**, was dehydrated at elevated temperature under vacuum to yield the ester **7** in 75% yield from **5**. Addition of an aqueous solution of **7** to a distilling aqueous solution of sodium hydroxide resulted in immediate separation of the desired product by steam distillation. Extraction of the aqueous distillate with ether followed by evaporation of the ether and distillation of the residual amine gave **1** in 54% yield, bp 107–110°, $[\alpha]^{28}\mathrm{D}$ −19°.



The infrared spectrum of **1** was quite distinctive having no absorption between 1500 and 2800 cm^{-1}. Below 1300 cm^{-1} there were many intense sharp bands with a characteristic trio of progessively stronger bands at 840, 790, and 720 cm^{-1}, respectively. The infrared spectra of **1** (from **4**) and (±) **1** (from **2**) were identical with each other and to a spectrum of authentic (±) **1**.[13]

In agreement with the bicyclic nature of **1**, the nmr spectrum substantiated the absence of vinyl protons. The nmr spectrum showed only a series of complex multiplets between τ 7.0 and 9.1.

Of particular interest was the mass spectrum of **1** which is summarized in Table I. It was determined by high-resolution mass measurements that the parent peak has a mass of 83.07349, which corresponds to C_5H_9N (calculated mass 83.07361). Assuming that the initial reaction can be represented by the loss of a nonbonding electron from the heteroatom, the molecular ion can be represented by **8**. The M − 1 species is of particular interest in this case since the loss of an α-hydrogen atom to yield **9** seems unlikely. Other explanations would be loss of a β-hydrogen atom to yield **10** or homolytic cleavage of the 1–5 bond to produce **11** followed by loss of a hydrogen atom to yield the allylic nitrenium ion **13** or the homoallylic



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[1] National Science Foundation Cooperative Graduate Fellow, 1961–1963.

[2] P. G. Gassman and D. Heckert, *Tetrahedron*, **21**, 2725 (1965).

[3] P. G. Gassman and B. L. Fox, *J. Am. Chem. Soc.*, **89**, 338 (1967).

[4] A. L. Logothetis, *ibid.*, **87**, 749 (1965).

[5] R. Buyle, *Chem. Ind.* (London), 195 (1966).

[6] C. Schopf, German Patent 1,054,088 (1959); *Chem. Abstr.*, **55**, P8439*i* (1961).

[7] E. M. Fry, *J. Org. Chem.*, **30**, 2058 (1965).

[8] See also G. Magnanini, *Ber.*, **21**, 2874 (1888); B. Oddo and F. Tognacchini, *Gazz. Chim. Ital.*, **53**, 265 (1923).

[9] H. Wenker, *J. Am. Chem. Soc.*, **57**, 2328 (1935).

[10] P. A. Leighton, W. A. Perkins, and M. L. Renquist, *ibid.*, **69**, 1540 (1947).

[11] W. A. Reeves, G. L. Drake, Jr., and C. L. Hoffpauir, *ibid.*, **73**, 3522 (1951).

[12] P. Karrar, P. Portmann, and M. Suter, *Helv. Chim. Acta*, **31**, 1617 (1948).

[13] We wish to thank Dr. A. L. Logothetis for providing us with the spectrum.

nitrenium ion **12**. Of the possible choices, **10** appears quite attractive in analogy with the proposed[14] stability of the trishomocyclopropenyl cation, **14**. Unfortunately, detailed deuterium-labeling experiments would be required in order to reach a definitive conclusion as to which of the aforementioned intermediates was actually formed.

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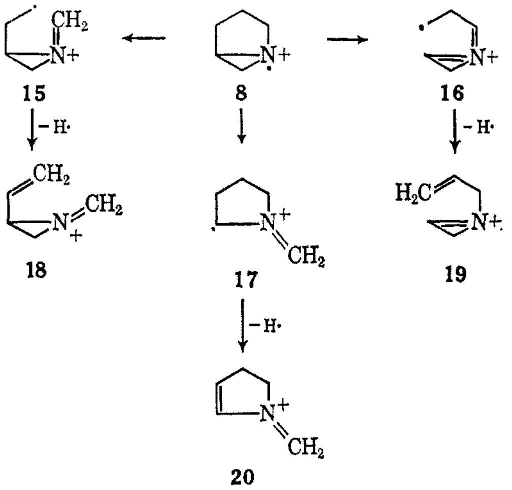
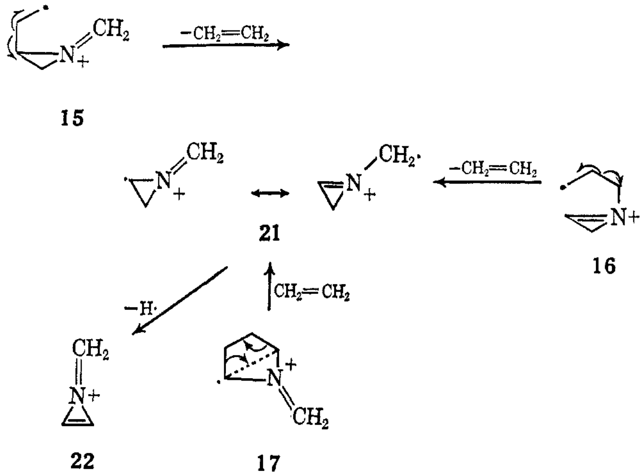
TABLE I

MASS SPECTRUM OF 1-AZABICYCLO[3.1.0]HEXANE

m/e	% of base peak	Metastable peaks, *m/e*
		14.3 (55 → 28)
		21.3 (83 → 42)
27	14	
28	50	
29	10	
31	4	
32	7	
		36.5 (83 → 55)
		37.0 (82 → 55)
39	9	
41	19	
42	33	
53	5	
54	26	
55	100	
56	8	81.2 (83 → 82)
82	51	
83	45	
84	4	

An alternate possibility is that **8** is rapidly converted to either **15**, **16**, or **17** by α cleavage. All of these ions would have *m/e* 83 and could be converted to **18**, **19**, or **20**, respectively, by loss of a hydrogen atom.[15] The subsequent fragmentation pattern makes the intermediacy of **15**, **16**, and/or **17** appear reasonable. The presence of a metastable peak at *m/e* 36.5 indicates the loss of ethylene from the molecular ion (*m/e* 83) to yield the base peak (*m/e* 55). The ions **15**, **16**, and **17** are all ideally set up for this type of transformation. Indeed all three of these would be expected to yield the same ion, **21**. The metastable peak *m/e* 37.0 shows that the M − 1 ion also gives rise to the ion **21**. This transformation would indicate loss of a vinyl radical. The presence of a significant peak at *m/e* 54 might be attributed to the loss of a hydrogen atom from **21** to yield **22**.





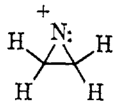
A major peak occurred at *m/e* 42. The metastable peak at *m/e* 21.3 established that a fragment of mass 42 arose from the molecular ion *via* loss of a mass 41 fragment. This fragment of *m/e* 42 could be assigned structure **23**, **24**, or **25**. Ion **25**, like ions **10**, **12**, and **13**, is a nitrenium ion.[16] Fragments **23** and **24** are of a more classical and well-documented nature.[15] The fragment lost in the 83 → 42 transformation (M = 41) was probably **26** or **27**. Both **15** and **17** could cleave to yield **23** and **26**. However, such a transformation would require a hydrogen atom shift. Somewhat more attractive would be the cleavage of either **15** or **17** to yield **23** and **27**, since this would not require a hydrogen migration. Alternately, ion **16** could cleave to produce **25** and **27** *via* a hydrogen atom shift.

$CH_2{=}\overset{+}{N}{=}CH_2$

23

$CH_3\overset{+}{N}{\equiv}CH$

24



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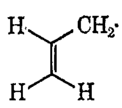

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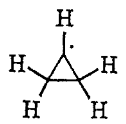

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The last fragment to merit comment is the *m/e* 28 peak. As shown by high-resolution mass spectra, the peak consists of both C_2H_4 and CH_2N. The presence of the metastable peak at *m/e* 14.3 indicates that the *m/e* 28 peak arises from fragmentation of **21** (*m/e* 55). This can be rationalized by the cleavage of **21** to yield the vinyl radical and either **28** or **29**. The

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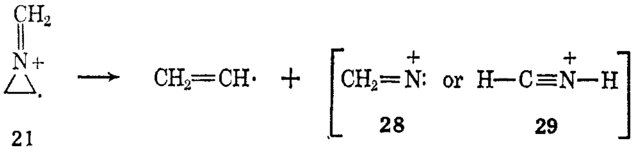
[14] S. Winstein and J. Sonnenberg, *J. Am. Chem. Soc.*, **83**, 3235, 3244 (1961), and references contained therein.

[15] Ample precedent exists for this type of α cleavage and subsequent loss of hydrogen atom. For a recent discussion, see A. M. Duffield, H. Budzikiewicz, D. H. Williams, and C. Djerassi, *ibid.*, **87**, 810 (1965).

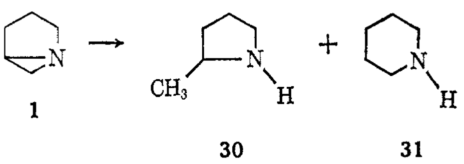
[16] For a review of nitrenium ion chemistry, see ref 3.

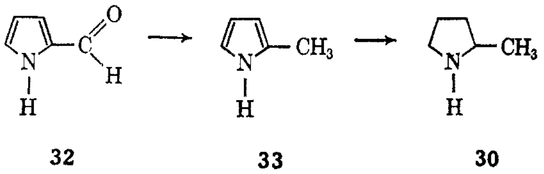


structures of the intermediates discussed above are only tentative assignments. More definitive evidence would require deuterium labeling and additional high-resolution mass spectrometry.

1-Azabicyclo[3.1.0]hexane is very reactive. It reacts violently with methyl iodide. On standing for a period of several weeks at room temperature, it polymerizes to an opaque white solid. However, **1** could be stored at 5° over potassium hydroxide for several months without appreciable deterioration.

The catalytic hydrogenolysis of **1** merits discussion. When 1-azabicyclo[3.1.0]hexane was reduced with hydrogen in the presence of palladium on charcoal, two products were formed in the ratio of 2:1. These products were shown to be 2-methylpyrrolidine (**30**) and piperidine (**31**), respectively, by comparison of vpc retention times and infrared spectra of samples of **30** and **31** isolated by preparative vpc with spectra of authentic material. A sample of **30** was prepared as shown below starting with 2-pyrrolecarboxaldehyde (**32**), converting **32** to **33** *via* a Wolff–Kishner reaction,[17] and subsequent catalytic reduction[18] of **33** to **30**.





Experimental Section

All melting points and boiling points are uncorrected. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark, and Battelle Memorial Institute, Columbus, Ohio. Mass spectral determinations were carried out on an AEI MS-9.

1-Azabicyclo[3.1.0]hexane. A. From 3-Hydroxypiperidine.—To 5 g of 3-hydroxypiperidine in 5 ml of water was added 2.6 ml of concentrated sulfuric acid in 5 ml of water with ice cooling. The solution was placed in a 100-ml, round-bottomed flask and subjected to the vacuum of a water aspirator. The flask was then heated with a free flame until the temperature reached 200°. After cooling, 30 ml of 40% sodium hydroxide solution was added and the mixture distilled until 10–15 ml of distillate was collected. When 5 g of potassium hydroxide pellets were added to the distillate, two layers formed. The clear liquid was separated and distilled to give trace amounts of 1-azabicyclo[3.1.0]hexane, identified at a later time by comparison of its infrared spectrum with the infrared spectrum of an authentic sample which was obtained *via* an alternate route.

L-Prolinol (5).—In a 1-l., three-neck, round-bottomed flask equipped with a reflux condenser, calcium sulfate drying tube, and a mechanical stirrer was placed 500 ml of tetrahydrofuran, which had been distilled from lithium aluminum hydride. To the tetrahydrofuran was added with external cooling 25 g of lithium aluminum hydride followed after 30 min stirring by the addition of 25 g of L-proline (Sigma Chemical Co.) with external ice cooling. The temperature was slowly raised to 75° and maintained at that temperature for 4 days. The mixture was then cooled and 85 ml of water was added dropwise, with external ice cooling, over 2–2.5 hr, after which the mixture was stirred for an additional 0.5 hr. The salts were filtered using a sintered-glass funnel and washed three times with 100-ml portions of tetrahydrofuran. The combined filtrate and washings were dried over anhydrous magnesium sulfate and filtered; the solvent was evaporated *in vacuo* to give a light yellow oil. The crude product was distilled to yield 12.4 g (57%) of **5**, bp 69–72° (2 mm).[12]

2-Pyrrolidylmethylsulfuric Acid (7).—To 12.0 g of L-prolinol in 12 ml of water was added, with ice cooling, 12.0 g of concentrated sulfuric acid (96%) which had been diluted with 12 ml of water. The solution was then placed in a 100-ml, three-neck, round-bottomed flask equipped with a thermometer, magnetic stirring bar, and an outlet to a vacuum line. Using a heating mantle, the temperature was gradually increased as the pressure was decreased. Eventually, enough water was evaporated that the pot temperature reached 35° (8–10 mm). The pressure was held constant while the temperature was raised. At 60°, the temperature was increased at a rate of 20° every 4 min until at 120–130° a precipitate began to form. At 145–160° the entire mass had solidified. Heating was then discontinued and the flask cooled. The light tan solid was broken up and recrystallized from ethanol and water to yield 14.0 g of **7** as fine white needles, mp 233.0–233.5°. Addition of ether to the mother liquor gave an additional 1.4 g with the same melting point. The total yield was 15.4 g (75%). *Anal.* Calcd for $C_5H_{11}NSO_4$: C, 33.14; H, 6.12; N, 7.73; S, 17.69. Found: C, 33.21; H, 6.21; N, 7.71; S, 17.69.

(5*S*)-1-Azabicyclo[3.1.0]hexane (1).—2-Pyrrolidylmethylsulfuric acid (12.3 g) was dissolved in 100 ml of water and the resulting solution was added over a 25-min period to 200 ml of a rapidly distilling solution of 20% sodium hydroxide. The distillate was collected in an ice-cooled receiver containing 75 g of potassium hydroxide pellets and 50 ml of ether. Distillation was continued for an additional 30 min after addition was complete. After the distillation was stopped, the potassium hydroxide remaining in the receiver was dissolved in water and the ether layer was separated. The aqueous layer was extracted with three 50-ml portions of ether. The ethereal extracts were combined and dried over anhydrous magnesium sulfate. After removal of the drying agent, the ethereal solution was concentrated to 20 ml by careful fractional distillation to remove the solvent. The residue was fractionally distilled to yield 3.0 g (54%) of **1**, bp 107–110°. Very pure samples were obtained by preparative vapor phase chromatography on a 6 ft × 0.5 in. stainless steel column packed with 20% Carbowax 20 M on Chromosorb W at 80°. The rotation of **1** was $[\alpha]^{28}\mathrm{D}\ -19°$.

Hydrogenolysis of 1-Azabicyclo[3.1.0]hexane (1).—In 20 ml of pure hexane was placed 200 mg of 10% palladium-on-charcoal catalyst and 1.0 g of 1-azabicyclo[3.1.0]hexane. The mixture was placed in a bomb at 50 lb of hydrogen pressure and shaken overnight. Chromatographic analysis indicated that only about 50% of the starting material had been reduced. Another 500 mg of catalyst was added and the mixture again shaken overnight at 50 lb of hydrogen. Only a trace of starting material remained at this time. The catalyst and solvent were removed and the residue was shown by vapor phase chromatography to contain two components in the ratio of 2:1 which were identified as 2-methylpyrrolidine (**30**) and piperidine (**31**), respectively.

On a 10 ft × $^1/_8$ in. stainless steel, 10% Apiezon L, 10% KOH-treated Chromosorb W column at 70° with a carrier gas of nitrogen and a flow rate of 30 ml/min the first product and authentic 2-methylpyrrolidine were found to have retention times of 5 min and 3 sec and the second product and authentic piperidine had a retention time of 6 min and 59 sec. On a 12 ft × 0.25 in., 20% SE-30 on Chromosorb W column at 95° using helium as carrier gas at a flow rate of 80 ml/min, both 2-methylpyrrolidine and the first product had a retention time of 4 min and 40 sec and piperidine and the second product had a retention of 6 min. On a 10 ft × 0.25 in. aluminum column containing 10% Carbowax 20 M on 10% KOH-washed Chromosorb P at 94° using helium as carrier gas at a flow rate of 80 ml/min, both 2-methylpyrrolidine and the first product had a retention time of 5 min and 20 sec; the piperidine and the second product had

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[17] For typical Wolff–Kishner conditions, see L. J. Durham, D. J. McLeod, and J. Cason, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 510.

[18] M. L. Jong and V. P. Wibaut, *Rec. Trav. Chim.*, **49**, 237 (1930).

a retention time of 7 min and 20 sec. Isolation of **30** and **31** by preparative vpc gave samples whose infrared spectra were identical with the infrared spectral of authentic samples of **30** and **31**.

2-Methylpyrrole (33).—To a round-bottomed flask fitted with a side arm for distillation and a thermometer to observe actual pot temperature was added 170 ml of diethylene glycol and 30 g of potassium hydroxide pellets. The flask was heated with a free flame until the potassium hydroxide began to fuse and dissolve. A magnetic stirrer was used to stir the solution. After the potassium hydroxide had all dissolved, the flask was cooled and 14.8 g of 2-pyrrolecarboxaldehyde was added followed by 22 ml of 95% hydrazine. The flask was then heated with a heating mantle. At 130° distillation began and distillate was collected until the pot temperature reached 200°. This required 1.5 hr. The distillate was poured into 100 ml of water and extracted three times with 75-ml portions of ether. The ethereal extracts were combined, dried over anhydrous magnesium sulfate, filtered, and the ether evaporated *in vacuo* to give 11.7 g of crude product. The crude product was fractionated through a Vigreaux column to give 9.0 g (75%) of water-white **33**, bp 149°.

2-Methylpyrrolidine (30).—In a glass bomb was placed 20 ml of glacial acetic acid, 4.0 g of 2-methylpyrrole, and 0.5 g of commercial Adams catalyst. The ampoule was flushed several times with hydrogen and then pressurized to 49.2 lb with hydrogen. After 5 hr, 85% of the theoretical amount of hydrogen had been consumed. On continued shaking overnight, only another 2% was consumed. The viscous yellow oil was filtered through a sintered-glass funnel and the catalyst washed with a small amount of acetic acid. The filtrate was then diluted with 50 ml of water and then made strongly basic with sodium hydroxide, with external ice cooling. The basic solution was then extracted three times with 50-ml portions of ether. The ether solutions were combined, dried over anhydrous magesium sulfate, filtered, and concentrated to 30 ml by evaporation. The solution was then distilled and the fraction boiling from 90 to 92° was collected. The water-white liquid weighed 0.8 g (19%).[18]

Registry No.—**1**, 13118-58-6; **5**, 5044-49-5; **7**, 13118-60-0; **30**, 765-38-8; **33**, 636-41-9.

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Conformational Analysis. LVI. Chlorocyclohexane and 1-Chloro-1-methylcyclohexane[1,2]

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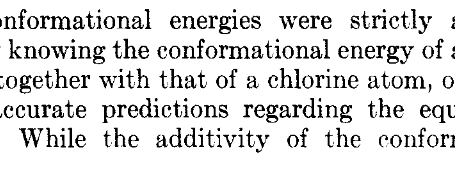
From studies on chlorocyclohexane, 1-chloro-1-methylcyclohexane, *cis*- and *trans*-4-*t*-butyl-1-chlorocyclohexane, *cis*- and *trans*-4-*t*-butyl-1-chloro-1-methylcyclohexane, and 1-chloro-1,4,4-trimethylcyclohexane, the conformational energy of chlorine was determined by a study of the molar absorbance of the C–Cl stretching frequency in the infrared, supplemented by variable-temperature infrared spectroscopy and equilibrium measurements, to be 0.4 kcal/mole, favoring the equatorial conformation when the chlorine was secondary, and it was found that, when the chlorine and methyl were geminal, the conformational energy was 1.1 kcal/mole, favoring the chlorine axial and methyl equatorial.

The conformational energies of substituents on cyclohexane rings have been widely studied, both because of the wide occurrence and importance of this ring system, and also because of the simplicity of the theoretical treatment of the data so obtained.[3,4] During the last few years, both the accuracy obtainable in the experimental measurements, and also the theoretical interpretation of the conformational energies available have continuingly increased, so that now energies of the order of 0.2 kcal/mole are often attainable by measurement, and they provide stringent tests of current conformational theory.[5,6]

While the first step in studying the conformational energies of groups was concerned with securing and understanding average numerical values for these quantities, it is now clear that the values are not constant to within experimental error, but vary with the immediate molecular environment,[9,10] sometimes with more distant molecular environment,[11] and also with intermolecular environment.[12]

If conformational energies were strictly additive, then by knowing the conformational energy of a methyl group, together with that of a chlorine atom, one could make accurate predictions regarding the equilibrium shown. While the additivity of the conformational energies might be assumed as a first approximation, the available theory indicates that it would not in general be exactly correct.[13] The present work reports an experimental study of this problem.



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[1] Paper LV: N. L. Allinger, L. W. Chow, and R. A. Ford, *J. Org. Chem.*, **32**, 1994 (1967).

[2] This research was supported by Grant GP 4290, from the National Science Foundation.

[3] J. A. Hirsch in "Topics in Stereochemistry," N. L. Allinger and E. L. Eliel, Ed., Vol. I, Interscience Publisher, Inc., New York, N. Y., 1967, p 199.

[4] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, p 435.

[5] For a discussion of the current methods of physical measurement of conformational energies, see ref 4, p 129.

[6] For a recent review and discussion of the status of the theory of conformational analysis, see ref 4; more recent papers are ref 7–9.

[7] J. B. Hendrickson, *J. Am. Chem. Soc.*, **86**, 4854 (1964).

[8] K. B. Wiberg, *ibid.*, **87**, 1070 (1965).

[9] N. L. Allinger, M. A. Miller, F. A. Van-Catledge, and J. A. Hirsch, *ibid.*, in press.

[10] (a) E. L. Eliel and T. J. Brett, *ibid.*, **87**, 5039 (1965); (b) E. L. Eliel, S. H. Schroeter, T. J. Brett, F. J. Biros, and J. C. Richer, *ibid.*, **88**, 3327 (1966).

[11] D. H. R. Barton, F. McCapra, P. J. May, and F. Thudium, *J. Chem. Soc.*, 1297 (1960).

[12] See ref 3 for a recent summary.

[13] That this is the case follows as an extension of the discussion given in ref 9. The detailed theoretical treatment will be published elsewhere.