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Insertion of Sulfonylnitrenes into the Carbon–Hydrogen Bonds of Saturated Hydrocarbons. Acid-Catalyzed Thermolysis of *N*-Alkyl Sulfonamides

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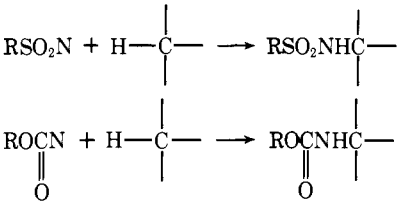
Abstract: Alkanesulfonylnitrenes, generated by azide thermolysis, are relatively unselective reagents; methane- and 1-pentanesulfonylnitrenes insert into the primary, secondary, and tertiary C–H bonds of 2,4-dimethylpentane in the ratios 1:2.3:6.0. The insertion of methanesulfonylnitrene into the tertiary C–H bonds of *cis*- and *trans*-1,2-dimethylcyclohexane is completely stereospecific, even under conditions which should favor intersystem crossing. Thus, it appears that insertion is a concerted singlet reaction and that triplet sulfonylnitrene does not insert into C–H bonds of saturated hydrocarbons. In the course of this investigation, the acid-catalyzed decomposition of certain *N*-alkyl sulfonamides was observed. Thus, *N*-(2,4-dimethyl-2-pentyl)methanesulfonamide (**3**) decomposed to methanesulfonamide and a 1:4 mixture of 2,4-dimethyl-1- and -2-pentenes in approximately 30 min at 90° when heated with a catalytic quantity of SO_2 in *n*-decane. *N*-(*cis*-1,2-Dimethylcyclohex-1-yl)methanesulfonamide (**4**) was less stable than the trans isomer (**5**); other sulfonamide stabilities were also studied.

Introduction

Considerable interest in nitrene chemistry has been evidenced in recent years.[1] Our interest was stimulated by the discovery that sulfonylnitrenes and carbalkoxynitrenes insert into the carbon–hydrogen bonds of saturated hydrocarbons, making them useful for the modification of hydrocarbon polymers.[2] Although the course of this reaction has been investigated in considerable detail for carbalkoxynitrenes,[3] very little is known about the mechanism of sulfonylnitrene insertion.[4,5] Inasmuch as our work showed very definite differences



between sulfonyl- and carbalkoxynitrenes in their reactions with cyclohexane,[6,7] a study of the sulfonylnitrene insertion reaction was initiated.

Our first goal was the determination of the relative reactivity of primary, secondary, and tertiary C–H bonds in a simple alkane. A previous attempt, using the thermolysis of tosyl azide as a nitrene source and 2-methylbutane as the hydrocarbon, was only partially successful; column decomposition prevented complete separation of the four expected isomeric sulfonamides by GLC.[6] We therefore turned to methanesulfonyl azide to increase volatility of the products, and to 2,4-dimethylpentane, which would yield only three isomeric amides and which bears at least a superficial resemblance to polypropylene, a polymer of considerable interest to us for many years.[8] We then planned to investigate the spin multiplicity of the nitrene in the C–H insertion reaction.

However, our discovery that certain of the expected reaction products were unstable under the reaction conditions necessitated a prior investigation of the product decomposition.

Acid-Catalyzed Thermal Cleavage of *N*-Alkyl Sulfonamides. Preliminary experiments seemed to indicate no insertion of methanesulfonylnitrene, prepared by thermolysis of methanesulfonyl azide, into the tertiary C–H bond of 2,4-dimethylpentane; only the primary and secondary insertion products (**1** and **2**) were found by GLC analysis. The three isomeric

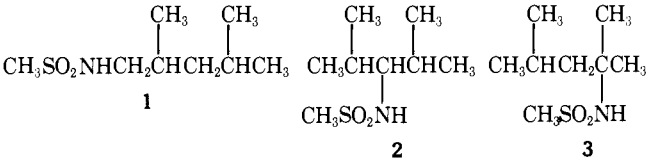


Table I. Thermolysis of Sulfonyl Azides in 2,4-Dimethylpentane

Expt. no.	RSO_2N_3, R =	Concn, M	*m*-$C_6H_4(NO_2)_2$ mol % of azide	Time at 150°, h	Insertion ratios[a] Sec/prim	Tert/prim
1	CH_3	0.25	0	1.25		0
2		0.039	0	1.5	2.2	4.0
3		0.048	0	8	1.9	1.0
4		0.033	1.8	1.5	2.1	5.6
5		0.033	2.8	8	2.3	6.0
6	*n*-C_5H_{11}	0.52	0	1.5	2.2	2.4
7		0.51	0	3	2.3	1.7
8		0.41	0	5	2.3	0.5
9		0.019	0	1.5	2.5	3.0
10		0.019	0	8	2.3	1.2
11		0.040	23.8	1.5	2.4	6.0
12		0.019	23.4	8	2.3	6.2
13		0.047	26.5	8	2.3	6.0

[a] Per C–H bond, calcd from GLC areas (see Experimental Section).

Table II. Relative Stabilities of *N*-Alkyl Sulfonamides[a]

$R'SO_2NHR$ R	R′	Concn, M	Additive (M)	Temp, °C	Time, h	% Dec
Prim 2,4-DMP[b]	CH_3	0.19[c]	SO_2 (0.043)	150	1	0
sec-2,4-DMP	CH_3					20
tert-2,4-DMP	CH_3					100
tert-2,4-DMP	CH_3	0.55	TsOH[d] (0.20)	150	<2	100
tert-2,4-DMP	CH_3	0.046	SO_2 (0.021)	90	0.28	94
					0.57	100
tert-2,4-DMP	*n*-C_5H_{11}	0.023	SO_2 (0.021)	130	0.75	48
					1.5	80
					1.8	94
					<2.3	100
tert-2,4-DMP	CH_3 + *n*-C_5H_{11}(1:1)	0.046	SO_2 (0.050)	90	17.5	0
tert-2,4-DMP	CH_3 + *n*-C_5H_{11}(1:1)	0.046	SO_2 (0.021)	90	1.6	0
				130	<0.3	100(CH_3) 76(C_5H_{11})
tert-2,4-DMP	*p*-$CH_3C_6H_4$	0.60	SO_2 (0.040)	150	<1	100
$(CH_3)_3C$	CH_3	0.80	SO_2 (0.040)	150	24	>50
$(CH_3)_3C$	C_5H_{11}	0.61	SO_2 (0.040)	150	24	20
$C_6H_5CH_2$	CH_3	0.31[e]	SO_2 (0.041)	150	8	~0
$C_6H_5CH_2$	CH_3	0.30[e]	CH_3SO_3H (0.045)	150	8	~0

[a] Heated in *n*-decane; analysis by GLC, column A (see Experimental Section). [b] Dimethylpentyl. [c] In 2,4-dimethylpentane; approximately equal amounts of the three sulfonamides. [d] *p*-Toluenesulfonic acid monohydrate. [e] In toluene.

sulfonamides, prepared by unequivocal syntheses, were found to be completely stable at 150° in 2,4-dimethylpentane for 8 h and to the analytical conditions. However, sulfur dioxide is always formed as a by-product of the decomposition of alkanesulfonyl azides in aliphatic hydrocarbons,[6] and addition of a small amount of sulfur dioxide to the expected sulfonamides showed that the tertiary insertion product (**3**) was decomposed completely in 1 h at 150°. Because of this unexpected result, the reaction was investigated in greater detail.

N-(2,4-Dimethyl-2-pentyl)methanesulfonamide (**3**) yielded methanesulfonamide and an approximately 1:4 ratio of the two olefins, 2,4-dimethyl-1-pentene and -2-pentene, when heated at 150° for 3 h in *n*-decane containing a catalytic quantity of sulfur dioxide. With the same amount of sulfur dioxide which led to complete decomposition of the sulfonamide, control experiments showed only slight isomerization of the olefins; approximately 2% of 2,4-dimethyl-1-pentene was isomerized to the 2-pentene, while only 0.2% of the 2-pentene was isomerized to the 1-pentene. The reaction is not limited to sulfur dioxide catalysis; *p*-toluenesulfonic acid also induces decomposition.

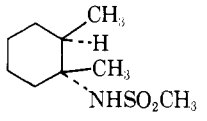
$$3 \xrightarrow[\Delta]{C_{10}H_{22},\ SO_2} CH_3SO_2NH_2 + CH_2{=}C(CH_3)CH_2CH(CH_3)_2 + (CH_3)_2C{=}CHCH(CH_3)_2$$

It was quite apparent from the azide decomposition experiments that *N*-(2,4-dimethyl-2-pentyl)-1-pentanesulfonamide is considerably more stable than the corresponding methane derivative (**3**) in the presence of sulfur dioxide. In the thermolysis of a concentrated solution of azide, the tertiary insertion product formed from methanesulfonyl azide was completely decomposed in less than 1.25 h at 150°, whereas some of the analogous product from 1-pentanesulfonyl azide was still present after 5 h (Table I, compare expt 1 with expts 6–8).[9] In order to investigate the relative stabilities more closely, the decomposition of the two sulfonamides was studied in *n*-decane with added sulfur dioxide (Table II). Here, too, the methane derivative (**3**) was much less stable; in the presence of approximately 50 mol % sulfur dioxide, it was 94% decomposed in 17 min at 90°, whereas the 1-pentane derivative in the presence of an equimolar amount of sulfur dioxide required almost 2 h at 130°. Considerable doubt was cast on these results, however, when competitive experiments were carried out. With equimolar amounts of the two amides and

either insufficient or excess sulfur dioxide, no decomposition was observed in 17 h at 90°; the pentanesulfonamide appeared to stabilize the methane derivative. At 130° both amides decomposed rapidly, but the methane derivative was again less stable than the pentane. The effect was observed under several different sets of conditions, although the actual rates could not be duplicated, probably because of poor gas–liquid mixing in the apparatus used. The presence of a stabilizer in the pentanesulfonamide, perhaps the free amine, would explain these results; however, careful purification of both the amine and the sulfonamide derived from it did not change the results, and no evidence for the presence of an impurity in the amide could be found by a variety of analytical techniques, including GLC. There can be little doubt, however, when these results are combined with those from sulfonyl azide thermolysis, that *N*-(2,4-dimethyl-2-pentyl)-1-pentanesulfonamide is more stable in the presence of sulfur dioxide than the corresponding methane derivative (**3**).

A number of other stabilities were investigated qualitatively under similar conditions. Thus, the secondary sulfonamide, *N*-(2,4-dimethyl-3-pentyl)methanesulfonamide (**2**), decomposed slightly when heated in a hydrocarbon solvent with sulfur dioxide at 150° for 1 h, while the primary derivative, *N*-(2,4-dimethyl-1-pentyl)methanesulfonamide (**1**), appeared to be completely stable. *N*-(2,4-Dimethyl-2-pentyl)-*p*-toluenesulfonamide decomposed at about the same rate as **3**. *N*-(*tert*-Butyl)methanesulfonamide was considerably more stable than **3**, about 50% decomposing in 24 h at 150°; the analogous 1-pentanesulfonamide showed even less decomposition. *N*-Benzylmethanesulfonamide was also very stable, showing little, if any, decomposition in 8 h at 150° in the presence of sulfur dioxide or methanesulfonic acid.

Our investigation of spin multiplicity (vide infra) showed an unexpected greater stability of *N*-(*trans*-1,2-dimethylcyclohex-1-yl)methanesulfonamide (**5**) as compared with the cis isomer (**4**). Although obviously a considerable amount of additional evidence would be needed to prove the mechanism, at the present time a concerted cis elimination with Saytzeff orientation seems to fit our data best.



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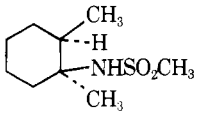

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Nitrene Insertion into Carbon–Hydrogen Bonds. The sulfur dioxide catalyzed thermolysis of tertiary sulfonamides interfered seriously with our initial attempts to determine the relative reactivity of methanesulfonylnitrene toward the three different C–H bonds in 2,4-dimethylpentane; typical results are shown in Table I (expts 1–3). For results to be meaningful, it was felt that reactivity ratios should be independent of the heating time. Since sulfur dioxide formation results from a radical-chain decomposition of the azide,[6] the addition of a radical trap, *m*-dinitrobenzene, in small quantities decreased the amount of sulfur dioxide formed and the corresponding sulfonamide decomposition, but not sufficiently to obtain reproducible results. Attempts to neutralize the sulfur dioxide were also unsuccessful; calcium oxide appeared to have some effect, but even with a combination of calcium oxide and *m*-dinitrobenzene, it was quite apparent that the ratios of primary:secondary:tertiary insertion products changed with the reaction time. It was finally demonstrated that with a very dilute solution (<0.05 M) of methanesulfonyl azide in 2,4-dimethylpentane containing a trace of *m*-dinitrobenzene, the ratios of **1:2:3** remained almost constant over a period of 8 h (Table I, experiments 4 and 5).[10] Since less than half the azide had been decomposed in the first sample taken, the effect of destroying unreacted azide with trialkyl phosphite[11] before analysis was investigated. The insertion ratios were essentially unchanged, however, demonstrating that reaction of the azide on the GLC column was not interfering with the analysis.

Table III. Selectivity of Nitrenes[a] in Insertion into Hydrocarbon C–H Bonds[b]

Hydrocarbon	Nitrene	
	EtOCON	CH_3SO_2N
2-Methylbutane		
Sec/prim	10[c]	4.2[d]
Tert/prim	32[c]	9.6[d]
3-Methylhexane		
Sec/prim	6.2[e]	
Tert/prim	17.6[e]	
2,4-Dimethylpentane		
Sec/prim	4.7	2.2
Tert/prim	12	5.8
cis-1,2-Dimethylcyclohexane		
Sec/prim		5.9
Tert/prim		11.7
trans-1,2-Dimethylcyclohexane		
Sec/prim		5.9
Tert/prim		9.0

[a] Formed by azide thermolysis, except where noted. [b] Per C–H bond. [c] Reference 7. [d] Formed by photolysis of the azide in dichloromethane.[8] [e] Reference 12.

Because of the greater stability of the pentanesulfonamides, the thermolysis of 1-pentanesulfonyl azide in 2,4-dimethylpentane was also studied. Within experimental error the relative reactivities were the same for the methane- and pentanesulfonylnitrenes (Table I, expts 5 and 13); relative reactivities of the two azides averaged 1:2.3:6.0 for insertion into the primary, secondary, and tertiary C–H bonds of 2,4-dimethylpentane.

Table III compares the insertion of carbethoxynitrene and methanesulfonylnitrene into the C–H bonds of a number of alkanes. It has been well documented that carbethoxynitrene inserts only as a singlet,[12] and that its selectivity resembles that shown by free radicals.[13] The results with 2-methylbutane[8] and with 2,4-dimethylpentane show that the sulfonylnitrene is an even less selective, or more reactive, intermediate than the carbalkoxynitrene. If one assumes a comparable size for the two, and a similar mechanism for C–H insertion (vide infra), this is in line with expectations; carbalkoxynitrenes can be stabilized by resonance between the nitrogen and the carbonyl group, whereas no resonance stabilization, other than that involving d-orbital expansion on the sulfur, is available to a sulfonylnitrene.

It appears that the reaction of carbethoxynitrene with acyclic hydrocarbons involves a small steric effect; it is interesting that the tertiary C–H bonds are approximately three times as reactive as the secondary; i.e., the relative steric hindrance at the secondary and tertiary positions appears to remain constant, but varies in relation to the primary position. It is unfortunate that more results are not available for the reaction of sulfonylnitrenes. Although the results reported by Shingaki, Inagaki, Torimoto, and Takebayashi[8] are in reasonable agreement with ours, the conditions used were so different that it is difficult to compare them. Their nitrene was generated photochemically in dichloromethane as solvent; the insertion yield was only 10%, the major product (45%) being methanesulfonamide, probably formed by abstraction of hy-

Table IV. Identification of Products from Thermolysis of Methanesulfonyl Azide in *cis*- and *trans*-1,2-Dimethylcyclohexane[a]

	Cis		Trans		Synthesized	
Assignment	Retention time, min[b]	Area, %	Retention time, min[b]	Area, %	Retention time, min[b]	Area, %
Methanesulfonamide	12.2	9[c]	12.1	4[d]		
Trans tertiary		0	26.7	24[e]	26	26
secondary			46.0	13		
secondary			53.3	15		
secondary			59.8	18		
secondary			64.4	18		
primary			84.9	8		
Cis tertiary	44.2	28[f]		0	43	74
secondary	60.4	28				
secondary	67.6	15				
secondary	77.8	13				
primary	108	7				

[a] With 2–20 mol % *m*-dinitrobenzene; heated 8 h at 150°. [b] GLC, 6 ft × ¼ in. glass column, Versamid 900, 10% on Gas Chrom Q; 178°. [c] In absence of dinitrobenzene, 17%. [d] In absence of dinitrobenzene, 10%. [e] In absence of dinitrobenzene, 22%. [f] In absence of dinitrobenzene, 6%.

drogen from the solvent by the nitrene. However, there is no evidence as to whether the photochemical reaction yields singlet or triplet sulfonylnitrene, and the unsubstituted amide might arise from the latter. The high selectivity found in our work with *cis*- and *trans*-1,2-dimethylcyclohexane is surprising, inasumuch as the Japanese workers reported the secondary C–H bonds in 2-methylbutane and in cyclohexane to have equal reactivity toward photochemically generated sulfonylnitrene.

In order to determine the spin multiplicity involved in the C–H insertion reactions of sulfonylnitrenes, the stereospecificity of the reaction of methanesulfonyl azide with *cis*- and *trans*-1,2-dimethylcyclohexane was investigated. For purposes of identification, a reported preparation of 1-amino-1,2-dimethylcyclohexane[14] was repeated and the amine was mesylated. GLC showed the presence of two isomers in a 74:26 ratio, and the proton magnetic resonance spectrum was that expected for a mixture of the two isomeric sulfonamides **4** and **5** (two CH_3CN singlets and two CH_3SO_2 singlets). However, since the absolute stereochemistry of the two isomeric amines has not yet been reported,[14b] the ^{13}C magnetic resonance spectrum of the mixture of sulfonamides was determined. The spectra were consistent with the expected structures, and spectral assignments could be made with the aid of single frequency off-resonance decoupling.[15] The major constituent was determined to be the cis compound (**4**) by virtue of the relative chemical shift of the C-1 methyls in the two isomers. The C-1 methyl resonance of the cis compound (18.2 ppm downfield from Me_4Si) appeared at higher field than the C-1 methyl of the trans compound (20.4 ppm). This is the expected arrangement of these methyl shifts, inasmuch as steric compression in model compounds leads to the same ordering of chemical shifts for a similar array of groups.[16]

Methanesulfonyl azide was thermolyzed in both *cis*- and *trans*-1,2-dimethylcyclohexane; product identification was of necessity indirect, since attempts to trap the individual compounds (six insertion isomers plus methanesulfonamide in each reaction) were unsuccessful. The results obtained, and the evidence used for structural assignments, are summarized in Table IV. Thus, heating methanesulfonyl azide in *cis*-1,2-dimethylcyclohexane containing a catalytic quantity of *m*-dinitrobenzene yielded a reaction mixture which gave five peaks (excluding solvent, dinitrobenzene, and methanesulfonamide) on a Versamid 900 column: one large peak with a retention time of 44 min, three closely spaced peaks (60, 68, and 78 min), with the first of the three approximately twice the area of the other two, and finally a smaller peak at 108 min. In our sulfonylnitrene insertion studies, using a variety of azides and hydrocarbons, we have found the retention times of the insertion products on a Versamid 900 column always to be in the order tertiary < secondary ≪ primary. We therefore tentatively assigned the 44-min peak to the tertiary alkylsulfonamide, the three closely spaced peaks to the four secondary insertion products, two of them eluting together, and the 108-min peak to the primary sulfonamide. The assignment of the 44-min peak to a tertiary sulfonamide was confirmed by repeating the thermolysis in the absence of *m*-dinitrobenzene; the 44-min peak was considerably smaller, as would be expected for a tertiary sulfonamide in the presence of sulfur dioxide. That the 44-min peak was assignable to *N*-(*cis*-1,2-dimethylcyclohex-1-yl)methanesulfonamide was demonstrated by adding the known cis–trans mixture to the reaction; the 44-min peak coeluted with the cis tertiary isomer.

Similar results were obtained with *trans*-1,2-dimethylcyclohexane. Here six peaks were observed. The first, presumably the tertiary sulfonamide, had a retention time (27 min) different from that of the tertiary isomer from *cis*-1,2-dimethylcyclohexane. This was followed by four closely-spaced peaks (46, 53, 60, and 64 min) of essentially equal areas, undoubtedly the expected four secondary isomers, and finally a single peak (85 min) assigned to the primary isomer. As with the cis isomer above, the 27-min peak coeluted with the authentic *N*-(*trans*-1,2-dimethylcyclohex-1-yl)methanesulfonamide. As already mentioned, the amount of tertiary isomer formed from *trans*-1,2-dimethylcyclohexane did not change on the addition of *m*-dinitrobenzene.

As shown in Table IV, the trans products always eluted before the corresponding cis products. The fact that the same phenomenon has been reported for several other 1,2-dimethylcyclohexane derivatives[14b] lends added support to the structural assignments made here. For these assignments to be incorrect, skeletal rearrangements would have had to occur during the insertion experiments and the rearranged products would have had coincidentally to coelute with the authentic sulfonamides. Skeletal rearrangements have not been observed in nitrene insertion reactions, and the expected number of isomeric sulfonamides were obtained in both reactions.

Only one tertiary sulfonamide was found in each insertion experiment; the reaction is virtually completely stereospecific. By adding the *cis*-1,2-dimethylcyclohexane reaction mixture to the trans, and vice versa, it was shown that 3% of the tertiary sulfonamide of opposite configuration could be readily observed. We can say with considerable confidence, therefore, that the insertion of a sulfonylnitrene into the carbon–hydrogen bonds of a saturated hydrocarbon is a concerted reaction involving singlet nitrene; in this respect it parallels the reaction of carbalkoxynitrenes.[3,17]

In order to study the reactions of triplet sulfonylnitrenes,

the thermolysis of methanesulfonyl azide in *cis*-1,2-dimethylcyclohexane diluted with equal volumes of bromobenzene or ethyl acetate was studied. Bromobenzene should catalyze intersystem crossing by the heavy atom effect, and Anastassiou[18] reported that ethyl acetate catalyzes singlet to triplet conversion of cyanonitrene. Even under these conditions, however, the insertion was completely stereospecific. Inasmuch as sulfonylnitrenes have triplet ground states,[19] it is difficult to believe that an equal volume of bromobenzene would not effect the conversion of singlet methanesulfonylnitrene to triplet; as little as 10% methylene chloride catalyzes intersystem crossing of singlet carbethoxynitrene.[3]

It would appear, therefore, either that triplet sulfonylnitrene does not insert into the C–H bonds of simple alkanes, or that the singlet nitrene reacts too rapidly under these conditions for intersystem crossing to compete. However, the selectivities of carbethoxynitrene and methanesulfonylnitrene towards insertion into C–H bonds, and presumably their relative reactivities, are not dramatically different (Table III); since triplet carbethoxynitrene has been demonstrated not to insert,[3] it is reasonable to conclude that triplet sulfonylnitrene also does not insert into the C–H bonds of saturated hydrocarbons.

It is generally accepted that triplet nitrenes abstract hydrogen, e.g., carbalkoxynitrenes yield unsubstituted carbamates[20] and arylnitrenes yield arylamines.[21] Yet alkanesulfonylnitrenes give unsubstituted sulfonamides when reacting with alkanes, predominantly, if not exclusively, by cleavage of the initially formed insertion product.[22] It is quite surprising that all of the sulfur present—in the azide, in the nitrene, and in the reaction products—does not appear to catalyze intersystem crossing. Of course, it is quite possible that triplet sulfonylnitrene is indeed present, but that it forms unidentified products;[23] some tar is almost invariably produced in these reactions.

Experimental Section

General Equipment and Techniques. Azide thermolyses and sulfonamide decompositions were carried out in heavy-walled tubes; except where noted, these were 18- or 44-ml tubes equipped with a side arm and a Teflon needle-valve Fisher–Porter closure. In all other cases they were 40-ml tubes equipped with magnetic stirring and a crown cap with butyl rubber liner. Air was displaced by nitrogen and the tubes were evacuated before closing. Azidoformate thermolyses were carried out at 120° and sulfonyl azide thermolyses at 150°, warming first at 90° with shaking to dissolve the azide.

GLC analyses of the sulfonamides and amines were carried out on an F & M Model 700 gas chromatograph with an F & M Model 240 temperature programmer. Except where noted, helium flow was 60 ml/min, 60 psig. Columns used were: column A, 5 ft × ¼ in. stainless steel, containing 20% Versamide 900 on Gas Chrom A; column B, 6 ft × ¼ in. glass, 10% Versamid 900 on Gas Chrom Q; column C, 12 ft × ¼ in. aluminum, 20% Carbowax on ABS; column D, 6 ft × ¼ in. aluminum, 28% Dowfax 9N10 on Chromosorb W, 10% KOH loaded.

Analysis for olefins was carried out on a Varian 200 gas chromatograph with a flame ionization detector, air 40 psig, H_2 14 psig, using column E, 30 ft × ⅛ in. stainless steel containing high performance OD-1 on silanized Anachrom; N_2 flow was 20 ml/min, 40 psig.

Peaks were identified by their retention times as compared with those of authentic standards, and confirmed in most cases by coelution with authentic standards. Peak areas were determined by height times width at half-height or by planimeter; in both cases reproducibility of measurements was within ±2%. Except where noted, response factors calculated from standard solutions of synthesized materials were used in determining ratios of compounds in the reaction mixtures. All calculations were based on at least three injections per point; deviation of individual injections from the average was within ±4%.

Melting points and boiling points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 237B spectrophotometer. Proton magnetic resonance spectra were taken on a Varian A-60A spectrometer, ^{13}C magnetic resonance spectra on a Bruker HFX-10 spectrometer; chemical shifts are reported in δ units (parts per million from tetramethylsilane internal standard).

Table V. *N*-(2,4-Dimethylpentyl)urethans

Substituent	Bp, °C (mm)	% C	% H	% N
1–	76 (0.17)	64.08	11.49	7.32
3–	95 (1.6)	64.11	11.62	7.52
2–	76 (4.6)	64.08	11.49	7.36
Calcd for $C_{10}H_{21}NO_2$		64.13	11.30	7.48

Materials. 2,4-Dimethylpentane (Aldrich), *cis*- and *trans*-1,2-dimethylcyclohexane (Phillips, pure grade), *m*-dinitrobenzene (Eastman), benzylamine (Aldrich), ethyl chloroformate (Eastman reagent grade), sodium azide (Fisher), and cyclohexane (Eastman spectro grade) were used as received.

Methane- and 1-pentanesulfonyl azides were prepared by reaction of the corresponding sulfonyl chlorides [methanesulfonyl chloride, Aldrich, redistilled, bp 81 °C (50 mm); 1-pentanesulfonyl chloride,[6] bp 84–84.5 °C (4.5 mm)] with sodium azide in aqueous acetone as described previously.[6] For reasons of safety they were stored at 5° in dilute solution. Immediately prior to use, the solvent (ethylene dichloride) was removed from small portions of the solution by aspiration; analysis of representative stripped samples by reaction with triphenylphosphine in benzene–acetic acid at 25° [25] gave 98–100% of the calculated quantity of nitrogen.

Ethyl azidoformate was prepared from ethyl chloroformate and sodium azide as described by Lwowski and Mattingly.[26] It was isolated in small portions, as needed, by removal of solvent and distillation through a 5-in. Vigreux column, bp 40–41 °C (34 mm).

Preparation of 2,4-Dimethylpentylamines. 1-Amino-2,4-dimethylpentane. 2-Bromo-4-methylpentane was prepared by the procedure of Stevenson and co-workers,[27] bp 40–43 °C (25–28 mm). The bromide was converted to the nitrile,[28] bp 153–155 °C, which was reduced with $LiAlH_4$[29] to the amine, bp 135–136 °C; GLC (column D) and ir detected no impurities.

2-Amino-2,4-dimethylpentane was prepared from 2,4-dimethyl-2-pentanol (Columbia Organic Chemicals) and sodium cyanide by the Ritter reaction,[30] followed by saponification of the formamide; bp 116–118 °C (760 mm) or 47–50 °C (50 mm) [lit.[31] 52.5 °C (68 mm)]: analysis by GLC showed only one peak; ^1H NMR (CCl_4) δ 0.88 (s, NH_2), 0.94 (d, Me_2C), 1.05 (s, Me_2CN), 1.23 (d, CH_2), 1.65 (m, CH); with Eu(fod)$_3$ shift reagent δ 1.03 (6 H, d, J = 6 Hz, Me_2C), 1.34 (6 H, s, Me_2CN), 1.48 (2 H, d, J = 5 Hz, CH_2), 1.84 (1 H, m, CH), 2.65 (s, NH_2). No other peaks were observed.

3-Amino-2,4-dimethylpentane. Diisopropyl ketoxime was prepared, bp 182–186.5 °C, and reduced to the amine with $LiAlH_4$ in THF; bp 130–132 °C (lit.[32,33] 124–126 °C, 125–127 °C). Analysis by GLC (column D) showed it to be >97% pure.

Synthesis of Urethans. The 2,4-dimethylpentylamines were converted into the corresponding urethans by reaction with ethyl chloroformate, using the procedure of Hartman and Brethen,[34] and fractionated in vacuo through a Vigreux microcolumn. Analytical data are shown in Table V.

Synthesis of Sulfonamides. *N*-(2,4-Dimethylpentyl)methanesulfonamides and 1-pentanesulfonamides were prepared by reacting the appropriate amine with methane- or 1-pentanesulfonyl chloride.

The methanesulfonamides were prepared by a Schotten–Baumann procedure using ether as solvent and aqueous NaOH.[34] The ether solutions were washed repeatedly with water, dried, and distilled. After fractional distillation or recrystallization, purity was confirmed by ir, ^1H NMR, GLC, and elemental analysis; results are summarized in Table VI.

The tertiary isomer, *N*-(2,4-dimethyl-2-pentyl)methanesulfonamide, after distillation contained some solid, identified as methanesulfonamide by GLC, apparently formed by decomposition during distillation. It was filtered under nitrogen pressure, the filtrate dissolved in methylene chloride, washed with 5% NaOH and with water, dried, and the solvent was removed under vacuum with a nitrogen sparge. Analyses were obtained on the washed sample: ^1H NMR (CCl_4) δ 0.95 (6 H, d, J = 5 Hz, Me_2C–), 1.35 (6 H, s, Me_2CN), 1.52 and 1.7 (3 H, overlapped d + m, J = 5 Hz, CH_2 and CH, respectively), 2.94 (3 H, s, $MeSO_2$), 5.25 (1 H, s, NH). Analysis by GLC on column A at 170° gave a single peak; no impurity peaks were detected even with very large injections. No amine peak was observed using column D.

Table VI. Sulfonamide Standards

Compd	Bp, °C (mm)	Mp, °C	Calcd, %				Found, %			
			C	H	N	S	C	H	N	S
N-(2,4-Dimethyl-1-pentyl)-methanesulfonamide	115–115.5 (0.1)		49.71	9.91	7.25	16.59	49.30	9.95	7.53	
N-(2,4-Dimethyl-3-pentyl)-methanesulfonamide		61–62.5[a]							7.45	
N-(2,4-Dimethyl-2-pentyl)-methanesulfonamide	99 (0.15)						49.73	9.92	7.08	16.77
N-(2,4-Dimethyl-1-pentyl)-1-pentanesulfonamide	142–147 (0.1)		57.79	10.91	5.62	12.86	57.81	10.97	5.56	12.88
N-(2,4-Dimethyl-3-pentyl)-1-pentanesulfonamide	128–133 (0.15)						57.78	10.56	5.39	13.05
N-(2,4-Dimethyl-2-pentyl)-1-pentanesulfonamide	129–133 (0.4)						57.75	10.76	5.73	13.10
N-(2,4-Dimethyl-2-pentyl)-*p*-toluenesulfonamide		109.4–111.4[a]			5.20				5.13	
N-(*tert*-Butyl)methanesulfonamide	79–80 (2)				9.26				9.26	
N-(*tert*-Butyl)-1-pentanesulfonamide	114–116 (0.15–0.35)		52.14	10.21	6.76		52.26	9.89	6.82	
N-Benzylmethanesulfonamide		64.2–65.6[b]	51.87	5.99	7.56	17.31	52.18	5.87	7.53	17.29
Methanesulfonamide		89.8–91.8[c]	12.63	5.30	14.73		12.96	5.55	14.97	
1-Pentanesulfonamide		61–63[d]	39.71	8.66	9.26	21.20	39.71	8.00	9.30	20.79

[a] Recrystallized from hexane. [b] From aqueous ethanol (lit.[35] 64.5–65 °C). [c] From benzene–ethanol (lit.[36] 89–91 °C). [d] From methylene chloride–hexane (lit.[37] 65–66 °C).

N-(2,4-Dimethylpentyl)-1-pentanesulfonamides were prepared in anhydrous benzene with triethylamine as acid acceptor. The benzene solutions were filtered, washed repeatedly with water, dried, and distilled. Purity was confirmed by ir, ^{1}H NMR, GLC (column B, 190°), and elemental analysis (Table VI). The tertiary isomer, *N*-(2,4-dimethyl-2-pentyl)-1-pentanesulfonamide, was given an extra workup after distillation, similar to that given the corresponding methanesulfonamide isomer, before analysis. No amine peak was observed using column D. The ^{1}H NMR spectrum in CCl_4 was consistent with the expected isomer, although the alkyl region was very complex and poorly resolved; addition of Eu(fod)$_3$ shift reagent did not improve the overall resolution.

The other sulfonamides listed in Table VI were prepared by reacting the corresponding sulfonyl chlorides in benzene with either excess amine or with amine plus triethylamine and purified by distillation and/or recrystallization.

Thermolysis of Ethyl Azidoformate in 2,4-Dimethylpentane. A 0.29–0.33 M solution of ethyl azidoformate in 2,4-dimethylpentane was heated at 120° for 4 h. Analysis by GLC was carried out on column C, oven 155°, inlet 213°, detector 215°, helium 50 ml/min. Peak areas, corrected for response factors, were used to calculate the insertion ratios shown in Table III.

Thermolysis of Methanesulfonyl Azide in 2,4-Dimethylpentane. The azide and *m*-dinitrobenzene (where used) were weighed directly into the decomposition tube, and 5 ml of 2,4-dimethylpentane was added. Azide concentrations varied from 0.3 to 0.03 M; the more concentrated solutions (0.2–0.3 M) led to excessive decomposition of some of the insertion products (see Table I). The azide solutions were heated at 150° for the indicated times, cooled to room temperature, and the solvent was evaporated in a stream of nitrogen. The products were redissolved in 0.5–1 ml of methylene chloride and analyzed by GLC: column A, oven 175°, inlet 210°, detector 255°. Typical retention times for the three isomeric insertion products were: tertiary 16.8–17.2 min, secondary 20.0–20.5 min, primary 42.9–43.6 min; unsubstituted methanesulfonamide eluted at 32–32.5 min, *m*-dinitrobenzene at 23.6–23.9 min. The areas were corrected for response factors; the insertion ratios are shown in Table I.

A synthetic reaction mixture, prepared from weighed amounts of the three *N*-(2,4-dimethylpentyl)methanesulfonamides and methanesulfonamide, was given a similar workup with no change in the relative areas.

That the tertiary insertion product (**3**) had actually been formed and decomposed in the reaction was demonstrated by carrying out a thermolysis of methanesulfonyl azide (0.37 M) in 2,4-dimethylpentane in the presence of 19 mol % of the authentic insertion product (**3**). After 8 h at 150°, no **3** was found by GLC.

Thermolysis of 1-Pentanesulfonyl Azide in 2,4-Dimethylpentane. The azide solutions were heated and worked up as in the previous section. GLC conditions were: column B, oven 190°, inlet 219°, detector 222°. Typical retention times for the three isomeric insertion products were: tertiary 20.9–22.1 min, secondary 25.1–25.5 min, primary 49.3–52.4 min; 1-pentanesulfonamide eluted at 33.1–34.4 min. An unknown product (approximately 18% of the total product area), eluting at 28–29 min, was probably the five- or six-membered cyclic sultam. Peak areas were corrected for response factors in calculating the insertion ratios (Table I).

Destruction of Azide with Alkyl Phosphite. Several thermolysis products of 1-pentanesulfonyl azide (0.5 M) in 2,4-dimethylpentane which had been heated at 150° for only 1.5 h (0.75 half-life) were used to compare analyses before and after treatment with triisooctyl phosphite; triethyl and tributyl phosphites interfered with GLC analysis. The phosphite was added dropwise at room temperature until no further gas evolution was observed; after standing at room temperature overnight, analysis was carried out on column A, oven 185°, inlet 240°, detector 234°. Under these conditions, typical retention times for the three insertion products were: tertiary 31.4 min, secondary 35.9 min, primary 71.1 min; unsubstituted 1-pentanesulfonamide eluted at 57 min. Before treatment to destroy the azide, an additional broad peak eluted at 49 min with a shoulder at 53 min; this peak was virtually absent after the phosphite treatment. Insertion ratios before and after treatment for three separate thermolyses were: primary:secondary:tertiary = 1:2.0:2.3 and 1:1.8:2.7; 1:1.6:2.0 and 1:1.6:1.9; 1:1.7:1.9 and 1:1.7:1.9.

Sulfur Dioxide Catalyzed Sulfonamide Decompositions. General Procedure. Experiments summarized in Table II were carried out in heavy-walled tubes with Teflon needle-valve closure. The sulfonamide, biphenyl internal standard, and any solid or liquid additive were weighed directly into the tubes; *n*-decane (Aldrich, >99%) was added by pipet. After evacuation and flushing with nitrogen, sulfur dioxide was introduced by gas syringe through the evacuated side-arm. A few experiments were carried out in capped tubes (butyl rubber liners) wiih magnetic stirring; the results were essentially the same.

Decomposition of *N*-(2,4-Dimethyl-2-pentyl)methanesulfonamide (3). A 0.30 M solution of **3** in *n*-decane containing 13 mol % SO_2 was warmed in a 90° bath for 15 min with shaking, then heated at 150° for 3.25 h. The liquid portion of the reaction product was analyzed

by GLC on column A as described earlier, and found to contain no remaining **3**. The solid which had precipitated from the reaction mixture was identified by GLC as unsubstituted methanesulfonamide. The reaction mixture was analyzed for olefins by GLC on column E at 25°, inlet 150°, detector 300° [Vr (relative to *n*-hexane) 1.40, 1.50]: 2,4-dimethyl-1-pentene, 19.4% of total olefin; 2,4-dimethyl-2-pentene, 80.6%. In a separate experiment, methanesulfonamide was isolated in 57% yield after one recrystallization and its identity confirmed by comparison of melting point and infrared spectrum with an authentic sample.

Solutions (0.34 M) in *n*-decane of pure samples of 2,4-dimethyl-1-pentene and -2-pentene (Aldrich) containing no detectable amounts of the other olefin were heated for 3.25 h with 13 mol % SO_2 under the conditions described above, and analyzed on column E; 2.07% 2,4-dimethyl-2-pentene was formed by isomerization of the 1-pentene, and 0.17% 2,4-dimethyl-1-pentene was formed from the 2-pentene.

***N*-(1,2-Dimethylcyclohexyl)methanesulfonamides.** Following the procedure of Hamlin and Freifelder,[14a] a 1:1 mixture of *cis*- and *trans*-1,2-dimethylcyclohexane was nitrated with aluminum nitrate monohydrate at 135° for 6 h in a stainless steel bomb; bp 88–90 °C (7 mm) [lit.[14a] 89–90 °C (7 mm)].

Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C 61.53; H 9.75; N 8.75.

The mixture of nitro compounds was hydrogenated with Raney nickel catalyst until the ir spectrum of the product showed no nitro absorption band at 1540 cm^{-1}. After workup,[14a] the resulting mixture of amino-1,2-dimethylcyclohexane isomers was reacted with methanesulfonyl chloride as described earlier.

Anal. Calcd for $C_9H_{19}NSO_2$: N 6.82; S 15.61. Found: N 6.96, S 14.98.

Dissolution in hot hexane and cooling to room temperature removed a small amount of crystalline solid which appeared (by GLC) to be a mixture of secondary isomers. The remaining product, a yellow oil, was identified as a mixture of the tertiary sulfonamides **4** and **5** (predominantly **4**) by its ^{13}C spectra, with and without SFORD, in $CDCl_3$ at 29°.[15] The product was analyzed by GLC on column B, oven 178°, inlet 207°, detector 212°. The two major peaks were assigned on the basis of ^{13}C spectra to the tertiary *N*-(1,2-dimethylcyclohexyl)methanesulfonamides: trans (**5**) at 26 min and cis (**4**) at 43 min; ratio of **4**:**5** 2.8. The ^1H NMR spectrum of the product was consistent with a mixture of sulfonamides, predominantly **4** and **5**: two CH_3CN singlets at δ 1.24 and 1.45 (ratio 2.6); two SO_2CH_3 singlets at δ 3.02 and 2.96 (ratio 2.6). On the basis of peak ratios compared with ^{13}C spectra, the peaks at δ 1.24 and 3.02 were attributed to the cis isomer and those at δ 1.45 and 2.96 to the trans.

Thermolysis of Methanesulfonyl Azide in *cis*- and *trans*-1,2-Dimethylcyclohexane. Solutions of the azide (0.033–0.044 M) in the hydrocarbon, with or without *m*-dinitrobenzene, were heated at 150° for the indicated times, evaporated, and redissolved in methylene chloride as in other sulfonyl azide thermolyses. GLC analysis was carried out on column A, 200°, inlet 210°, detector 260°, and on column B, 180°, inlet 207°, detector 212°. Typical retention times of major peaks in the thermolyses are shown in Table IV. Special care was taken to keep conditions exactly the same for both analyses, as was confirmed by identical *m*-dinitrobenzene retention times.

In calculating insertion ratios, corrections were made for the number of hydrogens, but response factors were not determined. Peak assignments were based on the evidence shown in Table IV and on the usual order of elution (tertiary < secondary ≪ primary) of azide insertion products on Versamid 900 columns.

Assignment of the peaks due to the tertiary insertion products was confirmed by coelution experiments. Addition of a small amount of the mixture of authentic tertiary sulfonamides **4** and **5** to the decomposition mixtures resulted in an increase in peak heights at 27 (trans) and 44 min (cis) without broadening or distortion of peak shape.

Experiments were carried out to determine the minimum level of detection of the tertiary insertion products, in mixtures of the two isomers. Thermolyses in *cis*- and *trans*-1,2-dimethylcyclohexane were done in capped tubes with magnetic stirring, and the products were concentrated by distillation in vacuo. After injection on column B to determine relative areas of the tertiary insertion products, a portion of the cis thermolysis product was mixed with the trans thermolysis product in proportions to give a cis tertiary peak ~3.3% of the trans tertiary peak. Another sample was prepared similarly, calculated to give a cis tertiary peak ~6.4% of the trans tertiary peak. In both samples the cis tertiary was clearly detectable as a shoulder on the first trans secondary insertion product; the shoulder was not present in the original trans thermolysis product. Areas were not calculated, but the height of the shoulder in the second mixed sample was twice that in the first. A similar experiment mixing the trans thermolysis product with enough of the cis thermolysis product to give trans tertiary peaks approximately 2.5, 4.9, and 9.5% of the cis tertiary peak gave peaks which calculated as 5, 7.6, and 10.3% of the cis tertiary.

To determine the effect of different diluents on the stereochemistry of the insertion reaction, solutions of methanesulfonyl azide (0.04 M on total solution) in a mixture of *cis*-1,2-dimethylcyclohexane and solvent, with 18–20 mol % *m*-dinitrobenzene, were heated at 150° for 8 h. The product was concentrated by distillation in vacuo and analyzed by GLC (Column B, 180°), comparing the results with similar thermolyses in undiluted hydrocarbon and in solvent alone. At 10% hydrocarbon concentrations, reaction with solvent predominated to such an extent that little meaningful information on hydrocarbon insertion products could be obtained. At 50% (by volume) of hydrocarbon in ethyl acetate and in bromobenzene, the only tertiary insertion product detected was the cis isomer (**4**); no **5** was found. A peak eluting at about the retention time of methanesulfonamide accounted for >15 (in ethyl acetate) and ~21% (in bromobenzene) of the total peak area, including products from reaction with solvent.

In thermolyses in methylene bromide as diluent, neither **4** nor **5** was detected, presumably because of decomposition by traces of HBr formed in the reaction with the solvent.

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(22) The situation is quite different in other solvents. Thus, methanesulfonamide was formed in considerable quantity in the reactions in ethyl acetate and in bromobenzene, and was the major product in the photolysis of methanesulfonyl azide in methylene chloride.[8] The source of the hydrogen atoms in the products of thermolysis of sulfonyl azides in aromatic solvents is a puzzle of long standing; unsubstituted sulfonamides are often major products. Abramovitch[5a] accounted for all the methanesulfonyl azide decomposed in toluene (but not in benzene) as methanesulfonamide and -toluidide. The fact that only a trace of 1,2-diphenylethane was isolated would appear to eliminate the formation of benzyl radicals by hydrogen abstraction from the toluene methyl group, while the possibility that an *N*-benzylsulfonamide is formed by insertion into the toluene side chain, which then decomposes, would seem to be eliminated by the results pre-

sented here. Of course, neither could be the hydrogen source with benzene.
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Steric Acceleration of Lactonization Reactions: An Analysis of "Stereopopulation Control"

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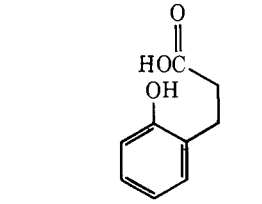
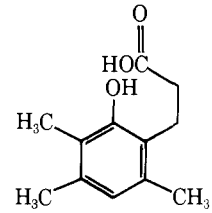
Abstract: The rapid lactonization of compounds of type **4** and **5a** relative to **1** (a rate acceleration of about 10^{11}) has been attributed to conformational restriction in the former compounds; the acceleration of rates due to this conformational restriction has been termed *stereopopulation control*. In this paper, we show that conformational restriction can account for a maximum rate enhancement of about 10^4, leaving a rate factor of at least 10^7 to be accounted for in other ways. Thus, compounds **7a** and **8a** are found to lactonize with rates relative to that of **1** of 1.5×10^2 and 2.4×10^4, respectively. Consistent with the postulation of a large relief of ground-state strain in the lactonizations of **4** and **5a** is the observation of a secondary deuterium isotope effect in the lactonization of **6a** relative to **5a**: $k_H/k_D = 1.09 \pm 0.02$. Although "stereopopulation control" may lead to sizable rate enhancements in certain cases, its importance in the reactions discussed here has apparently been overestimated.

In 1970, Milstein and Cohen,[3] in their study of the lactonization of a series of hydrocoumarinic acids **1–4**, found that the relative rates for hydrogen ion catalyzed reaction showed a dramatic effect of increasing methyl substitution, such that the ratio of rates of **4** relative to **1** was a spectacular 10^{11}. In



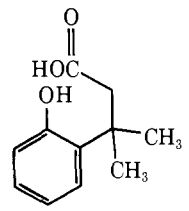
k_{rel} 1

1



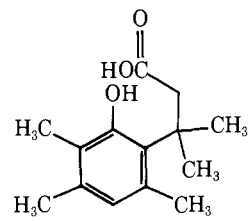
1.05

2



k_{rel} 4400

3



ca. 10^{11}

4

further comparison of their reactions to bimolecular counterparts, they concluded that the rate of lactonization of **4** is accelerated by a factor of about 10^{16} M, an acceleration which certainly approaches that observed for some enzyme-catalyzed reactions over their bimolecular counterparts. These authors recognized these observations as an extension of the well-known[4] gem-dialkyl effect, by which rates and equilibria of many ring-closure reactions are enhanced by increasing alkyl substitution on the backbone of the ring. These authors attributed these effects to a restriction of rotational freedom primarily about the bond between the aryl group and the carboxylic acid side chain in the reactive species " . . . which serves to narrow the distribution of conformational populations, ideally by eliminating nonproductive isomers". This putative restriction of rotational freedom was given the name *stereopopulation control*, and thus was initiated an extensive series of investigations[5] of similarly accelerated reactions, all of which were postulated to be examples of the operations of this principle. The authors recognized that conformational restriction as a factor in catalysis had been known for some time; their point was that its maximum effect had been grossly underestimated.

In this paper, we report our experimental results which show that (a) the dramatic rate accelerations in the lactonizations of methylated hydrocoumarinic acids can be understood as an effect brought about by relief of the extreme steric compression in these compounds, and (b) the effect of freezing conformations without simultaneously introducing van der Waals repulsions is a rate acceleration of a considerably more modest magnitude than that advocated by the proponents of stereopopulation control, and is more in accord with previous estimates. In the accompanying paper, Winans and Wilcox[21] provide theoretical support for the importance of relief of steric compression as a significant driving force in these reactions.

Results

Synthesis of Compounds. Compounds **5, 6, 7,** and **8** were used in the investigations reported herein. The synthesis of **6** was completed using a modification of that used for **5**[6] with the