

Reactivity of Conformational Isomers

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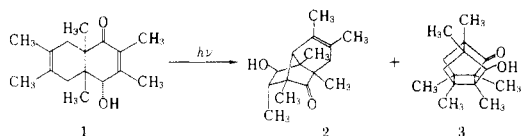
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Organic compounds are thought to be pure even though they may be a mixture of conformational isomers. This is because the isomers convert rapidly with each other at room temperature and their individual reactivities are little known. However, since conformational isomers are often diastereomers, their reactivities should be different, in principle, even under achiral conditions. As stated by the Curtin-Hammett principle,¹ the product ratio is governed by the rate constants for reaction of each isomer in addition to the equilibrium constant. This principle may not hold, however, if the equilibration rate becomes slow relative to the reaction rates.²

In earlier days of physical organic chemistry, model compounds were used for showing the differences in reactivities of conformational isomers: 4-*tert*-butylcyclohexyl derivatives³ and 3,5-dimethylcyclohexyl derivatives⁴ are examples in this area. In recent years, however, a number of examples showing different reactivity in conformational isomers has been reported. The difference in rates can amount to in excess of 10 000. Therefore, one cannot overlook the difference in reactivities of conformational isomers, if one hopes to carry out a highly selective organic synthesis. This Account reviews recent developments in this area to demonstrate factors affecting the reactivity of conformational isomers.

Shirahama et al.⁵ have discussed the formation of different compounds from different conformations of humulene 9,10-epoxide. Definite characterization of the conformations is lacking however; the conformations are inferred from the products. Papers by Appel et al.⁶ are a little more definite than the above example. They report that one isomer of 5-hydroxy-1,3,4,6,8,9-hexamethylbicyclo[4.4.0]deca-3,8-dien-2-one (1) produces 2 and 3 on irradiation at -70°C in a solid state. If 1 was irradiated in benzene solution at room temperature, 3, which was a minor product from the solid, became a major product. This is a clearer example of the conformational effect on the reactivity than that mentioned above, yet the conformation in solution is not well characterized.



Chupp and Olin were able to isolate stable rotamers of 2,6-disubstituted *N*-(haloacetyl)-*N*-methylanilines (4) and to show that their reactivities were quite different.⁷ The reaction of (*Z*)-4 with pyridine proceeded with

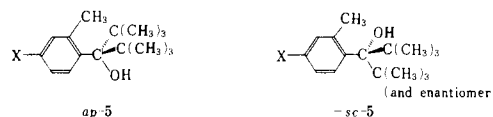
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reasonable rates, whereas that of (*E*)-4 was slow. The



rates of reaction of (*E*)-4 were essentially equal to the rates of rotation about the $\text{C}_{\text{CO}}\text{-N}$ bond. The results were explained on the basis that the backside of the XCH_2 group is protected by the aryl group in the *E* form.

Another example was provided by Lomas and Dubois.⁸ These authors were able to isolate $\pm sc$ and *ap* rotamers of di-*tert*-butyl-*o*-tolylmethanols (5) and to examine their reactivity in dehydration. They found that the *ap* form was at least 10 000 times more reactive than the $\pm sc$ in dehydration. The difference is derived from the strain in the ground state.



9-Arylfluorenes

Although the study of an atropisomers mentioned above is limited because of the functionalities necessary for the isolation of atropisomers, we recently demonstrated that 9-arylfluorenes provide stable rotamers that can carry a wide variety of functional groups.^{9,10} 9-Arylfluorenes give barriers to rotation of 24-35 kcal/mol, if the aryl group is either 2,6-disubstituted phenyl or 2-substituted 1-naphthyl. Therefore, it is now possible to undertake a systematic study of conformational effects on reactivities in these systems.

9-(2,6-Dimethylphenyl)fluorene (6) carries a pair of diastereotopic methyls. Treatment of 6 with *N*-bromosuccinimide, in boiling benzene for 17 h, yielded 2:2:1 *sp*- and *ap*-9-[2-(bromomethyl)-6-methylphenyl]fluorene (7).¹¹ Although internal rotation should take

(1) Hammett, L. P. "Physical Organic Chemistry", 2nd ed.; McGraw-Hill, New York, 1970; pp 119-20. See also: Seeman, J. I. *Chem. Rev.* 1983, 83, 83-134.

(2) Seeman, J. I.; Farone, W. A. *J. Org. Chem.* 1978, 43, 1854-64.

(3) Winstein, S.; Holness, N. J. *J. Am. Chem. Soc.* 1955, 77, 5526-78.

(4) Capon, D.; Cornubert, R.; Fagnoni, Y.; Ivanowsky, G. *Bull. Soc. Chim. Fr.* 1961, 240-53.

(5) Shirahama, H.; Hayano, K.; Kanemoto, Y.; Misumi, S.; Ohtsuka, T.; Hashiba, N.; Furusaki, N.; Murata, S.; Noyori, R.; Matsumoto, T. *Tetrahedron Lett.* 1980, 21, 4835-8.

(6) Appel, W. K.; Greenhough, T. J.; Scheffer, J. R.; Trotter, J.; Walsh, L. *J. Am. Chem. Soc.* 1980, 102, 1158-60, 1160-1.

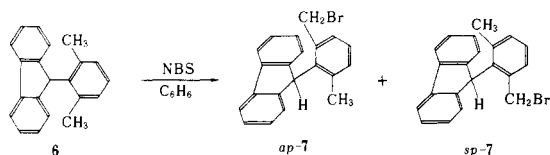
(7) Chupp, J. P.; Olin, J. F. *J. Org. Chem.* 1967, 32, 2297-303.

(8) Lomas, J. S.; Dubois, J. E. *Tetrahedron* 1978, 34, 1597-604.

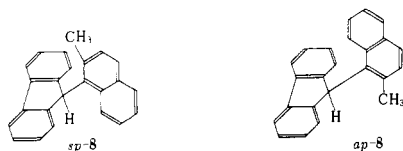
(9) Ōki, M. *Angew. Chem.* 1976, 88, 67-74; *Angew. Chem., Int. Ed. Engl.* 1968, 15, 87-93.

(10) Ōki, M. *Top. Stereochem.* 1983, 14, 1-81.

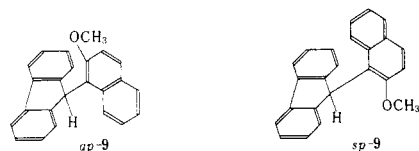
place to some extent under the conditions, the $[sp]/[ap]$ ratio is still different from the equilibrium constant ($[sp]/[ap] = 3.6$) at that temperature. We may attribute the results to a steric effect, since one side of the ap -CH₃ group is blocked to the attack of radicals derived from *N*-bromosuccinimide, while the sp -CH₃ is open.



For deprotonation, the *sp* form of 9-(2-methyl-1-naphthyl)fluorene (8) gave a pseudo-first-order rate constant of $3.6 \times 10^{-5} \text{ s}^{-1}$ in benzene-hexane, when it was treated with butyllithium, whereas the *ap* counterpart exhibited a rate constant of $5.2 \times 10^{-6} \text{ s}^{-1}$ at room temperature.¹² The 9-H in the *ap* conformation seems to be better protected by a methyl group than the 9-H in the *sp*, which is protected by the π -system.



If one considers steric effects only, one may predict that the *sp* form of 9-(2-methoxy-1-naphthyl)fluorene (9) should react a little faster than the *ap* form. In practice, *sp*-9 reacted with butyllithium in hexane-benzene with a pseudo-first-order rate constant of $>3 \times 10^{-2} \text{ s}^{-1}$ at 40 °C, whereas the *ap* form reacted with a constant of $7 \times 10^{-5} \text{ s}^{-1}$ under the same conditions.¹³ These results suggest that the oxygen atom in the methoxyl group assists lithiation. Since butyllithium is known to be a hexamer in hydrocarbons,¹⁴ the reagent must be very bulky. With assistance from the methoxyl group, the hexamer will deaggregate.¹⁵ Thus if a methoxyl group exists in proximity to the reaction site, 9-H, the reaction will be facilitated. In contrast, the methoxyl group in the *ap* conformation is too far from the reaction site to assist by deaggregation.



Methanolysis of 9-[2-(bromomethyl)-6-methylphenyl]fluorene (7) proceeded smoothly if the conformation was *sp* but was sluggish in the *ap* conformation.¹⁶ As an application, selective methanolysis of diastereotopic bromomethyl groups may be cited: Methanolysis of 9-[2,6-bis(bromomethyl)phenyl]fluorene (10) proceeded only in the *sp*-bromomethyl of

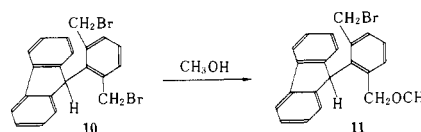
Table I
Rates of Reactions of
9-[2-(Bromomethyl)-6-methylphenyl]fluorene (7)
Rotamers with Pyridine Bases

	pyridine	α -picoline
temp/°C	35	45
$k_2/\text{L mol}^{-1} \text{ s}^{-1}$		
<i>sp</i> -7	8.5×10^{-4}	2.3×10^{-4}
<i>ap</i> -7	3.9×10^{-5}	6.7×10^{-6}
k_{sp}/k_{ap}	22	35

Table II
Relative Rates of Silver Salt Assisted Ionization of *ap*-7
and *sp*-7 and the Products

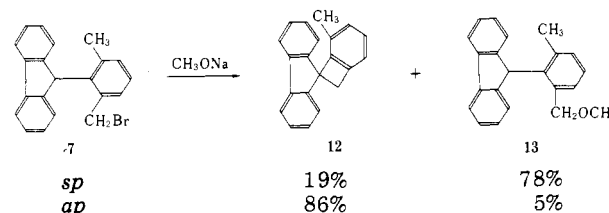
conditions	rel rates (k_{sp}/k_{ap})	products
CH ₃ CN-AgNO ₃	5.9	nitrate
CH ₃ CN-AgClO ₄	1.3	acetamide deriv
C ₆ H ₆ -AgClO ₄	1.6	phenyl deriv
(CF ₃) ₂ CHOH-AgClO ₄	0.78	cyclized (<i>ap</i>) polymers (<i>sp</i>)

the two to produce *ap*-9-[2-(bromomethyl)-6-(methoxymethyl)phenyl]fluorene (11).¹⁷



Other S_N2 type reactions were examined with pyridine bases in acetone. The reactions of organic halides with pyridine bases are known to be of the pure S_N2 type.¹⁸ The reaction gave the corresponding pyridinium salts and the results are given in Table I.^{16,18} The results indicate that S_N2 reactions are slower in *ap* conformations than in the *sp*, which can be attributed to the fact that S_N2 type reactions are space demanding in their transition states. The greater ratio (k_{sp}/k_{ap}) for the reactions of α -picoline than of pyridine is a clear indication of the space-demanding nature.

Treatment of 7 with sodium methoxide in methanol proceeded to afford 1-methyltribenzo[*a,e,g*]spiro[3.4]octa-1,5,7-triene (12) and 9-[2-(methoxymethyl)-6-methylphenyl]fluorene (13). An interesting point here is the fact that, whereas the major product from *sp*-7 was the methoxy compound 13, the spiro compound being minor, the spiro compound 12 is a major product and the methoxy compound is minor in the reaction of the *ap* isomer.¹⁷



The spiro compound 12 was apparently formed via a 9-anion, which should be the product of deprotonation, followed by an internal S_N2 type reaction. The results indicate that deprotonation is the major reaction in *ap*-7, whereas S_N2 substitution is the main reaction in *sp*-7. Steric effects in the S_N2 reaction are the con-

(11) Nakamura, M.; Ōki, M. *Tetrahedron Lett.* 1974, 505-8.

(12) Nakamura, M.; Nakamura, N.; Ōki, M. *Bull. Chem. Soc. Jpn.* 1977, 50, 1097-101.

(13) Nakamura, M.; Ōki, M. *Chem. Lett.* 1975, 671-4.

(14) Margerison, D.; Newport, J. P. *Trans. Faraday Soc.* 1963, 59, 2058-63.

(15) Langer, A. W. "Polyamine-Chelated Alkali Metal Compounds"; American Chemical Society: Washington, D.C., 1974; *Adv. Chem. Ser.* No. 130.

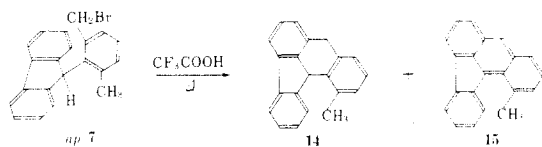
(16) Murata, S.; Kanno, S.; Tanabe, Y.; Nakamura, M.; Ōki, M. *Angew. Chem.* 1981, 93, 580-1; *Angew. Chem., Int. Ed. Engl.* 1981, 20, 606-7.

(17) Murata, S.; Kanno, S.; Tanabe, Y.; Nakamura, M.; Ōki, M. *Bull. Chem. Soc. Jpn.* 1984, 57, 525-8.

(18) Baker, J. W. *J. Chem. Soc.* 1934, 987-92.

trolling factors in the product distribution.

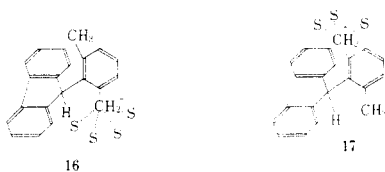
In a solvolytic reaction in trifluoroacetic acid, *ap*-7 reacted with a rate constant of $7 \times 10^{-4} \text{ min}^{-1}$ at 61 °C, whereas *sp*-7 remained intact.¹⁶ The products from *ap*-7 were proved to be 12-methyl-8,12-dihydrobenz[*a*]aceanthrylene (14) and its dehydrogenated product 15.



The *sp* and *ap* forms of 7 were treated with silver salts under various conditions.¹⁹ The results are shown in Table II. In many examples, *sp*-7 is more reactive than *ap*-7, in contrast to their behavior in trifluoroacetic acid. The products are not the cyclized ones (14 and 15) but those that are derived by the reaction of the cation with an anion or a solvent molecule. The only exception is the reaction in hexafluoro-2-propanol in which the rate ratio k_{sp}/k_{ap} is 0.78 and the *ap* gives the cyclized products, whereas the *sp* gives polymers. Solvolytic reactions in solvents that are poorly nucleophilic but strongly ionizing show that, whereas the *sp* form is more reactive than the *ap* in formic acid and in other solvents in Table II, it is recovered while the *ap* form produces the cyclized products in hexafluoro-2-propanol.

Since it is difficult to consider that the *sp* form does not ionize in trifluoroacetic acid or in hexafluoro-2-propanol, whereas it does in formic acid, we must conclude that *sp*-7 does ionize in hexafluoro-2-propanol and in trifluoroacetic acid to ion pairs, which return to the covalent species owing to poor²⁰ nucleophilicity of the solvent molecule. Indeed, hexafluoro-2-propanol containing 3% methanol produced the methoxy compound 13 with a k_{sp}/k_{ap} value of 0.18.

The results are attributed to a solvent effect. Whereas the cation produced from the *sp* form is surrounded by a solvation shell (16), the solvation shell for the cation from *ap* (17) is constituted from the benzene ring in the fluorene moiety and a lesser number of solvent molecules than that for 16. If a molecule of solvent is a good nucleophile, 16 will be more stable than 17, whereas the reverse is true if a solvent molecule is poorly nucleophilic.

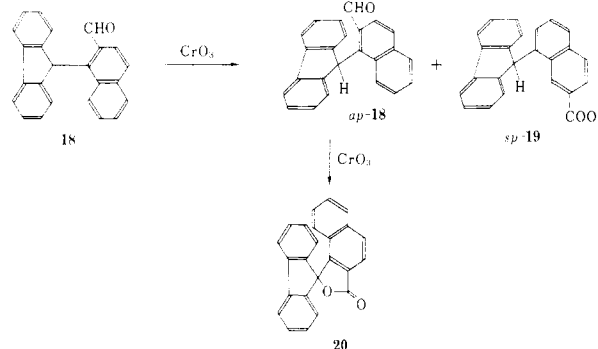


Reactions of carbonyl compounds in 9-arylfluorene systems provide another intriguing area. The first striking indication was that, whereas *sp*-9-(2-formyl-1-naphthyl)fluorene (18) was smoothly oxidized with chromium(VI) oxide to give a carboxylic acid (19) under acidic conditions, the *ap* form was recovered almost quantitatively.²¹ Prolonged oxidation of *ap*-18 gave

Table III
Relative Rates in Oxidation of Alcohols (21)
with Chromium(VI) Oxide in Aqueous Acetone

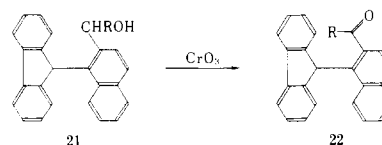
compd	R	rel rates (k_{sp}/k_{ap})
primary alcohol	H	0.67
secondary alcohol	CH ₃	27
	C ₆ H ₅	34

9-hydroxy-9-(2-carboxy-1-naphthyl)fluorene lactone (20) instead of the expected *ap*-19.



Various model reactions were carried out.²¹ Treatment of the aldehydes with hydroxylamine hydrochloride and sodium acetate in aqueous ethanol produced the corresponding oximes with the relative rate (k_{sp}/k_{ap}) of 2.3. Thus the addition step to the carbonyl group cannot explain the large difference in the reactivity of aldehyde 18 in oxidation.

The results of the oxidation of the related alcohols 21 to the corresponding carbonyl compounds 22 are



summarized in Table III.^{21,22} If the substrate is a primary alcohol, the reaction rate is almost the same for *sp* and *ap* forms, whereas the reaction is definitely slow in the *ap* form relative to the *sp*, if the alcohol is secondary. This can be understood if one inspects the molecular models of these compounds. In models of the secondary alcohols (21, R = CH₃ or C₆H₅), the hydrogen that is to be removed at the last step is buried in a pocket made by the R group, the OH group, and the fluorene moiety. If a space-demanding transition state is required, the reaction is slow in the *ap* form relative to the *sp*.

Dehydration of oximes is known to take place with an E₂ type mechanism if the conformation is *Z*.²³ When the oximes (23) of the aldehyde were treated with thionyl chloride, they were smoothly dehydrated at room temperature to produce the corresponding nitriles (24).²¹ The relative rate of reaction of the *sp* form was 18 if that of the *ap* form was unity. Thus the rule of space-demanding transition state is proved to be generally applicable to other reactions.

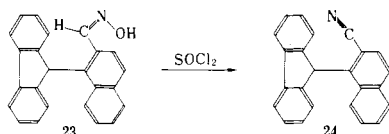
(19) Murata, S.; Kanno, S.; Tanabe, Y.; Nakamura, M.; Ōki, M. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1522-30.

(20) Schleyer, P. v. R.; Fry, J. L.; Lam, L. K. M.; Lancelot, C. J. *J. Am. Chem. Soc.* **1970**, *92*, 2542-4. Bentley, T. W.; Bowen, C. T.; Parker, W.; Watt, C. I. F. *Ibid.* **1979**, *101*, 2486-8.

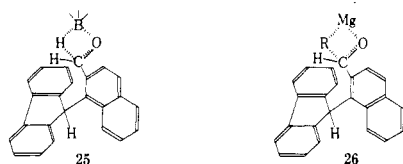
(21) Ōki, M.; Saito, R. *Chem. Lett.* **1981**, 649-52.

(22) Saito, R.; Ōki, M. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3267-72.

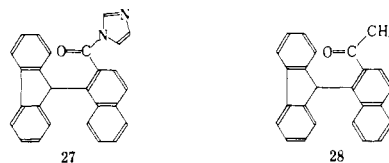
(23) Mowry, D. T. *Chem. Rev.* **1948**, *42*, 189-283.



Sodium borohydride reduction²⁴ and Grignard addition reactions²⁵ of carbonyl groups are often cited to take a four-membered cyclic transition state (25 and 26). If the above rule is applicable to these cases, k_{sp}/k_{ap} should be large in these reactions because the transition states are space demanding. Sodium borohydride reduction was found to give a k_{sp}/k_{ap} value of ca. 9. In contrast, Grignard addition reaction of phenylmagnesium bromide gave a small k_{sp}/k_{ap} value of 1.8; methylmagnesium iodide gave a k_{sp}/k_{ap} value of 1.7.²² Thus it seems that Grignard addition reactions generally give a rather small k_{sp}/k_{ap} value. It is tempting to consider that there is a path in Grignard reactions that does not require a large space in the transition state.



In view of steric effects, addition to the aldehydic carbonyl group may not be space demanding to a great extent, if the aldehydic hydrogen directs toward the fluorene ring. What will happen then if a large group has to approach the fluorene ring in the transition state of a reaction? This kind of reaction should take place in carboxylic acid derivatives or in ketones. Imidazolid 27 was found to be a suitable example to examine this point because its *sp* form was hydrolyzed at room temperature. The *ap*-27 isomer was recovered almost quantitatively after treatment with hydrochloric acid in aqueous acetone overnight.²⁶ Reduction with sodium borohydride and Grignard addition reaction of methylmagnesium iodide proceeded smoothly if the conformation of ketone 28 was *sp*, but the *ap* form was completely recovered under the same conditions.²⁶



Conformational effects should not be confined to relatively high temperatures. Sugawara and Iwamura have examined the reactions of nitrene rotamers of a similar system.²⁷ When 9-azatriptycene (29) is photolyzed, production of *ap*-*o*-(9-fluorenyl)phenylnitrene (30) is expected because of the geometry of 29. In contrast, since *o*-(9-fluorenyl)phenyl azide (31) is known to exist largely in its *sp* conformation,²⁸ its photolysis

Table IV
Relative Reactivity of $\pm sc$ and *ap* Methyls in Substituted 9-*tert*-Butyltrityptycenes toward Chlorination with Sulfuryl Chloride

substituent				product ratio ($\pm sc/ap$)	rel reactivity of a $\pm sc$ methyl
1	2	3	4		
Cl	Cl	Cl	Cl	3.2	1.6
Cl	H	H	H	3.8	1.9
H	Cl	Cl	H	1.9	0.95

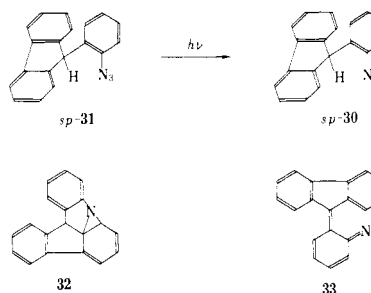
Table V
Relative Reactivity of Methyls in Competitive Halogenation of 9-*tert*-Butyl-1,2,3,4-tetrachlorotriptycene (34) and 9-*tert*-Butyl-1-chlorotriptycene (36) with 9-*tert*-Butyltrityptycene (37)

halogenating reagent	relative rates				
	37	34		36	
		<i>sc</i>	<i>ap</i>	<i>sc</i>	<i>ap</i>
Cl ₂	1.0	0.84	0.83	0.94	0.92
SO ₂ Cl ₂	1.0	0.95	0.60		
Br ₂	1.0	2.7	0.86	4.2	1.05

should produce *sp*-30 if reaction is carried out at a low temperature.



Photolysis of 29 at 77 K caused absorptions due to *ap*-30 in addition to an azanorcarane derivative (32) that was formed by addition of the nitrene moiety to the benzene ring in proximity. In contrast, photolysis of 31 under the same conditions did not show an absorption due to 32 but showed an absorption that was ascribed to an *o*-quinone imine (33) in addition to the



sp-nitrene 30. Compound 33 could be formed if 9-H, which is close to the nitrene center in *sp*-30, migrates to the nitrogen. When the reaction temperature was raised from 77 K to room temperature after photolysis of 31, products derived from 32 are detected. This is reasonable because internal rotation about the C₉-(fluorene)-to-phenyl bond can occur at relatively high temperatures in *sp*-30.

9-*tert*-Alkyltrityptycenes

9-*tert*-Alkyltrityptycenes are another system that gives a high enough barrier to rotation to enable one to isolate stable rotational isomers. The barriers are usually 30–40 kcal/mol.^{9,10}

The first indication of the differential reactivity in this system was noticed in radical halogenations of 9-*tert*-butyl-1,2,3,4-tetrachlorotriptycene (34). When

(24) Wigfield, D. C.; Gowland, F. W. *Tetrahedron Lett.* 1979, 2209–12 and papers cited therein.

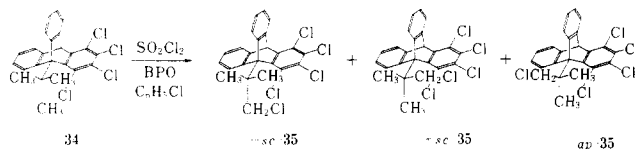
(25) Ashby, E. C.; Laemmle, J.; Neuman, H. M. *Acc. Chem. Res.* 1974, 7, 272–80. Ashby, E. C. *Pure Appl. Chem.* 1980, 52, 545–69.

(26) Saito, R.; Ōki, M. *Bull. Chem. Soc. Jpn.* 1982, 55, 3273–6.

(27) Sugawara, T.; Iwamura, H. *J. Am. Chem. Soc.* 1980, 102, 7134–6. Sugawara, T.; Nakashima, N.; Yoshihara, K.; Iwamura, H. *Ibid.* 1983, 105, 858–62. Sugawara, T., private communication.

(28) Tukada, H.; Iwamura, M.; Sugawara, T.; Iwamura, H. *Org. Magn. Reson.* 1982, 19, 78–85.

34 was heated with sulfuryl chloride in chlorobenzene in the presence of benzoyl peroxide, it gave a 3.2:1 mixture of $\pm sc$ - and ap -1,2,3,4-tetrachloro-9-(2-chloro-1,1-dimethylethyl)tritycene (**35**).²⁹ The results suggest that each of the $\pm sc$ methyls is 1.6 times more reactive than the ap methyl.

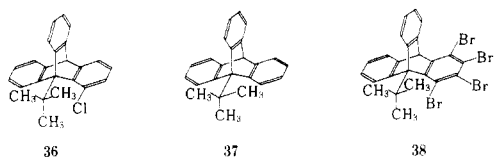


This difference is caused by the presence of the 1-chlorine atom. As is seen in Table IV, each of the $\pm sc$ methyls in 9-*tert*-butyl-1-chlorotriptycene (**36**) is more reactive than the ap methyl by a factor of 1.9. However, as soon as we remove the 1-substituent, the product ratio becomes a statistical one. Namely, 9-*tert*-butyl-2,3-dichlorotriptycene gives a product ratio ($\pm sc/ap$) of 1.9 under the same conditions.

There were two potential reasons for the enhanced reactivity of the $\pm sc$ methyl relative to the ap methyl. One is tilting of the *tert*-butyl group,³⁰ which will result in the steric protection of the ap methyl. Another is the neighboring participation of the 1-chlorine atom. Although the extent is small, a chlorine atom is known to participate in stabilizing a radical center in proximity.³¹

If steric effects were the main reason, a change in halogenating reagents would show little effect because steric protection of the ap methyl is not changed. In contrast, if the participation of the 1-chlorine atom is the main cause, a change in the halogenating agents should exhibit a significant change.

The results of competitive reactions between 9-*tert*-butyltriptycene (**37**) and 9-*tert*-butyl-1,2,3,4-tetrachlorotriptycene (**34**) and those between **37** and 9-*tert*-butyl-1-chlorotriptycene (**36**) are shown in Table V.³² The relatively low reactivities of the methyls in



34 and **36** are attributed to the inductive effect of the chlorine atoms, since the halogenating radicals are electron demanding.³³ The larger reactivities of the methyls in **36** than those in **34** support this interpretation. The most revealing point in these results is that, whereas the relative reactivities of the $\pm sc$ methyls were higher than those of the ap in a compound in chlorination with sulfuryl chloride, those of the $\pm sc$ and ap methyls were the same within the experimental error when the chlorination was carried out with chlorine.

(29) Morinaga, T.; Seki, S.; Kikuchi, H.; Yamamoto, G.; Ōki, M. *J. Am. Chem. Soc.* **1980**, *102*, 1173-4.

(30) Mikami, M.; Toriumi, K.; Konno, M.; Saito, Y. *Acta Crystallogr. Sect. B* **1975**, *B31*, 2474-8.

(31) Everly, C. R.; Schweinsberg, F.; Traynham, J. G. *J. Am. Chem. Soc.* **1978**, *100*, 1200-5.

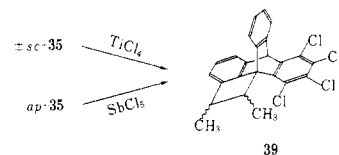
(32) Seki, S.; Morinaga, T.; Kikuchi, H.; Mitsuhashi, T.; Yamamoto, G.; Ōki, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1465-9.

(33) Walling, C.; Miller, B. *J. Am. Chem. Soc.* **1957**, *79*, 4181-7.

This is expected if the 1-chlorine participation is the main cause for the difference, because the chlorination with chlorine is known to be the least selective.^{34,35} Chlorine participation is further supported by the high reactivity of the $\pm sc$ methyls in **34** and **36** in bromination.

In bromination of **34** with bromine and *N*-bromosuccinimide, the relative reactivity of each of the $\pm sc$ methyls to a methyl in **37** seems to be reduced somewhat, 1.6 ± 0.08 , from that in the reaction with bromine, whereas that of the ap methyl is 0.82 ± 0.04 . In bromination of 1,2,3,4-tetrabromo-9-*tert*-butyltriptycene (**38**) with bromine-*N*-bromosuccinimide, the relative reactivity of each of the $\pm sc$ methyls in **38** under the conditions was 4.1 ± 0.8 , whereas that of the ap methyl was 0.8 ± 0.2 .³⁶ Thus each of the $\pm sc$ methyls is ca. 5 times more susceptible toward bromination than the ap methyl in **38** and a practically pure $\pm sc$ -bromo-methyl compound can be obtained. The results must be attributed to better participation of the bromine atom.

Ionizing reactions of **35** under the influence of Lewis acids have been carried out. The $\pm sc$ form of **35** reacted in the presence of a large excess of titanium tetrachloride.³⁷ The product was proved to be a mixture of 1,2-dimethyl-7,8,9,10-tetrachloro-1,2,6,10b-tetrahydro-6,10b-benzoaceanthrylenes (**39**). In contrast,



ap -**35** did not show a sign of reaction under the same conditions but gave the same mixture of stereoisomeric **39** when treated with a stronger Lewis acid, $SbCl_5$, than $TiCl_4$. The products (**39**) were undoubtedly derived by a Friedel-Crafts cyclization of a cation that was formed after extensive Wagner-Meerwein rearrangements of an initially formed cation. Since titanium tetrachloride is a very weak Lewis acid,³⁸ the ap form of **35** is not an exception, but $\pm sc$ -**35** is an exception. The developing cation **40** from $\pm sc$ -**35** is stabilized by the participation of the 1-Cl atom, whereas such participation is not possible in the ap conformation (**41**).

When $\pm sc$ -**35** was treated with silver nitrate in acetonitrile, an olefin (**42**) was formed.³⁹ This compound is also formed from $\pm sc$ -**35** if a relatively small amount of titanium tetrachloride is used. In contrast, ap -**35** remained intact under the same conditions. This is another piece of evidence that the formation of a cation **40** from $\pm sc$ -**35** is preferred because of the chlorine participation over that of a cation **41** from ap -**35**, because the olefin **42** can easily be formed from a cation,

(34) Poutsma, M. L. In "Free Radicals"; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. 2, pp 159-229.

(35) Tedder, J. M. *Q. Rev., Chem. Soc.* **1960**, *14*, 336-56.

(36) Skell, P. S.; Shea, K. J. In "Free Radicals"; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. 2, pp 809-52.

(37) Kikuchi, H.; Mitsuhashi, T.; Nakamura, N.; Ōki, M. *Chem. Lett.* **1980**, 209-12.

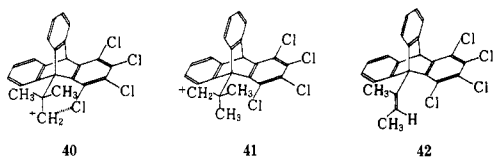
(38) Collinane, N. M.; Leyshon, D. M. *J. Chem. Soc.* **1954**, 2942-7. Mastagli, P.; Lambert, P.; Hirigoyen, C. *C. R. Acad. Sci.* **1959**, *249*, 1764-5. Olah, G. A.; Kobayashi, S.; Tashiro, M. *J. Am. Chem. Soc.* **1972**, *94*, 7448-61.

(39) Kikuchi, H.; Seki, S.; Yamamoto, G.; Mitsuhashi, T.; Nakamura, N.; Ōki, M. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1914-21.

Table VI
Time (s) Required for Conversion of 5% of an Isomer to Another in Irreversible Isomerization at Given Temperature and Given Free Energy of Activation

T/K	$\Delta G^\ddagger/\text{kcal mol}^{-1}$				
	20	15	10	7.5	5.0
100			1.6×10^8	5.7×10^2	2.0×10^{-3}
150		1.1×10^8	5.8×10^0	1.3×10^{-3}	3.0×10^{-7}
200	8.2×10^7	2.9×10^2	9.9×10^{-4}	1.8×10^{-6}	
250	2.8×10^3	1.2×10^{-1}	5.2×10^{-6}		
300	2.9×10^0	6.6×10^{-4}			
350	2.1×10^{-2}				

which is formed after a series of Wagner–Meerwein rearrangements, by removal of a proton.



Conclusion

Examples of molecules that show different reactivities due to rotational isomerism have been presented. Diastereotopic methyls and other groups can show differential reactivities, but their relative reactivities may be exaggerated to some extent because, in a system that gives stable rotamers, the molecule is usually in a congested state. Two groups may be highly proximate, a kind of situation that may not be realized in normal molecules. Yet the factors presented here must be operative in every reaction that is performed in organic laboratories.

In Table VI, calculated times required for conversion of 5% of an isomer to another at a given temperature and a given free energy of activation are summarized

by assuming an irreversible reaction. Free energies of activation of 5.0 and 7.5 kcal/mol correspond to the high of the two ($ap \rightleftharpoons \pm sc$ and $\pm sc \rightleftharpoons \mp sc$) possible barriers to rotation about a C–C bond connecting two primary alkyl groups and two secondary alkyl groups, respectively.⁴⁰ A free energy of 10 kcal/mol corresponds to the barrier to inversion of cyclohexanes⁴¹ and to rotation about a C–C bond connecting two tertiary alkyl groups.⁴² A free energy of 20 kcal/mol is a barrier to rotation of amides⁴³ and to aziridine inversion.⁴⁴

Since conformational change becomes slow at low temperatures, we suggest that any one who performs reactions at low temperatures should take the points raised in this account into consideration.

(40) Ōsawa, E.; Shirahama, H.; Matsumoto, T. *J. Am. Chem. Soc.* 1979, 101, 4824–32. Lunazzi, L.; Macciantelli, D.; Bernardi, F.; Ingold, K. U. *Ibid.* 1977, 99, 4573–6.

(41) Anet, F. A. L.; Anet, R. In "Dynamic Nuclear Magnetic Resonance Spectroscopy"; Jackman, L. M., Cotton, F. A., Eds.; Academic: New York, 1975; Chapter 14.

(42) Sternhell, S. In ref 41, Chapter 6.

(43) Kessler, H. *Angew. Chem.* 1970, 82, 237–53; *Angew. Chem., Int. Ed. Engl.* 1970, 9, 219–35. Stewart, W. E.; Siddall, T. H., III *Chem. Rev.* 1970, 70, 517–51.

(44) Bottini, A. T.; Roberts, J. D. *J. Am. Chem. Soc.* 1958, 80, 5203–8. Lambert, J. B. *Top. Stereochem.* 1971, 6, 19–105.