

# The Origin of the Anisochronism of Geminal Groups in Conformationally Mobile Systems. I. Intrinsically Diastereotopic Nuclei<sup>1</sup>

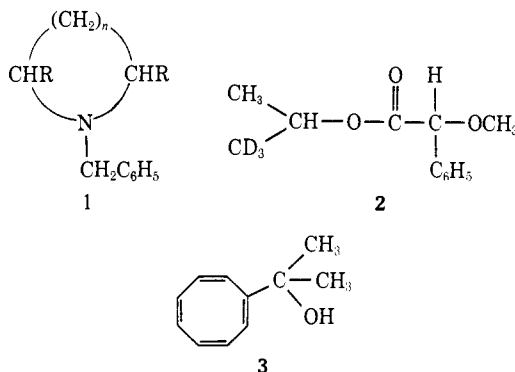
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**Abstract:** A formal analysis of the origin of the chemical shift nonequivalence (anisochronism) of two identical geminal groups G attached to a tetragonal center in the nmr spectra of molecules undergoing rapid conformational equilibrations reveals that for compounds satisfying certain symmetry requirements the only term contributing to the anisochronism is the so-called intrinsic term, which is independent of conformer populations around a central single bond. It is shown that these symmetry requirements are met by two classes of compounds, characterized by the general formulas  $\text{RCG}_2\text{CX}_3$  (class A), where X is a chiral ligand of a definite configuration, and  $(\text{RCG}_2)_3\text{CCXYZ}$  (class B). Model compounds of type A, which proved suitable for a study of the differential response of various groups G to the intrinsic effect, were obtained by controlled oxidation of derivatives of the 2,6,7-trithiabicyclo[2.2.2]octane system, the general features of which are described in some detail. Bridgehead-substituted derivatives of 3,5,7-trimethyladamantane, chosen as models for class B compounds, lent themselves to an elucidation of the structure, temperature, and solvent dependence of the magnitude of the intrinsic anisochronism of geminal protons.

The observation of unequal time-averaged chemical shifts for identical geminal nuclei or groups of nuclei initially appeared to represent a rare and puzzling anomaly in nmr spectroscopy, but must now be regarded as a commonly encountered and, after passing through several stages of misinterpretation, also reasonably well-understood phenomenon.<sup>5</sup> The recognition of this effect is of crucial importance in structure elucidations by nmr spectroscopy and has in addition been put to practical advantage in a number of novel applications, highlighted by the following three examples. (1) The stereochemistry of  $\alpha, \alpha'$ -disubstituted



cyclic amines of the type **1**, which would be quite tedious to determine in general by conventional means, is simply and unequivocally established if one member of the pair of diastereomers shows an AB pattern for the benzyl methylene protons, identifying this member as

the trans isomer, whereas in the cis compound the benzyl methylene protons must necessarily be isochronous.<sup>6</sup> (2) The effect has been ingeniously exploited for a facile quantitative determination of optical purity in compounds owing their chirality to isotopic substitution, such as in the 2-propanol-*d*<sub>3</sub> residue of **2**.<sup>7</sup> (3) Anisochronous geminal groups are often employed as sensor nuclei for the quantitative study of intramolecular rate processes by dynamic nmr spectroscopy. The cyclooctatetraene ring reversal, brought to light by the dimethylcarbinol substituent in **3**, serves as an intriguing case in point.<sup>8</sup>

Stated most concisely, the necessary condition for geminal groups to be anisochronous is that they are diastereotopic<sup>9</sup> on the time scale of the measurement. In the present context we shall be concerned with the situation where rotation about a central single bond is fast on the nmr time scale, either in reality or in imagination, which means that we are interested in time-averaged parameters. According to Gutowsky<sup>10</sup> the chemical shift difference  $\langle \Delta \rangle$  between the geminal groups may then be partitioned into a "conformational" term  $\langle \Delta \rangle_c$  depending on differences of conformer populations around the central single bond and an "intrinsic" term  $\langle \Delta \rangle_i$  that is independent of these conformer populations. Knowledge about the relative magnitudes and signs of these two terms is indispensable if one intends to exploit such time-averaged chemical shift differences for the conformational analysis of open-chain compounds, but in spite of the great activity in this field and the inherent interest of such studies for biomolecules, unambiguous information of this kind is virtually nonexistent.

We now wish to report on two general modes of at-

(1) Preliminary communication: G. Binsch and G. R. Franzen, *J. Amer. Chem. Soc.*, **91**, 3999 (1969).

(2) Taken in part from the Ph.D. dissertation of G. R. Franzen, University of Notre Dame, 1971.

(3) Alfred P. Sloan Research Fellow.

(4) The Radiation Laboratory is operated by the University of Notre Dame under contract with the U. S. Atomic Energy Commission. This is AEC Document No. COO-38-801.

(5) For reviews, see M. L. Martin and G. J. Martin, *Bull. Soc. Chim. Fr.*, 2117 (1966); M. van Gorkom and G. E. Hall, *Quart. Rev., Chem. Soc.*, **22**, 14 (1968); T. H. Siddall and W. E. Stewart, *Progr. Nucl. Magn. Resonance Spectrosc.*, **5**, 33 (1969).

(6) R. K. Hill and T. H. Chan, *Tetrahedron*, **21**, 2015 (1965); D. G. Pucci, Ph.D. Thesis, University of Notre Dame, 1971.

(7) M. Raban and K. Mislow, *Tetrahedron Lett.*, 3961 (1966); *Top. Stereochem.*, **2**, 199 (1967).

(8) F. A. L. Anet, A. J. R. Bourn, and Y. S. Lin, *J. Amer. Chem. Soc.*, **86**, 3576 (1964).

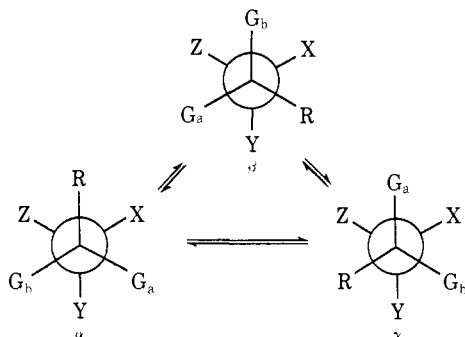
(9) K. Mislow and M. Raban, *Top. Stereochem.*, **1**, 1 (1967).

(10) H. S. Gutowsky, *J. Chem. Phys.*, **37**, 2196 (1962).

tack to this problem. In the present paper we are concerned with model compounds in which the anisochronism is exclusively intrinsic. In the accompanying paper<sup>11</sup> we use low-temperature fluorine chemical shifts of frozen conformers for calculating both  $\langle\Delta\rangle_e$  and  $\langle\Delta\rangle_i$ , adopting an approach that was first applied by Raban<sup>12</sup> to the nmr data of Newmark and Sederholm<sup>13</sup> on  $\text{BrCF}_2\text{CFBrCl}$  and  $\text{BrCF}_2\text{CHBrCl}$ .

### Formal Analysis

We begin with a brief summary of Gutowsky's<sup>10</sup> analysis, which applies to all those molecules whose essential structural features are formally derivable from a central ethane framework by substitution.



Consider the three rapidly equilibrating conformers  $\alpha$ ,  $\beta$ ,  $\gamma$  with populations  $p_\alpha$ ,  $p_\beta$ ,  $p_\gamma$ . For  $R \neq G$ , the system is characterized by six different chemical shifts for G, and the time-averaged chemical shift difference may be written as

$$\langle\Delta\rangle = \sum_{j=\alpha,\beta,\gamma} p_j (\nu_a - \nu_b)_j = \sum_{j=\alpha,\beta,\gamma} p_j \Delta_j \quad (1)$$

whereas for  $R = G$  the pairwise identities of the chemical shifts,  $\nu_\alpha^a = \nu_\gamma^b$ ,  $\nu_\alpha^b = \nu_\beta^a$ ,  $\nu_\beta^b = \nu_\gamma^a$ , and the symmetry-imposed restriction on the populations,  $p_\alpha = p_\beta = p_\gamma = 1/3$ , ensure that  $\langle\Delta\rangle = 0$ . Denoting the chemical shift difference in a particular conformer  $j$  of the system having  $R = G$  by  $\Delta_j^0$  and the change in this quantity induced on making  $R \neq G$  by  $\Delta_j'$ , Gutowsky<sup>10</sup> has shown that eq 1 can be reformulated as

$$\langle\Delta\rangle = \sum_j (p_j - 1/3) \Delta_j^0 + \sum_j (p_j - 1/3) \Delta_j' + \sum_j \Delta_j' / 3 \quad (2)$$

which may be partitioned into

$$\langle\Delta\rangle = \langle\Delta\rangle_e + \langle\Delta\rangle_i \quad (3)$$

where

$$\langle\Delta\rangle_e = \sum_j (p_j - 1/3) \Delta_j^0 + \sum_j (p_j - 1/3) \Delta_j' = \sum_j (p_j - 1/3) \Delta_j \quad (4)$$

stands for the population-dependent conformational and

$$\langle\Delta\rangle_i = \sum_j \Delta_j' / 3 \quad (5)$$

for the population-independent intrinsic contribution.

The following conclusions emerge from this analysis.

(1) The intrinsic term only depends on the changes in

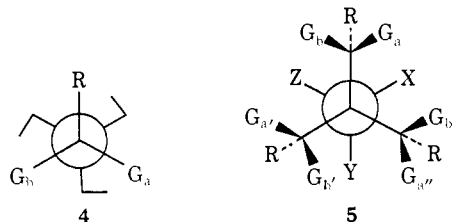
(11) R. D. Norris and G. Binsch, *J. Amer. Chem. Soc.*, **95**, 182 (1973).

(12) M. Raban, *Tetrahedron Lett.*, 3105 (1966).

(13) R. A. Newmark and C. H. Sederholm, *J. Chem. Phys.*, **39**, 3131 (1963); **43**, 602 (1965).

the chemical shifts induced by the substituent R. Hence, if with the purpose of essentially eliminating the conformational term one were to choose an R very similar to G, as, for example, a different isotope, the intrinsic term would likewise be minimized, and such a trick would then only amount to throwing the child out with the bath water. This reasoning, as already pointed out by Gutowsky,<sup>10</sup> invalidates an early claim<sup>14</sup> based on an experiment purportedly showing that the intrinsic term should be negligible. Conversely, in order to maximize  $\langle\Delta\rangle_i$  one should utilize a substituent R whose introduction is likely to cause substantial distortions of the molecule. (2) The formal analysis clearly shows that  $\langle\Delta\rangle_e$  and  $\langle\Delta\rangle_i$  may differ in relative sign, a property for which we shall adduce experimental examples in paper II of this series,<sup>11</sup> but this fact seems to have been universally overlooked by previous workers.<sup>5,15</sup> In particular, it means that  $\langle\Delta\rangle_e$  and  $\langle\Delta\rangle_i$  are both of substantial magnitude. (3) It has frequently been stated, in research papers as well as in review articles, that  $\langle\Delta\rangle_e$  and  $\langle\Delta\rangle_i$  always occur lumped together, but that  $\langle\Delta\rangle_i$  could be extracted from extrapolations to high temperature. The former statement is false, as will be shown presently, and the latter rests on three unproven assumptions: first, conformer populations tend toward equality on increase of the temperature only if entropy differences are zero; second, the extrapolation procedure tacitly assumes that  $\langle\Delta\rangle_i$  itself is independent of temperature; third, chemical shift measurements can in practice only be carried out over a limited temperature range, and extrapolations rely on the hypothesis of a monotonic behavior of the measured quantity as a function of temperature, but since  $\langle\Delta\rangle_e$  and  $\langle\Delta\rangle_i$  may differ in sign, such a monotonic behavior is by no means guaranteed.

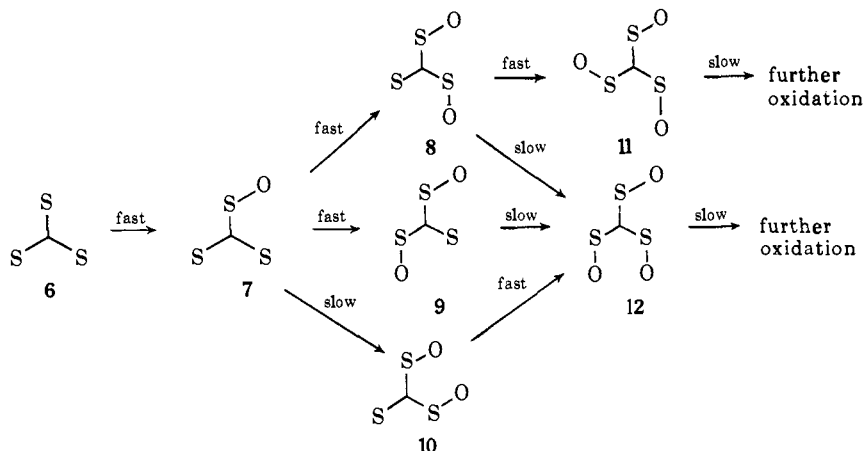
While it is indeed logically impossible to construct molecules that would only exhibit conformational but not intrinsic anisochronism for geminal groups, the reverse is not true. There are in fact two general possibilities for realizing this goal. The first type of model compound, referred to as class A, is characterized by the general formula  $\text{RCG}_2\text{CX}_3$ , with X being a chiral substituent of a definite configuration; the isolated moiety  $-\text{CX}_3$ , in which the empty bond may be regarded as a phantom atom, must therefore belong to the  $C_3$  symmetry point group. This kind of molecule can perhaps best be visualized by way of the "windmill" or "propeller" symbol of **4**. The second, referred to as class B, must conform to the general formula  $(\text{RCG}_2)_3\text{-CCXYZ}$  and is represented by **5**. A few examples fall-



(14) G. M. Whitesides, F. Kaplan, K. Nagarajan, and J. D. Roberts, *Proc. Nat. Acad. Sci. U. S.*, **48**, 1112 (1962).

(15) For two recent instances, see M. I. Foreman, R. Foster, and M. J. Strauss, *J. Chem. Soc. B*, 147 (1970); J. Bergman, *Tetrahedron*, **27**, 1167 (1971).

Chart I



ing into the latter class, which was first suggested by Mislow and Raban<sup>9</sup> as a possibility, have recently been reported.<sup>16</sup> The feature common to classes A and B is that they may both be thought of as consisting of two moieties joined together by a single bond (the "central" single bond), such that this bond represents a threefold degenerate axis of internal rotation, thereby enforcing conformer populations of exactly 1/3. One of the moieties must be chiral by itself, the other must contain two groups of sensor nuclei that are being placed into diastereotopic environments on juncture to the chiral moiety.<sup>17</sup> The two classes A and B differ in that in 4 the time-averaged chemical shift difference  $\langle \Delta \rangle = \langle \Delta \rangle_i$  is equal to the chemical shift difference  $\Delta$  in each of the three stable conformations, whereas 5 shows six different chemical shifts for G in a frozen conformer that average out to the intrinsic chemical shift difference on rapid rotation.

## Results and Discussion

**Class A.** 4-Methyl-2,6,7-trithiabicyclo[2.2.2]octane<sup>18</sup> (**13a**) was chosen as the common precursor for the preparation of model compounds in class A. This choice was motivated by the known fact<sup>19</sup> that **13a** can be substituted at the bridgehead position *via* the lithium derivative **13b** and the expectation that the stereochemistry of the corresponding trisulfoxides should be easy to determine by nmr. Furthermore, since a very complex reaction mixture had to be anticipated on oxidation of ortho thioesters, practical success depended on the ability to steer the reaction in the desired direction. For acyclic analogs the formation of the propeller trisulfoxide is kinetically disfavored with respect to the

(16) J. McKenna, J. M. McKenna, and B. A. Wesby, *Chem. Commun.*, 867 (1970).

(17) In our preliminary communication,<sup>1</sup> we stated that the two groups of sensor nuclei must be enantiotopic in the absence of the chiral moiety. This condition implies that the moiety containing the sensor nuclei is itself achiral, and does therefore not apply to certain special situations where this is not the case. In the molecule  $(X_R)_3CCG_2C(X_S)_3$ , for instance, the intrinsically diastereotopic groups G are already (intrinsically) diastereotopic before the second chiral moiety is joined on. At the same time we wish to point out that the combination of a threefold degenerate axis of internal rotation and overall chirality is neither a necessary nor a sufficient requirement for intrinsic anisochronism. The hypothetical molecule just mentioned as well as  $(RCG)_3CCXYC(CG_2R)_3$  are achiral but contain intrinsically diastereotopic groups, whereas in the chiral molecule  $(X_R)_3CCG_2C(X_R)_3$  the groups G are homotopic and thus isochronous.

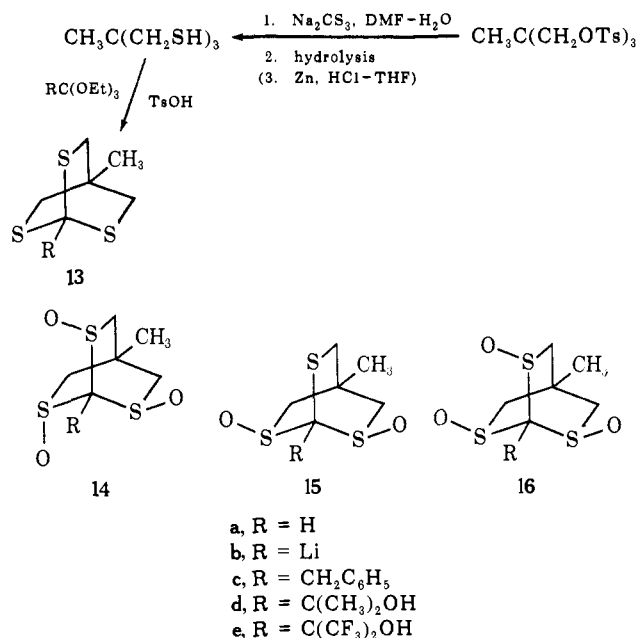
(18) W. von E. Doering and L. K. Levy, *J. Amer. Chem. Soc.*, 77, 509 (1955).

(19) D. Seebach, *Angew. Chem.*, 79, 468 (1967); *Angew. Chem., Int. Ed. Engl.*, 6, 442 (1967).

"anti-propeller" (symbolized by 12 in Chart I) of unwanted stereochemistry by a statistical factor of 3, disregarding asymmetric induction. We speculated that with more rigid bicyclic analogs steric and electronic effects should control the relative oxidation rates as indicated schematically in Chart I, so that of the 11 possible oxidation products (not counting enantiomers) 9 and 11 be formed preferentially. As it turned out, this reasoning proved to be substantially correct.

Since our attempts to scale up the published procedure<sup>15</sup> for the preparation of **13a** invariably resulted in very low yields, we were led to the alternative route outlined in Chart II, which takes advantage of the re-

Chart II



cently introduced<sup>20</sup> use of sodium trithiocarbonate in efficient thiol syntheses. The best yields of **13a** were obtained when the reaction with triethyl orthoformate was carried out in the absence of a solvent. The lithium derivative **13b**<sup>19</sup> yielded **13c** on treatment with benzyl chloride, and **13d** and **13e** on addition to acetone and hexafluoroacetone, respectively.

The method of choice for the oxidation proved to be the addition of 3 equiv of hydrogen peroxide in formic

(20) D. J. Martin and C. C. Greco, *J. Org. Chem.*, 33, 1275 (1968).

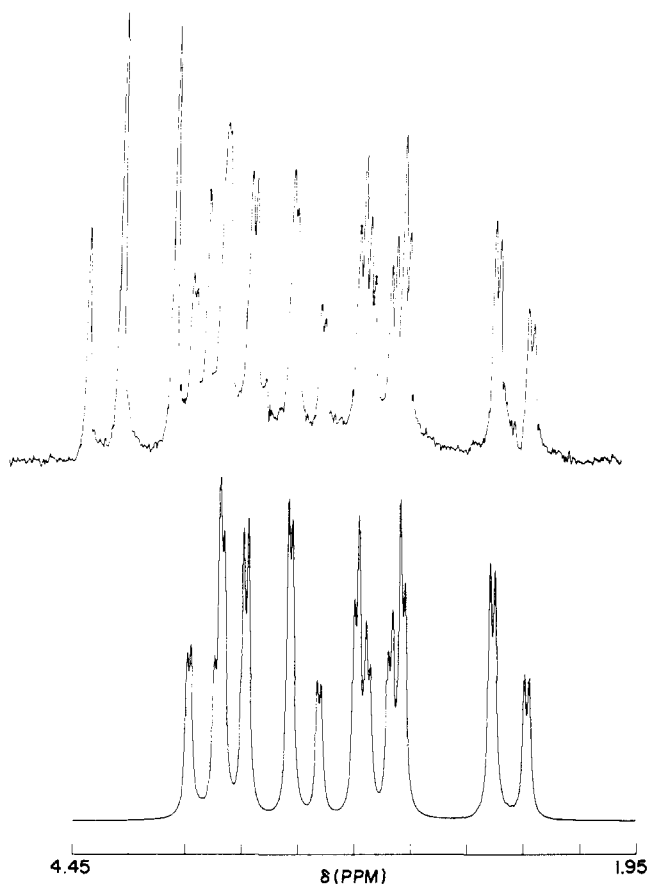
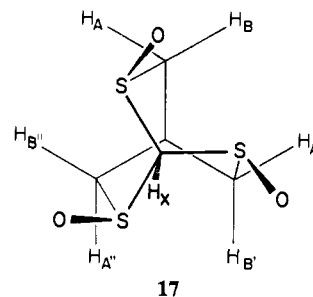


Figure 1. (a) Upper trace: section of the proton nmr spectrum of **16c** in  $\text{CDCl}_3$  at 100 MHz. (b) Lower trace: ABCDEF sub-pattern computed with  $\delta_A$  2.57 ppm,  $\delta_B$  3.10 ppm,  $\delta_C$  3.17 ppm,  $\delta_D$  3.48 ppm,  $\delta_E$  3.78 ppm,  $\delta_F$  3.90 ppm,  $J_{AB} = (-)15.2$  Hz,  $J_{AE} = (-)2.5$  Hz,  $J_{BC} = (-)2.2$  Hz,  $J_{CF} = (-)14.8$  Hz,  $J_{DE} = (-)12.9$  Hz,  $J_{DF} = (-)1.9$  Hz,  $J_{AC} = J_{AD} = J_{AF} = J_{BD} = J_{BE} = J_{BF} = J_{CD} = J_{CE} = J_{EF} = 0$ .

acid to a stirred slurry of **13** in formic acid at room temperature or  $0^\circ$ . The results depend on how long one allows the resulting homogeneous solution to stand before work-up. After 2 hr the isolated material consisted of three major components, I–III, in all cases. The nmr spectra of the crude product mixtures obtained on oxidation of **13a,c–e** are so similar as to leave little doubt that one is dealing with analogous mixtures of components throughout the series. The component ratio could be determined in the a series from integration of the well-separated bridgehead proton resonances, yielding I:II:III = 1:0.65:0.65. After 12 hr the ratio had changed to I:II:III = 1:1.2:0, indicating that III is a precursor of II.

In all cases a single component, I, could be separated and purified by recrystallizations, and it fortunately proved to be that having the desired propeller stereochemistry **14**. Because of the very low solubility of the oxidation products derived from **13a,d,e** in all solvents, preparative chromatography was rendered impractical in these cases but succeeded in the c series, which we will therefore take as representative in the discussion of the spectral and chemical evidence for the proposed structures. Additional information extracted from the spectra of mixtures can be found in the Experimental Section.

The most characteristic feature in the proton nmr spectra of I is the  $[\text{AB}]_3$  pattern<sup>21</sup> observed for the ring methylene protons, which is only consistent with the propeller structure **14**. The ir spectra show the expected presence of sulfoxide and absence of sulfone bands. The experimental  $[\text{AB}]_3$  pattern of **14c** is matched by a theoretical spectrum computed with  $\delta_A$  2.74 ppm,  $\delta_B$  3.92 ppm,  $J_{AB} = (-)14.3$  Hz,  $J_{AB'} = (-)2.2$  Hz,  $J_{AB''} = J_{AA'} = J_{BB'} = 0$ . An additional long-range coupling,  $J_{AX} = 1.2$  Hz, to the bridgehead proton shows up in the  $[\text{AB}]_3\text{X}$  pattern of **14a**. The two large four-bond coupling constants in **14a**, together with the zero values observed for  $J_{AB''}$  and  $J_{BX}$ , strongly suggest the twisted geometry **17**, in which the



nuclei A and B' as well as A and X are connected by a planar or nearly planar zigzag bond path, a situation well known<sup>23</sup> to be favorable for the effective transmission of nuclear spin information through  $\sigma$  electrons. The direction of the twist is in accord with the expected release of steric strain and leads to the assignments of the proton chemical shifts as shown.

The component II in the c series was found to be isomeric with **14c**, and since its ir spectrum does not show strong bands in the regions expected for sulfones it most likely has the structure **16c**. This conclusion is corroborated by the 100-MHz nmr spectrum, showing an ABCDEF pattern superposed on an AB (Figure 1a), the complete analysis of which presented no difficulties (Figure 1b). The characteristic range of the chemical shifts of the six coupled protons and the peculiar combination of geminal and long-range coupling constants (Figure 1) establish structure **16c** beyond reasonable doubt. A lengthy argument can be made<sup>2</sup> that leads to an assignment of all protons in this molecule, but it is not judged sufficiently relevant to be reproduced in this paper. It should be mentioned, however, that the chemical shift difference of 0.35 ppm between the diastereotopic benzyl methylene protons, which give rise to the AB spectrum of Figure 1a, necessarily also contains a conformational contribution in this case.

A symmetrical disulfoxide structure must be assigned to the third major component III. This follows from the elemental analysis, from the absence of sulfone bands in the ir, and from the nmr displaying singlets at  $\delta$  2.51 for two ring methylene and at  $\delta$  3.88 for the benzyl methylene protons, and an AB pattern corresponding to four protons with  $\delta$  3.27 and 3.54 and  $J_{AB} = (-)14.0$  Hz, whose upfield part is broadened by a small long-range coupling to the ring methylene singlet. As a further confirmation, the nmr spectrum of a sample

(21) The notation of Haigh<sup>22</sup> is adopted throughout this paper.

(22) C. W. Haigh, *J. Chem. Soc. A*, 1682 (1970).

(23) S. Sternhell, *Quart. Rev., Chem. Soc.*, 23, 236 (1969).

in trifluoroacetic acid slowly disappeared on addition of a drop of hydrogen peroxide, to be replaced by that of **16c**. Of the two remaining possibilities, structure **15c** is favored on the basis of the kinetic scheme of Chart I. Further support comes from the fact that the unresolved long-range coupling is to the upfield portion of the AB pattern, which is consistent with the shielding effects in **15c**, but would be expected to be the reverse in a symmetrical disulfoxide containing the structural element **10**.

At 60 MHz the benzyl methylene protons in **14c** give rise to a singlet, whose line width is about 0.3 Hz in excess of the field-inhomogeneity line width. This residual broadening is removed by double irradiation of the aromatic protons. The spectra recorded at 220 MHz<sup>24</sup> or in the presence of 0.50 equiv of the shift reagent Eu(DPM)<sub>3</sub>,<sup>25</sup> which displaces the resonance by 4.8 ppm to lower field, likewise failed to reveal a chemical shift difference. The intrinsic anisochronism is detectable in **14d**, where the methyl resonance of the dimethylcarbinol substituent is split into a doublet, whose separation is a linear function of the magnetic field strength and is found to depend on solvent: 0.038 ppm in pyridine, 0.020 ppm in DMSO, 0.007 ppm in D<sub>2</sub>O, and <0.003 ppm in CDCl<sub>3</sub>. As expected from the known higher sensitivity of fluorine as a sensor nucleus, the intrinsic anisochronism in **14e** is about one order of magnitude larger than in **14d**. The tightly coupled A<sub>3</sub>B<sub>3</sub> pattern (Figure 2a) observed for **14e** in DMSO at 56.4 MHz yielded  $\langle\Delta\rangle_i = 0.282$  ppm and  $J_{AB} = 12.3$  Hz on computer analysis (Figure 2b). The isotropic spin-spin coupling exhibited in the A<sub>3</sub>B<sub>3</sub> pattern of the latter compound establishes beyond doubt that the chemical shift difference is indeed due to two geminal groups in one molecule and cannot be attributed to diastereomeric associates in solution.

The unobservably small intrinsic anisochronism in **14c** is clearly not a consequence of the differential shielding effect of a sulfoxide group being negligible, since this effect manifests itself quite prominently in the nmr of the ring methylene protons in **14**, **15**, and **16** as well as in the benzyl methylene protons of **16c**, but must be attributed to the small change  $\Delta'$  induced by the phenyl substituent. One might have suspected that the larger  $\langle\Delta\rangle_i$  observed for **16d** is mainly caused by some preferred mode of intramolecular hydrogen bonding of the hydroxyl substituent, but this hypothesis does not seem to be borne out by the solvent effect; the intrinsic chemical shift difference is at a maximum in pyridine, which should most strongly favor intermolecular over intramolecular hydrogen bonding. The difference between **14c** and **14d** is more likely due largely to the fact that the sensor nuclei are one additional bond removed from the sulfoxide groups in **16d**. One (or two) of the three methyl hydrogens thus gets "folded back" toward the bicyclic moiety, which causes the methyl protons to experience the time-averaged differential shielding effect of the sulfoxide groups more strongly than the benzyl methylene protons in **16c**. That the magnitude of the *total* anisochronism is not a monotonic function of the number of bonds separating the geminal groups from the dissymmetric environment, but

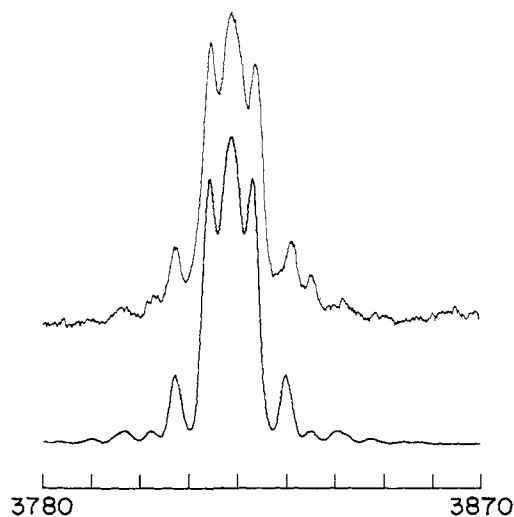
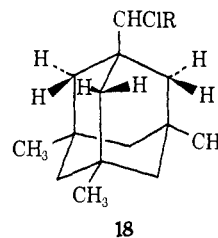


Figure 2. (a) Upper trace: fluorine nmr spectrum of **14e** in DMSO at 56.4 MHz. (b) Lower trace: computed spectrum; the scale is in Hz upfield from internal CFCl<sub>3</sub>.

goes through a maximum for  $n = 5$ , has previously been noticed in a series of open-chain compounds.<sup>26</sup>

**Class B.** A search of the literature revealed that a compound, **18a**, satisfying the structural requirements of class B models had already been described,<sup>27</sup> but its nmr spectrum was not reported. The three methyl substituents prove particularly convenient, since they insulate the spin system of interest, and the carboxyl ligand can easily be functionalized. The derivatives **18b-j** were prepared by standard methods. Reaction of the thallium salt of **18a** with bromine produced **18k**.



- |  |   |
|--|---|
| a, R = COOH                                | g, R = COOCH(CH <sub>3</sub> ) <sub>2</sub>                                 |
| b, R = COCl                                | h, R = COOCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>                     |
| c, R = COOC <sub>6</sub> H <sub>5</sub>    | i, R = COC <sub>6</sub> H <sub>4</sub> OCH <sub>3</sub> <sup><i>m</i></sup> |
| d, R = COOC(CH <sub>3</sub> ) <sub>3</sub> | j, R = CON(CH <sub>3</sub> ) <sub>2</sub>                                   |
| e, R = COOCH <sub>3</sub>                  | k, R = Br   |
| f, R = COOC <sub>2</sub> H <sub>5</sub>    |   |

The nmr spectra all display a broadened AB-type pattern with  $J_{AB} = (-)12.7 \pm 0.4$  Hz for the six protons explicitly marked in **18**, the broadening presumably arising from unresolved long-range couplings in the [AB]<sub>3</sub> spin system. The other six methylene protons absorb as a singlet at higher field. The time-averaged intrinsic chemical shift differences measured at 60 MHz in two solvents are shown in Table I. Because of the broadening, the precision of the numbers is only about  $\pm 0.3$  Hz. Compound **18a** was selected for a more detailed investigation of solvent and temperature effects. The results are listed in Table II, together with the corresponding dielectric constants.

The following features are noteworthy. (1) The in-

(24) We are indebted to Dr. A. A. Lamola of Bell Telephone Laboratories for this experiment.

(25) C. C. Hinckley, *J. Amer. Chem. Soc.*, **91**, 5160 (1969).

(26) G. M. Whitesides, D. Holtz, and J. D. Roberts, *J. Amer. Chem. Soc.*, **86**, 2628 (1964).

(27) K. Bott, *Angew. Chem.*, **79**, 943 (1967); *Angew. Chem., Int. Ed. Engl.*, **6**, 946 (1967).

**Table I.** Intrinsic Anisochronism at 60 MHz

Compd	$\langle \Delta \rangle_i$ , Hz		Compd	$\langle \Delta \rangle_i$ , Hz	
	CDCl <sub>3</sub>	C <sub>6</sub> H <sub>6</sub>		CDCl <sub>3</sub>	C <sub>6</sub> H <sub>6</sub>
<b>18a</b>	10.4	12.0	<b>18g</b>	15.1 <sup>a</sup>	17.4
<b>18b</b>	9.7	12.7	<b>18h</b>	15.2	17.4
<b>18c</b>	13.6	15.2	<b>18i</b>	15.0	18.4
<b>18d</b>	13.6	15.5	<b>18j</b>	17.6	22.8
<b>18e</b>	14.5	17.1	<b>18k</b>	<3.5	<3.5
<b>18f</b>	14.8 <sup>a</sup>	16.8			

<sup>a</sup> Higher uncertainty of about  $\pm 1.0$  Hz due to overlap with other parts of the spectrum.

**Table II.** Intrinsic Anisochronism of **18a** at 60 MHz as a Function of Solvent and Temperature

Solvent	$\epsilon^a$	$\langle \Delta \rangle_i$ , Hz	Solvent	$\epsilon^a$	$\langle \Delta \rangle_i$ , Hz
Dioxane	2.21	11.8	<i>o</i> -Dichlorobenzene	9.93	10.9
Carbon tetrachloride	2.24	11.2	Pyridine	12.3	12.8
Benzene (39.5°)	2.244 <sup>b</sup>	12.0	Acetophenone	17.93	11.4
Benzene (61.0°)	2.204 <sup>b</sup>	11.6	Acetone- <i>d</i> <sub>6</sub>	20.7	10.4
Benzene (79.5°)	2.164 <sup>b</sup>	11.2	Benzonitrile	25.2	10.4
Benzene (100.5°)	2.13 <sup>c</sup>	10.8	Methanol	32.63	9.9
Chloroform- <i>d</i>	4.80	10.4	Nitrobenzene	34.82	10.0
Bromobenzene	5.40	10.7	Acetonitrile- <i>d</i> <sub>3</sub>	38.82	10.4
Methylene chloride	9.08	8.5	Dimethyl- <i>d</i> <sub>6</sub> sulfoxide	48.9	9.7

<sup>a</sup> "Handbook of Chemistry and Physics," 51st ed, The Chemical Rubber Co., Cleveland, Ohio, 1970-1971. <sup>b</sup> S. O. Morgan and H. H. Lowry, *J. Chem. Phys.*, **34**, 2385 (1932). <sup>c</sup> Extrapolated value.

trinsic anisochronism in **18a-j** is certainly not negligible; it is in fact of the same order of magnitude as that commonly observed for the total anisochronism of geminal protons in general.<sup>5</sup> The numbers are rather insensitive to the size of the alkyl groups in the ester derivatives, suggesting preferred conformations with the alkyl groups pointing away from the bicyclic moiety, but change more significantly on modification of the group directly attached to the carbonyl carbon and drastically on replacement of the carbonyl function by a rotationally symmetric halogen ligand. These trends indicate that proximity effects are of essential importance, which is in line with the explanation proposed for the difference between **14c** and **14d**. (2) The intrinsic chemical shift difference is consistently larger in benzene than in chloroform, following a roughly parallel trend throughout the series of compounds (Table I). This finding again mirrors the behavior of the total anisochronism most frequently encountered<sup>5</sup> and demonstrates that the origin of the "benzene effect" is at least partially, if not mainly, intrinsic. But whereas a previous systematic study of solvent effects on the magnitude of the total anisochronism<sup>28</sup> uncovered an approximate inverse correlation with dielectric constants, the dependence of  $\langle \Delta \rangle_i$  on solvent is appreciably weaker, albeit not negligible, and does not exhibit any clear-cut relationship to the dielectric properties of the medium (Table II). (3) The data of Table II attest to the view that the assumption of a temperature-independent intrinsic anisochronism cannot always be valid. The value for **18a** in benzene changes by 10% over a temperature range of 60°. Any such change will be superposed on the temperature dependence attributed to changes in conformer populations in the general case and could falsify the conclusions drawn from such studies. Attempts to obtain the intrinsic

(28) G. M. Whitesides, J. J. Grocki, D. Holtz, H. Steinberg, and J. D. Roberts, *J. Amer. Chem. Soc.*, **87**, 1058 (1965).

effect by extrapolation<sup>5,29</sup> must therefore be viewed with suspicion, an inference further strengthened by other experimental evidence gathered in our laboratory.<sup>11</sup>

### Conclusion

With the results of the present study we now possess the definite *knowledge* that the magnitude of the intrinsic anisochronism of geminal groups may indeed be negligibly small, but sometimes also surprisingly large. It is of interest, therefore, to speculate as to

which of the classes, A or B, is likely to be a more representative model for the numerous compounds investigated so far. It would appear that the prize must go to class B. For in class A we start with  $\Delta_j^0 = 0$  and the highly regular arrangement of the three identical chiral centers militates against the probability of introducing a large differential effect by the substituent R. In class B, however, finite chemical shift differences are already present for R = G, just as in the general case, and the inherent geometric and/or magnetic disparity at the chiral (or prochiral) center should more easily be capable of causing large chemical shift changes on introduction of R, a property also shared by the general case.<sup>30</sup> Exactly how these differential effects average out in time to produce the intrinsic anisochronism  $\langle \Delta \rangle_i$  depends not only on their magnitudes but also on their signs and is clearly very difficult to foresee in general. A large intrinsic term might reasonably be expected to be the norm if structural features permit the possibility of "back bending" so as to bring the chiral (or prochiral) center into close contact with the sensor nuclei and/or the substituent R, whereas in situations where this is impossible, such as in **18k** and in halogenated ethanes,<sup>11</sup> the intrinsic contribution is more likely to be small. It seems probable, however, that the intrinsic anisochronism in **18a-j** is somewhat magnified in comparison with open-chain analogs, since the geometric constraint of the bicyclic structure rigidly holds the sensor nuclei in the most favorable position.

These speculations may be highly suggestive, but are certainly far from conclusive. Although the results in this paper, as far as they go, are entirely free

(29) S. Seltzer and S. G. Mylonakis, *J. Phys. Chem.*, **72**, 754 (1968); G. Redl and G. J. D. Peddle, *ibid.*, **73**, 1150 (1969); J. Dabrowski, A. Ejchart, and W. Biernacki, *Org. Magn. Resonance*, **2**, 311 (1970).

(30) It is to be understood that, strictly speaking, class B molecules are not covered by Gutowsky's original analysis,<sup>10</sup> but the required extension is obvious.

of assumptions, they naturally cannot give a rigorous answer to the question of the *relative* importance of intrinsic and conformational terms in one and the same molecule. And since comparable model studies of the pure conformational term are excluded by logic, this problem can only be solved by the fundamentally different approach to be presented in the succeeding paper.<sup>11</sup>

## Experimental Section

**1,1,1-Trismercaptopmethylethane.** A 33% aqueous solution (720 ml) of sodium trithiocarbonate<sup>20</sup> was slowly added to a solution of 200 g (0.33 mol) of 1,1,1-tristosyloxymethylethane<sup>31</sup> in 1.3 l. of dimethylformamide; the resulting homogeneous mixture was heated under reflux for 6 hr, made acidic with 1.1 l. of 10% sulfuric acid, and extracted with two 1.5-l. portions of chloroform. The chloroform solution was washed with two 3-l. portions of degassed water and, after concentration to 500 ml, again with five 400-ml portions of degassed water. The liquid obtained upon removal of the solvent was dissolved in a mixture of 325 ml of tetrahydrofuran and 90 ml of concentrated hydrochloric acid and stirred with 40 g of zinc amalgam at reflux temperature for 2 hr. The chloroform extract yielded, after thorough washing with degassed water, drying (Na<sub>2</sub>SO<sub>4</sub>), and evaporation of the chloroform, 49.5 g of crude material, judged by vpc and nmr to contain about 10% of an unidentified by-product; the yield is thus estimated to be 78%. The product was used without purification for the subsequent reaction.

**4-Methyl-2,6,7-trithiabicyclo[2.2.2]octane (13a).** A mixture of 5.3 g (36 mmol) of triethyl orthoformate, 6.7 g (36 mmol) of 90% 1,1,1-trismercaptopmethylethane, and 20 mg of *p*-toluenesulfonic acid was subjected to slow distillation, the bath temperature being raised from 80 to 140° over a period of 2 hr, and then to sublimation under reduced pressure. The fraction collected between 150–220° (0.13 mm) yielded 3.7 g (57%) of **13a** upon crystallization from hexane, mp 126–128° (lit.<sup>18</sup> mp 130–131.5°).

**1-Benzyl-2,6,7-trithiabicyclo[2.2.2]octane (13c).** A 1.6 *M* solution (6.7 ml) of *n*-butyllithium in hexane (10.7 mmol) was diluted with 20 ml of dry tetrahydrofuran and added to 1.9 g (10.4 mmol) of **13a** in 10 ml of dry tetrahydrofuran at –78° under nitrogen. Benzyl chloride, 1.3 g (10.4 mmol), in 5 ml of dry tetrahydrofuran was then added over a 10-min period. The solution was stirred for 30 min at –78°, allowed to warm up to room temperature, and quenched with 35 ml of 5% acetic acid. The chloroform extract yielded 2.3 g (83%) of **13c** after recrystallization from carbon tetrachloride: mp 206–207.5°; mass spectrum parent *m/e* 268; nmr  $\delta$  (CDCl<sub>3</sub>) 1.18 (s, 3), 3.00 (s, 6), 3.33 (s, 2), 7.36 (s, 5).

*Anal.* Calcd for C<sub>13</sub>H<sub>16</sub>S<sub>3</sub>: C, 58.16; H, 6.01; S, 35.83. Found: C, 58.02; H, 6.14; S, 35.98.

The product was identical with the sample prepared<sup>32</sup> from 1,1,1-trismercaptopmethylethane and triethyl orthophenylacetate.

**1-(2-Hydroxyisopropyl)-4-methyl-2,6,7-trithiabicyclo[2.2.2]octane (13d)** was prepared in analogy to **13c** from 3.0 g of **13a** and 0.98 g of acetone. The ether extract yielded 3.0 g (75%) of **13d** after recrystallization from hexane: mp 98–100°; mass spectrum parent *m/e* 236; nmr  $\delta$  (CDCl<sub>3</sub>) 1.51 (s, 6), 1.22 (s, 3), 2.48 (s, 1), 2.99 (s, 6).

*Anal.* Calcd for C<sub>9</sub>H<sub>16</sub>S<sub>3</sub>O: C, 45.72; H, 6.82; S, 40.68. Found: C, 45.54; H, 6.85; S, 40.68.

**1-(2-Hydroxyhexafluoroisopropyl)-4-methyl-2,6,7-trithiabicyclo[2.2.2]octane (13e)** was prepared in 24% yield from **13b** and hexafluoroacetone: mp 189–190.5°; mass spectrum parent *m/e* 344; nmr  $\delta$  (CDCl<sub>3</sub>) 1.26 (s, 3), 3.08 (s, 6), 3.58 (s, 1). The fluorine nmr showed a singlet 67.7 ppm upfield from internal CFCl<sub>3</sub>.

*Anal.* Calcd for C<sub>9</sub>H<sub>16</sub>S<sub>3</sub>OF<sub>6</sub>: C, 31.39; H, 2.93; S, 27.93. Found: C, 31.85; H, 3.18; S, 27.66.

**Oxidation of 13c.** To a suspension of 1.5 g (5.6 mmol) of **13c** in 20 ml of formic acid was added, in one portion, 5.6 ml of a 2.94 *M* solution of hydrogen peroxide in formic acid. Most of the solid material had disappeared after 1 hr of stirring at room temperature. After an additional 2 hr, the solvent was stripped off at the rotary evaporator. The residue was digested with 5 ml of absolute ethanol, the solvent stripped off again, and the process repeated four times. The concentrated solution of the solid material in methylene chloride was introduced onto a column prepared from

140 g of alumina (Woelm, neutral, activity 1) packed in chloroform. Of the 40 50-ml fractions collected on elution with chloroform, the combined fractions 2–7 yielded 0.3 g of **14c** after recrystallization from acetone: mp 255° dec; mass spectrum parent *m/e* 316; nmr  $\delta$  (CDCl<sub>3</sub>) 1.54 (s, 3), 4.40 (s, 2), 7.65 (s, 5), [AB]<sub>3</sub> pattern (see text). The ir spectrum (KBr) showed a strong sulfoxide band at 1025 cm<sup>-1</sup>, but no prominent bands around 1150 and 1350 cm<sup>-1</sup>; a sample of 4-methyl-2,6,7-trithiabicyclo[2.2.2]octane 2,2,6,6,7,7-hexaoxide prepared<sup>18</sup> for comparison showed strong sulfone bands at 1148 and 1345 cm<sup>-1</sup>.

*Anal.* Calcd for C<sub>13</sub>H<sub>16</sub>S<sub>3</sub>O<sub>3</sub>: C, 49.34; H, 5.10; S, 30.38. Found: C, 49.57; H, 5.36; S, 29.91.

The combined fractions 10–23 yielded 0.4 g of **16c** on recrystallization from benzene–hexane: mp 192° dec; mass spectrum parent *m/e* 316; ir (KBr) 1040 cm<sup>-1</sup> (s, SO), no prominent bands around 1150 and 1350 cm<sup>-1</sup>; nmr  $\delta$  (CDCl<sub>3</sub>) 1.44 (s, 3), 7.50 (s, 5), AB and ABCDEF patterns (see Figure 1).

*Anal.* Calcd for C<sub>13</sub>H<sub>16</sub>S<sub>3</sub>O<sub>3</sub>: C, 49.34, H, 5.10. Found: C, 49.08; H, 5.10.

The material isolated from fractions 25–40 was recrystallized from ethanol to give 0.1 g of **15c**: mp 238° dec; mass spectrum parent *m/e* 300 (very weak); ir (KBr) 1065 cm<sup>-1</sup> (s, SO), no strong bands around 1150 and 1350 cm<sup>-1</sup>; nmr  $\delta$  (CDCl<sub>3</sub>) 1.33 (s, 3), 7.37 (s, 5), two singlets (2) and an AB (4) pattern (see text).

*Anal.* Calcd for C<sub>13</sub>H<sub>16</sub>S<sub>3</sub>O<sub>2</sub>: C, 51.97; H, 5.37; S, 32.01. Found: C, 52.31; H, 5.55; S, 32.31.

**Oxidation of 13a.** A 1.07 *M* solution (109 ml) of hydrogen peroxide in formic acid was added, with stirring, to 7.0 g (39.2 mmol) of **13a** suspended in 50 ml of formic acid at 0° over a period of 2 hr. Work-up after an additional 2 hr at room temperature gave 8.1 g of a solid, whose nmr in trifluoroacetic acid showed three methine resonances, corresponding to components I–III, at  $\delta$  7.67, 7.03, and 5.70 in the intensity ratio of 1:0.65:0.65. Recrystallizations from water produced 2.0 g (23%) of pure **14a**: mp 330° dec; mass spectrum parent *m/e* 226; ir (Nujol) 1015 cm<sup>-1</sup> (s, SO), no strong bands around 1150 and 1350 cm<sup>-1</sup>; nmr  $\delta$  (CF<sub>3</sub>CO<sub>2</sub>H) 1.65 (s, 3), [AB]<sub>3</sub>X pattern with  $\delta_A = 3.02$  ppm,  $\delta_B = 3.98$  ppm,  $\delta_X = 7.67$  ppm,  $J_{AB} = (-)15.0$  Hz,  $J_{AB'} = (-)2.0$  Hz,  $J_{AX} = 1.2$  Hz,  $J_{AB''} = J_{BX} = J_{AA'} = J_{BB'} = 0$ . (The  $J_{AX}$  coupling constant was extracted from the better resolved spectrum in liquid SO<sub>2</sub>).

*Anal.* Calcd for C<sub>8</sub>H<sub>10</sub>S<sub>3</sub>O<sub>3</sub>: C, 31.84; H, 4.45; S, 42.50. Found: C, 31.98; H, 4.50; S, 42.72.

In a corresponding oxidation, which was worked up after 12 hr, the intensity ratio of the methine resonances was 1:1.2:0.

Recrystallizations failed to yield any other pure components. In the nmr spectra of variously enriched mixtures the lines attributable to component III, **15a**, could clearly be discerned:  $\delta$  (CF<sub>3</sub>CO<sub>2</sub>H) 1.45 (s, 3), 2.62 (s, 2), 5.70 (s, 1), AB pattern (4) with  $\delta_A = 3.47$  ppm,  $\delta_B = 3.89$  ppm,  $J_{AB} = (-)15.0$  Hz. The difference spectrum due to component II showed singlets at  $\delta$  1.64 (3) and 7.03 (1) and a complex pattern between 3 and 4 ppm resembling that of Figure 1.

**Oxidation of 13d.** When **13d** was oxidized by a procedure analogous to that used for **13a**, a 26% yield of **14d** was obtained after recrystallizations from ethyl acetate and methylene chloride. The crystals partially decompose at 70°, resolidify, and decompose again at 330°, indicating a thermal loss of acetone, which is also suggested by the mass spectrum showing a parent peak corresponding to M<sup>+</sup> – 58 at *m/e* 226; ir (Nujol) 1040 cm<sup>-1</sup> (s, SO), nmr  $\delta$  (pyridine) 1.44 (s, 3), 2.28 (s, 3), 2.32 (s, 3), [AB]<sub>3</sub> pattern with  $\delta_A = 2.98$  ppm,  $\delta_B = 4.51$  ppm,  $J_{AB} = (-)14.5$  Hz,  $J_{AB'} = (-)2.1$  Hz,  $J_{AB''} = J_{AA'} = J_{BB'} = 0$ .

*Anal.* Calcd for C<sub>9</sub>H<sub>16</sub>S<sub>3</sub>O<sub>4</sub>: C, 38.01; H, 5.67; S, 33.82. Found: C, 38.53; H, 5.46; S, 33.63.

No other components could be obtained pure. The nmr spectra of mixtures are suggestive of the presence of **15d** and **16d**, but too complex to be unravelled with certainty.

**Oxidation of 13e.** The procedures and results were analogous to those of **13d**, yielding 17% pure **14e** after recrystallizations from chloroform: mp 145° dec; mass spectrum parent *m/e* 392; ir (Nujol) 1051 cm<sup>-1</sup> (s, SO); nmr  $\delta$  (CF<sub>3</sub>CO<sub>2</sub>H) 1.75 (s, 3), [AB]<sub>3</sub> pattern with  $\delta_A = 3.24$  ppm,  $\delta_B = 4.44$  ppm,  $J_{AB} = (-)14.1$  Hz,  $J_{AB'} = (-)1.7$  Hz,  $J_{AB''} = J_{AA'} = J_{BB'} = 0$ ; <sup>19</sup>F nmr, see Figure 2 and text.

**Derivatives of  $\alpha$ -Chloro-3,5,7-trimethyladamantaneacetic Acid (18b–j).** These compounds were prepared by standard procedures and their expected structures confirmed by their ir and nmr spectra. Reaction of **18a**<sup>27</sup> with thionyl chloride gave **18b** in 77% yield: mp 66–67.5°. Compound **18c** was prepared in 48% yield from **18b** and thallos phenoxide by the general procedure of Taylor,

(31) H. Stetter and W. Böckmann, *Chem. Ber.*, **84**, 834 (1951).

(32) We are indebted to Mr. R. C. Jackson for this experiment.

*et al.*:<sup>33</sup> bp 118–120° (0.9 mm). Methylation of **18a** with diazomethane yielded 79% of **18e**: mp 58–59.5°. The esters **18d,f-h** were prepared from **18b** and the corresponding alcohols in pyridine: **18d** (51%, mp 46.5–50°), **18f** (68%, bp 71–73° (0.04 mm)), **18g** (43%, bp 69–71° (0.04 mm)), **18h** (63%, bp 110–125° (0.03 mm)). Acylation of anisole with **18b** in CS<sub>2</sub> (AlCl<sub>3</sub>) produced 43% of **18i**, mp 101–103°. Dimethylamine and **18b** reacted to give 68% of **18j**, mp 73–77°.

**1-Bromochloromethyl-3,5,7-trimethyladamantane (18k)**. The procedure used to prepare **18k** is molded after that described by Taylor, *et al.*<sup>34</sup> One gram (3.7 mmol) of **18a** in 5 ml of petroleum ether was added to 0.92 g (3.7 mmol) of thallos ethoxide in 5 ml of petroleum ether. The thallos carboxylate was collected and

(33) E. C. Taylor, G. W. McLay, and A. McKillop, *J. Amer. Chem. Soc.*, **90**, 2422 (1968).

(34) A. McKillop, D. Bromley, and E. C. Taylor, *J. Org. Chem.*, **34**, 1172 (1969).

recrystallized from 95% ethanol, giving 1.33 g (76%), mp 97–99°. The salt was added to a solution of 0.67 g of bromine in 5 ml of carbon tetrachloride, and the mixture was refluxed under nitrogen for 4 hr. Water was then added, the organic layer washed with sodium bicarbonate solution, and the solvent evaporated. The residue consisted of 50 mg of an oil which slowly crystallized, mp 72–73°. The mass spectrum shows a triplet for the molecular ions at *m/e* 304, 306, and 308 with an intensity ratio of about 36:50:14, which is consistent with the presence of one chlorine and one bromine atom in the molecule. The ir spectrum is devoid of carbonyl bands.

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## The Origin of the Anisochronism of Geminal Groups in Conformationally Mobile Systems. II. Intrinsic and Conformational Contributions in Asymmetric Fluoroethanes

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**Abstract:** Fourteen asymmetrically substituted fluoroethanes were investigated by fluorine nmr spectroscopy (fmr) at ambient and low temperature. They include the ten compounds of the general formula BrCF<sub>2</sub>CXYZ, where the substituents X, Y, Z correspond to all possible combinations of the five ligands hydrogen, fluorine, chlorine, bromine, and phenyl; the remaining four are ClCF<sub>2</sub>CHClPh, ClCF<sub>2</sub>CHBrPh, ClCF<sub>2</sub>CFCIPh, and ClCF<sub>2</sub>CHFI. In 12 of the cases the fmr spectra of all three conformers could be detected at low temperature; for BrCF<sub>2</sub>CHBrPh and BrCF<sub>2</sub>CFCBrPh only two conformers were found to be significantly populated. The simultaneous application of several empirical criteria led to the assignment of each fmr subspectrum to a particular conformer and of each fluorine chemical shift within a subspectrum to a particular fluorine atom in that conformer. With this information it is possible to calculate the magnitudes and absolute signs of the intrinsic and conformational contributions to the total time-averaged anisochronism of the geminal fluorine nuclei at low temperature. It is found that the magnitude of the intrinsic term is in most cases smaller than 1 ppm, whereas the total anisochronism at low temperature covers the range from about –5 to +16 ppm. In six of the cases the intrinsic and conformational terms have opposite signs, thus partially or completely canceling one another.

The only rigorous method for the determination of standard free energy differences between preferred conformations of molecules in solution consists in the *direct* measurement of the conformer concentrations (or strictly speaking, activities) at equilibrium, but conformational analysis would be in poor shape if it were limited by the applicability of this technique. The rapid progress in the alicyclic and heterocyclic field dates from the breakthrough in chemical equilibration studies made possible by the idea<sup>3</sup> of the remote holding group. Since no *indirect* chemical method of comparable power and reliability has so far become known for acyclic systems, the bulk of the information about conformer populations around carbon-carbon single bonds<sup>4</sup> stems from indirect in-

vestigations using a variety of physical techniques, among which nmr spectroscopy now occupies the dominant position. For substituted ethanes in which symmetry restricts the number of diastereomeric conformational isomers to two, the measurement of time-averaged vicinal spin-spin coupling constants seems to represent a fairly promising approach,<sup>4,5</sup> especially when combined with the sophisticated theory of solvent effects recently developed by Abraham,<sup>6</sup> which serves to reduce the remaining uncertainties concerning the validity of the various assumptions to an unavoidable, and sometimes perhaps insignificant, minimum.

Asymmetrically substituted ethanes, in which all

(1) Taken in part from the Ph.D. Dissertation of R. D. Norris, University of Notre Dame, 1971.

(2) Alfred P. Sloan Research Fellow.

(3) S. Winstein and N. H. Holness, *J. Amer. Chem. Soc.*, **77**, 5562 (1955); E. L. Eliel and R. S. Ro, *Chem. Ind. (London)*, 251 (1956).

(4) For reviews, see S. Mizushima, "Structure of Molecules and Internal Rotation," Academic Press, New York, N. Y., 1954; N. Sheppard, *Advan. Spectrosc.*, **1**, 288 (1959); J. P. Lowe, *Progr. Phys. Org. Chem.*, **6**, 1 (1968).

(5) For some recent references, see (a) T. D. Alger, H. S. Gutowsky, and R. L. Vold, *J. Chem. Phys.*, **47**, 3130 (1967); (b) K. K. Deb and R. J. Abraham, *J. Mol. Spectrosc.*, **23**, 393 (1967); (c) G. M. Whitesides, J. P. Sevenair, and R. W. Goetz, *J. Amer. Chem. Soc.*, **89**, 1135 (1967); (d) G. Govil and H. J. Bernstein, *J. Chem. Phys.*, **47**, 2818 (1967); **48**, 285 (1968); (e) F. Heatley and G. Allen, *Mol. Phys.*, **16**, 77 (1969); (f) R. J. Abraham and G. Gatti, *J. Chem. Soc. B*, 961 (1969); (g) L. Cavalli and R. J. Abraham, *Mol. Phys.*, **19**, 265 (1970); (h) R. J. Abraham and R. H. Kemp, *J. Chem. Soc. B*, 1240 (1971).

(6) R. J. Abraham, L. Cavalli, and K. G. R. Pachler, *Mol. Phys.*, **11**, 471 (1966); R. J. Abraham and M. A. Cooper, *J. Chem. Soc. B*, 202 (1967); R. J. Abraham, *J. Phys. Chem.*, **73**, 1192 (1969).