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THE USE OF MID-POINTS OR AVERAGE *NMR* CHEMICAL SHIFTS IN STEREOCHEMICAL ASSIGNMENTS

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Abstract—A comparison of the mid-points or average chemical shifts of mirror-symmetrical spin patterns in the NMR spectra of structural isomers can be used in a straightforward manner to obtain stereochemical information. This result is anticipated from analysis of substituent contributions to chemical shifts and has been observed in a variety of chemical systems, especially cyclobutane derivatives, which comprise a group of compounds for which appreciable data is available and whose structure assignments have often entailed difficulty and even controversy. The method of mid-point comparison may also be useful for conformational analysis.

It would seem, perhaps, that after the more than 15 years of exhaustive study of the NMR spectra of organic compounds, no additional simple observations or features of these spectra remain to be described. However, during the course of structure assignments to the isomeric cyclobutanes resulting from photodimerization of olefins, it was noted that isomers having the same geometry of substitution (see below) had essentially identical mid-points of their symmetrical, but complicated, AA'BB', cyclobutane proton patterns.[1] These mid-points, which have not, to our knowledge, been previously discussed, are read without any calculations directly from the spectra and may be useful in the rapid and straightforward assignment of isomer structure and/or stereochemistry. We describe, first, the derivation of this result on the basis of additivity parameters, and then discuss examples which illustrate the scope, restrictions, and some further ramifications of this kind of analysis.

Proton chemical shift values have been predicted for some chemical systems on the assumption that they are made up of sums of a chemical shift of the basic unsubstituted structure (δ_0) and contributions from substituents (Σs_i). The numerical values of the substituent contributions (s_i) were generally derived from chemical shift data of the available compounds having the same basic structure by a regression analysis.[2,3] Although very useful in many cases this approach failed in compounds where the introduction of substituents caused an alteration in the basic structure, thus changing δ_0, or where the substituents interacted appreciably with one another, changing the s_i's.[2]† Other limitations of this approach are that the addivity parameters, s_i, are available for only a limited number of substituents and chemical systems, and are rarely obtainable by inspection of spectra. For all spectra other than first order, computer analysis is needed to both evaluate chemical shifts and to obtain the substituent additivity parameters.

In this paper we show that in certain cases the sums of some of the chemical shifts in two or more isomeric compounds may be equal when these are estimated by substituent contributions. This is so because each of the contributions in one compound has an equal counterpart in the other compounds. Consequently, the numerical values of the additivity parameters become dispensable and stereochemical relationships between the compounds can be derived from the sums of the chemical shifts directly from their NMR spectra when the spin patterns have mirror-symmetry. Consider, for example, the AA'BB' systems of two compounds **1** and **2** comprising the same basic carbon skeleton but differently substituted: since $\delta_0^{(1)} = \delta_0^{(2)}$ for the basic unsubstituted structure in both compounds, if $\Sigma s^{(1)}_{H_A} + \Sigma s^{(1)}_{H_B} = \Sigma s^{(2)}_{H_A} + \Sigma s^{(2)}_{H_B}$ (the superscripts refer to compounds **1** and **2** and the subscripts refer to protons at carbons having the indicated substituents), then $(\delta_0^{(1)} + \Sigma s^{(1)}_{H_A}) + (\delta_0^{(1)} + \Sigma s^{(1)}_{H_B}) = (\delta_0^{(2)} + \Sigma s^{(2)}_{H_A}) + (\delta_0^{(2)} + \Sigma s^{(2)}_{H_B})$, i.e., $\delta^{(1)}_{H_A} + \delta^{(1)}_{H_B} = \delta^{(2)}_{H_A} + \delta^{(2)}_{H_B}$, or $(\delta^{(1)}_{H_A} + \delta^{(1)}_{H_B})/2 = (\delta^{(2)}_{H_A} + \delta^{(2)}_{H_B})/2$ which is the mid-point of the AA'BB' patterns of both compounds. These mid-points are visually derived diricty from the spectra *even when the chemical shifts are unknown*, since the AA'BB' spin system is mirror symmetrical.

Fig 1 contains 17 possible positional and

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†In the case of ^{13}C NMR, additive relationships have proved to be excellent predictors of chemical shifts.[4]

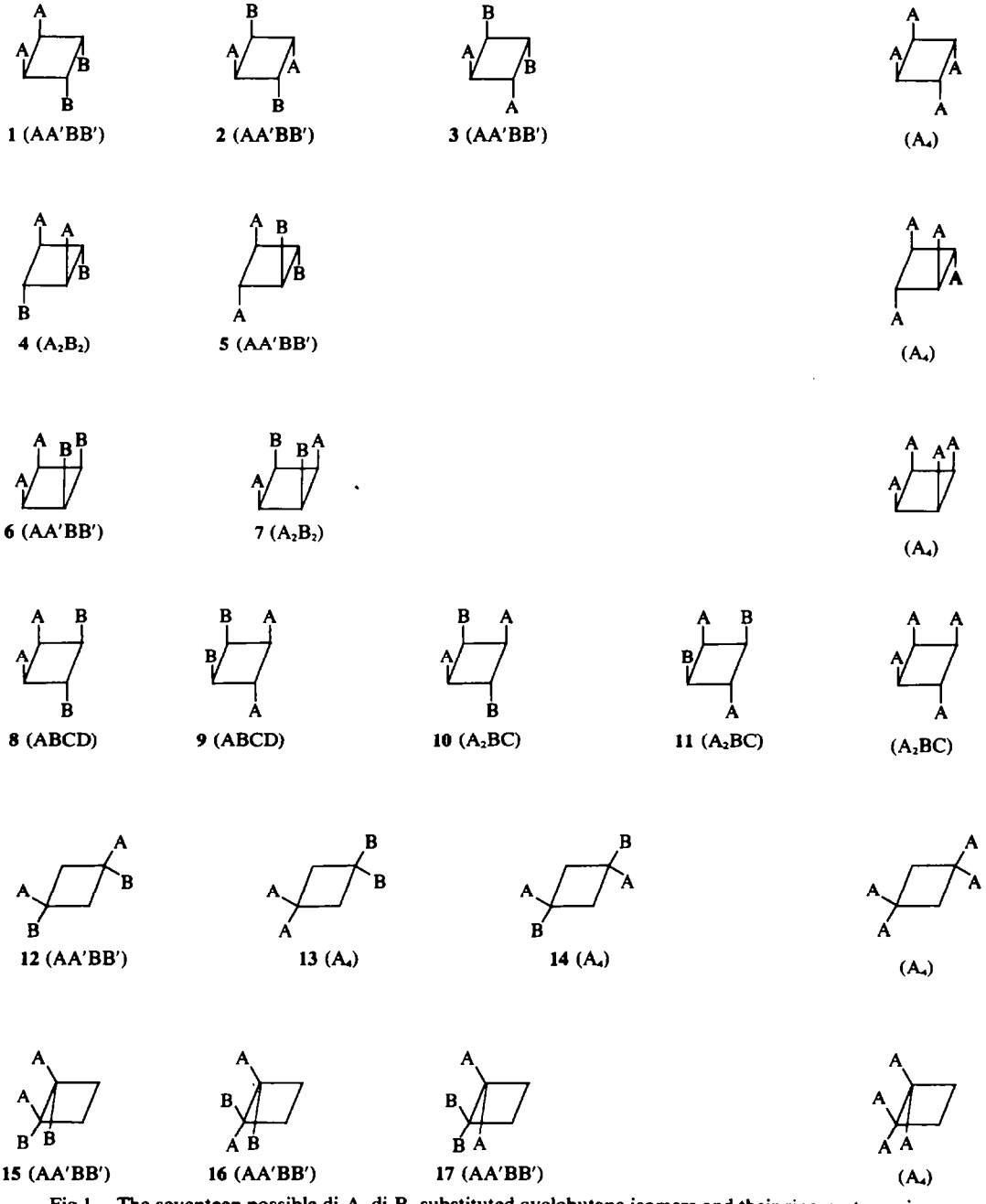


Fig 1. The seventeen possible di-A, di-B- substituted cyclobutane isomers and their ring-proton spin systems. To the right of each group is the basic structure type to which all members of the group belong.

configurational isomers (a single enantiomer is shown for chiral molecules) of cyclobutanes substituted with two pairs of substituents, A and B. Only the isomers resulting from the dimerization of a 1-A, 2-B-disubstituted olefin (**1–11**), the dimerization of a 1-A, 1-B-disubstituted olefin (**12**, **14–16**), or the mixed dimerization of 1,1-di-A- and 1,1-di-B-substituted olefins (**13**, **17**) have been considered in Fig 1. Structures **1**, **3**, **5**, **6**, **8** and **9** can also be looked upon as mixed dimers. The compounds are arranged in six groups such that making the substituents equal (A = B) leads in each group to a single structure, given on the right in Fig 1; this is a sufficient condition for the observation of identical mid-points

in each group if the spin systems are symmetrical. Thus all of the groups collapse to an A_4 spin system, except for the group **8–11** which leads to an A_2BC spin system even when the substituents are identical.

In order to establish for any two compounds whether the sums of the chemical shifts are equal, it is simply necessary to consider the substituent parameters. For example, the chemical shift of H_A of cyclobutane isomer **1**, $\delta_{H_A}\mathbf{1}$, is a function of the basic cyclobutane structure, δ_0, and the substituents: substituent A on the same carbon, A; substituent A, two carbons away and *trans*-disposed, $2A_t$; substituent B, three carbons away and *cis*-disposed, $3B_c$; and finally substituent B, two carbons away and *cis*-oriented, $2B_c$. There are two H_A protons so that the chemical shift is given by $\delta_{H_A}\mathbf{1} = 2(\delta_0 + A + 2A_t + 3B_c + 2B_c)$. Similar considerations for $\delta_{H_B}\mathbf{1}$ gives $\delta_{H_B}\mathbf{1} = 2(\delta_0 + B + 2A_c + 3A_c + 2B_t)$, while the substituent contributions to the chemical shifts of H_A and H_B of compound **2** are shown to be: $\delta_{H_A}\mathbf{2} = 2(\delta_0 + A + 2B_c + 3A_c + 2B_t)$; $\delta_{H_B}\mathbf{2} = 2(\delta_0 + B + 2A_t + 3B_t + 2A_c)$. It can readily be seen that $\delta_{H_A}\mathbf{1} + \delta_{H_B}\mathbf{1} + \delta_{H_A}\mathbf{2} + \delta_{H_B}\mathbf{2}$ or, as shown above, that the mid-points of the AA'BB' cyclobutane protons of compounds **1** and **2** can be expected to have the same position.

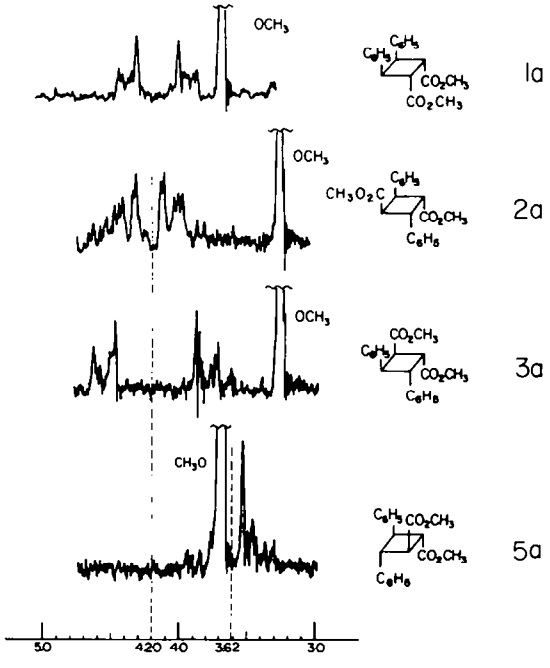


Fig 2. Cyclobutane ring proton signals of the dimethyl esters of β-truxinic acid (**1a**), α-truxillic acid (**2a**), μ-truxinic acid (**3a**), and δ-truxinic acid (**5a**). The spectra were recorded on a Varian A-60 instrument in acetone-d_6; the low field half of the cyclobutane pattern of **5a** is masked by the methoxyl singlet. We thank Miss M. Rejto for supplying us with compounds **3a** and **5a**.

Analysis of the substituent contributions to the chemical shifts of the remaining compounds in Fig 1 demonstrates that compound **3** also belongs to the group of **1** and **2** but none of the other compounds do. Except for **8–11**, the sum of substituent contributions to the proton chemical shifts for the molecules within each group are found to be equal. Compounds **8**, **9**, **10** and **11**, as noted above, are the only ones which do not generate the mirror-symmetric patterns whose mid-points are considered herein and can thus be differentiated from the remaining isomers on this basis. Consequently, any di-A, di-B-substituted cyclobutanes having the same mid-point of chemical shifts can be expected to have the same geometry of substitution (*i.e.*, will belong to the same group in Fig 1) while isomers with different mid-points will have different geometries of substitution.

Cyclobutane derivatives are often prepared by the photocyclodimerization of olefins and structure assignment to the isomers has been a classical problem whose solution often involved degradation and other chemical methods.[5] More recently NMR spectroscopy has been employed but the complexity of the ring proton patterns and the differences in spectral appearances between different isomers

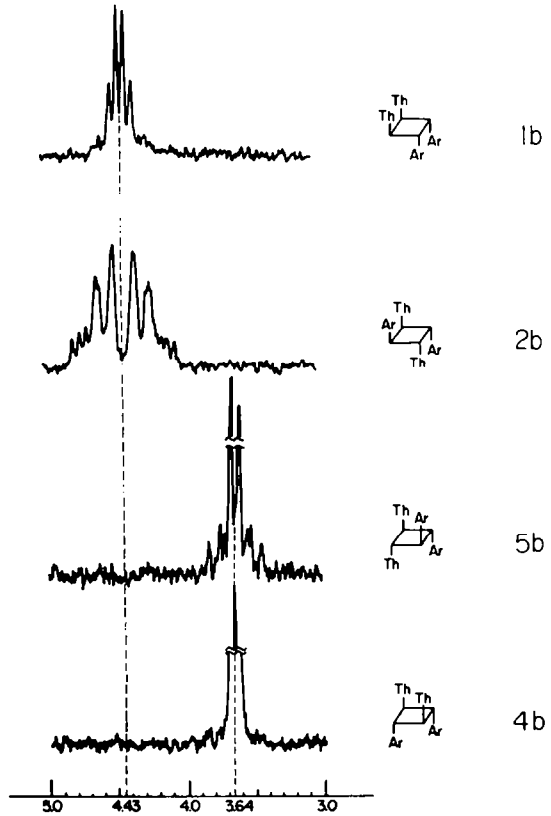
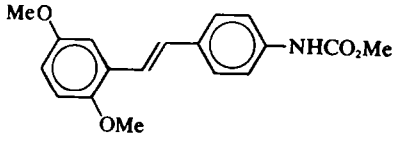


Fig 3. Cyclobutane ring proton signals for the four photodimers of 1- (3,4 - dichlorophenyl) - 2 - (2 - thienyl) - *trans* - ethene.[1b]

have sometimes prevented correct structure assignments. In Fig 2 are shown the 4-membered ring proton signals for four isomeric dimethyl diphenylcyclobutanedicarboxylates. As predicted above, the mid-points of compounds **1a**, **2a** and **3a** fall together (within 0·05 ppm) while that of **5a** differs by *ca* 0·6 ppm. Similarly, in Fig 3, the 4-membered ring signals of tetraarylcyclobutanes having the same geometry of substitution are shown to possess the same mid-point (pair **1b–2b** versus pair **4b–5b**). This relationship is general and holds for all of the cyclobutane isomers for which we have been able to find NMR data. Further examples are given in Table 1.

The extraction of a mid-point value directly from a spectrum is only possible when the pattern has mirror-symmetry; this is the case in the cyclobutane examples considered above where the coupling of the substituents' protons to the cyclobutane protons is insignificant. When the substituents are hydrogen, methyl, etc. (**15h**, **16h**; **12h**, **14h**; **12i**, **14i**; **12j**, **14j**; **19**, **20**; **21**, **22**; etc), coupling is observed and the cyclobutane patterns will no longer be mirror-symmetrical. In order to establish the average chemical shift values in such systems, it is possible in some cases to use double resonance techniques (irradiating at the frequency of the coupling protons of the substituent) which will again generate a mirror-symmetrical pattern whose mid-point can be visually estimated. Alternatively, the chemical shifts can be computed.

An example where the simple mid-point analysis avoids ambiguous or erroneous conclusions is provided, we feel, by the isomers isolated by Ulrich, *et al.* through the photodimerization of substituted *trans*-stilbene derivatives.[6] These workers obtained two dimers from compounds such as **18**. They assigned structure **1** to one of the photoproducts and suggested **4** or **5** for the second product on the basis of computer simulation of the spectra using coupling constants from the literature. However, the mid-points (δ 4·45, 4·49 ppm)* indicate immediately that the two dimers belong to the same group (have the same geometry of substitution) and the second dimer thus has structure **2**.†



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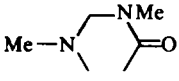
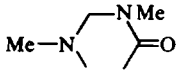
Other kinds of substitution pattern on a cyclobutane ring in addition to those of Fig 1 reveal identical mid-points when analyzed on the basis of substituent contributions to the chemical shift. For example, the methylene multiplets of **19** and **20** and

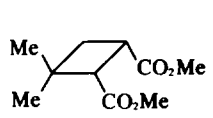
*All chemical shift values in this paper are given in δ-units.

†The positions of the OMe signals also support this conclusion. Dimer **3** is ruled out since it requires coupling of two *cis*-stibenes, a reaction which has not been observed.

Table 1

Compounds		A	B	Mid-points (in δ-units)		Difference	Ref
1c	**2c**	C_6H_5	2,4-$C_6H_3Cl_2$	4·62	4·62	(0·0	1*a*
1d	**2d**	2-C_4H_3S	2,4-$C_6H_3Cl_2$	4·65	4·73	(0·08)	1*b*
1e	**2e**	3,4-$C_6H_3Cl_2$	CO_2CH_3	4·1	4·1	(0·0)	1*b*
4e	**5e**	3,4-$C_6H_3Cl_2$	CO_2CH_3	3·53	3·55	(0·02)	1*b*
4f	**5f**	C_6H_5	C_6H_5CO	4·29	4·35	(0·06)	*a*, 8
15g	**16g**	Br	CO_2CH_3	2·70	2·84	(0·14)	*b*
15h	**16h**	Br	H	2·60	2·60	(0·00)	*c*
12h	**14h**	Br	H	3·13	3·08	(0·05)	*d*
12i	**14i**	Br	CH_3	3·19	3·21	(0·02)	1*c*
12j	**14j**	Cl	CH_3	2·96	2·88	(0·08)	1*c*
2l	**3l**			3·80	3·82	(0·02)	*e*
6l	**7l**			3·95	3·98	(0·03)	*e*

[a] M. Luwisch, Ph.D. Thesis, Weizmann Institute of Science, Rehovot, Israel, (1968).
[b] E. Lustig, E. P. Ragelis, N. Duy and J. A. Ferretti, *J. Am. Chem. Soc.*, **89**, 3953 (1967).
[c] Ref 16, Nos. 402, 403.
[d] K. B. Wiberg and G. M. Lampman, *J. Am. Chem. Soc.* **88**, 4429 (1966); K. B. Wiberg and D. E. Barth, *Ibid.* **91**, 5124 (1969).
[e] D. Elad, I. Rosenthal and S. Sasson, *J. Chem. Soc.* C 2053 (1971). We thank Prof. Elad and Dr. Rosenthal for these spectra.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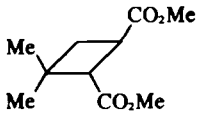
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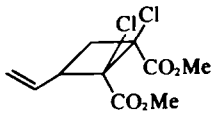
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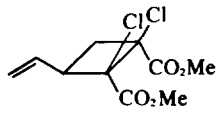
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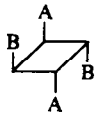
of **21** and **22**, respectively, should have similar mid-points. Computer simulation has provided the chemical shift values for these compounds; the mid-point of **19** is at 2·08 while that for **20** is at 1·89 (a difference of 0·19). For the corresponding free acids the values are 2·09 and 1·94 (a difference of 0·15);[3,7] the difference in average chemical shift for the geminal C–Me singlets, observed directly from the spectra, is only 0·04.[7] The mid-point of the methylene multiplet is at 2·78 for **21** and at 2·68 for **22**, a difference of 0·10.[3]

When the mid-points of two isomers differ significantly it can be argued that the isomers belong to different groups. For example, the spectra of compounds assigned structures **2f** and **5f** (difference in mid-point of 0·61) and **2k** and **5k** (difference, 0·41 ppm) corroborate the conclusion that the molecules have different geometries of substitution.[8] This is also demonstrated in the examples presented in Table 1 and Figs 2 and 3.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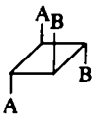
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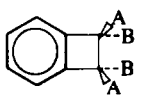
f: A = C_6H_5, B = C_6H_5CO

k: A = 2-C_4H_3S, B = (2-C_4H_3S)CO

The arguments concerning substituent contributions developed earlier can be extended to a variety of chemical systems such as 5-, 6-, or larger-membered rings, fused ring systems, bicyclic compounds, aromatic compounds, and open chain molecules. Some examples follow.

The mid-points of the symmetric aromatic multiplets of the benzocyclobutenes **23** and **24** differ by 0·06.[9]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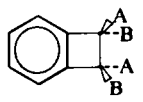
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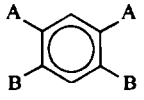
A = H, B = Br

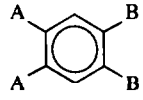
A = H, B = I

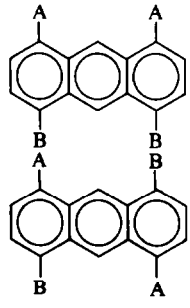
Many aromatic compounds fall within the scope of our treatment. Any two isomers with the same ring skeleton having symmetry C_s and C_2 should have identical ring proton mid-points. The aromatic signals of **25** and **26** are indeed the same[10,11] as are the signals of four pairs of isomers **27** and **28** (where Ar is a polysubstituted phenyl group).[12]

Examples in the 5-membered ring series are provided by four pairs of *cis*- and *trans*-isomers of 1,3-dioxolanes (acetonides) **29** and **30**, where the position of the singlet due to the two methyls in compounds **30** falls at exactly the same position as the mid-point between the methyl singlets in the corresponding compounds **29**.[13,14] The isolated methylene signals in the 6-membered ring compounds **31** and **32** fall at the same average value (difference, 0·04).[15]

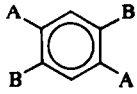
C_s-isomers

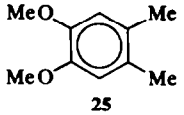






C_2-isomers

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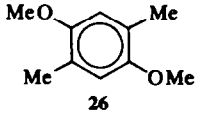
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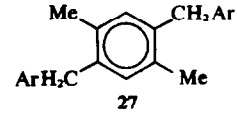
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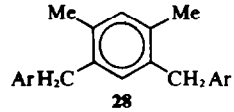
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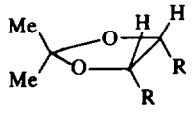

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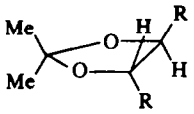

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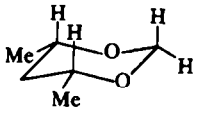
R = CH_2NO_2, CO_2Me, $CONH_2$, Me



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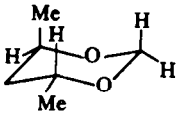
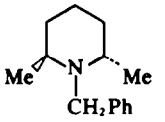


32

The cyclopropane series provides a much more limited number of isomers than larger rings; the spectra available again illustrate the validity of the mid-point analysis. The methylene signals in identically substituted compounds **33** and **34** all have, respectively, closely similar mid-points. The isomers **35** and **36** (mid-point difference, 0·09) provide another example[19] and illustrate, as can readily be shown by a substituent contribution analysis, that isomers with three or even four or more different substituents can exhibit spectra where the sums of the chemical shifts are equal (see also compounds **19**, **20** and **21**, **22**).



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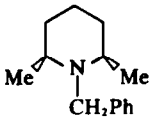

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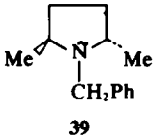

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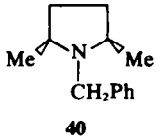

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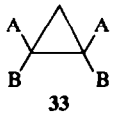

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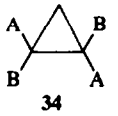

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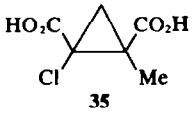

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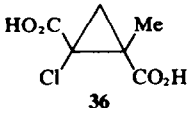


36

A	B	Difference	Ref
Me	CO_2H	0·05 ppm	16
H	I	0·01	17
Cl	CO_2H	0·11	18

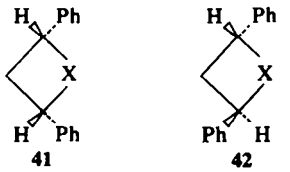
An exocyclic group can also probe the substitution on a ring. The center of the methylene AB quartet of the benzylic group in **37** falls 0·07 ppm away from the singlet in **38**; also in **39** and **40** the quartet and singlet have identical mid-points.[20]

It was pointed out earlier that for two isomers of the same group (*i.e.* making the substituents equal transforms the isomers to one and the same molecule) to have an identical mid-point for a symmetric group of signals it is essential that the contribution of the basic skeleton, δ_0, be the same for both isomers. This implies that the time-averaged geometry of the two isomers is identical and, on the other hand, that if the two isomers differ in geometry of the basic skeleton then the mid-points should no longer fall at the same value. The interesting possibility is thus raised of using the differences in mid-point values to carry out conformational analysis.

In the spectra of the four tetraaryl cyclobutane isomers, Fig 3, we note that the two pairs have identical mid-points, respectively. This, we suggest, implies essentially identical bond lengths and angles for the cyclobutane ring in both isomers. However, in the two isomeric compounds **1d** and **2d** (Table 1), the mid-point difference, *ca* 0·08 ppm, implies slight differences in the cyclobutane geometry of the two isomers, perhaps as a result of greater steric repulsion by the *cis*-2,4-dichlorophenyl groups in **1d**.

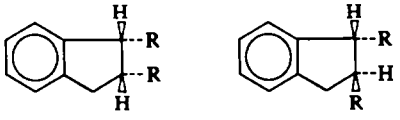
The mid-points of the methylene signals in the *cis*- and *trans*-diphenyl thietanes **41** and **42** (X = S) differ by 0·07 ppm; the mid-points of the analogous sulfones (X = SO_2) differ by 0·11 ppm. However, for the two sulfoxides (X = SO) the difference in mid-points is 0·66 ppm.[21] It is clear from these results that the time-averaged geometries of the sulfides and sulfones, respectively, differ to some extent but nowhere near as drastically as the sulfoxide isomers. Indeed, on the basis of a detailed analysis of the coupling constants the authors conclude that the *trans*-sulfoxide is badly distorted relative to the *cis*-isomer.[21]

In an NMR study of some *cis* and *trans*-1,2-



41 42

disubstituted indan derivatives[22] (**43** and **44**), the conformations of the 5-membered rings were estimated by determining the values of the coupling constants. The methylene hydrogens are amenable to our mid-point analysis and from the differences listed we would conclude that, on the NMR time scale, the indan skeletal geometry of the *cis*- and *trans*-diols is essentially identical but differences in geometry increasingly appear as one goes from the dimethoxy isomers to the diacetates; the differences in geometry are greatest for the dichloro compounds. These conclusions cannot be drawn from the coupling constant data of these compounds.[22] It is noteworthy that the dichloro iosmers constitute the extreme case and this is reminiscent of the many cases of anomalous behavior of dichloro and other halogen-substituted molecules.[23]



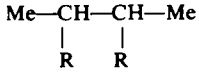
43 44

R	Differences
OH	0·0 Hz
OMe	0·05
OCOMe	3·8
Cl	8·7

In several of the compounds discussed earlier (e.g., **15g–16g**; **19–20**) relatively large mid-point differences are observed and we believe differences in skeletal geometry are implied. It should also be noted that hydrogens attached directly to a ring are much more sensitive to such differences than are methyl groups (**19** and **20**).

The mid-point method might also be applicable to open-chain compounds such as *meso*- and *d,l*-isomers. An analysis of substituent contributions in such materials shows that the same mid-point can be expected if there were equal populations of all three conformers in each of the two isomers. More importantly, the substituent contributions of the *meso*-anti-conformer and the *d,l*-anti-conformer are equal so that similar mid-points can be anticipated if this is the dominant conformer in both isomers. Indeed, the anti-conformers are generally the most stable.[24] In several pairs closely similar average chemical shifts are observed[25,26,27] while in others significant differences are found.[27]

The differences in average chemical shift observed in some *meso*- and *d,l*-2,3-disubstituted butanes (**45**) can be interpreted by assuming that the diacetoxy and diphenyl isomers exist predominantly in anti-conformations while the dihalo-substituted molecules populate the gauche conformations to a much larger degree.



45

R	Differences in average chemical shift of methine signals between *meso*- and *d, l*-isomers*
Br	0·31 ppm
Cl	0·22
OCOMe	0·02
Ph	0·03

*Values derived from data in Ref 27.

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