Table II. Microscopic Dissociation Constants for Tetracycline Hydrochloride

Calcd	Lit. data[a]	Calcd	Lit. data[a]
$pk_1 = 4.40$	$pk_1 = 4.49$	$pk_{123} = 9.25$	$pk_{123} = 9.11$
$pk_{12} = 8.65$	$pk_{12} = 8.00$	$pk_{132} = 9.66$	$pk_{132} = 8.60$
$pk_{13} = 8.24$	$pk_{13} = 8.51$		

[a] Rigler et al.

stants k_{12} and k_{13} were calculated using the relationship $K_1K_2K_3 = k_1k_{12}k_{123} = k_1k_{13}k_{132}$.

The microscopic dissociation constants determined in this manner are compared in Table II to those reported by Rigler et al.[12] The differences arise for several reasons. First, Rigler et al.[12] did not make an assumption that the A site is totally deprotonated at pH 6, even though they observed a distinct break in this region. Their protonation data also included a reprotonation at the A site at higher pH values which is difficult to justify even when considering the zwitterionic character of the A ring. The other differences arise because Rigler et al.[12] believe that the B site is deprotonated prior to the C site while the ^{13}C data indicates that initially the two sites are nearly equivalent and later deprotonation at the C site is favored (see Table I).

Acknowledgment. This research was partially supported by Pfizer, Inc.

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Charge Distributions and Chemical Effects. 11. On the Charge Dependence of ^{13}C Chemical Shifts in Adamantane and Related Six-Membered Polycyclic Molecules

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Abstract: The analysis of ab initio charge distributions in adamantane and selected polycycloalkanes constructed from chair and/or boat cyclohexane units indicates that no effect beyond what is included in the relationship $\delta_C = -237.1q_C + 242.64$ ppm from TMS between ^{13}C chemical shifts and C net charges (as determined for acyclic alkanes and cyclohexanes) contributes to any significant extent to the shielding of the carbon atoms. The optimized ab initio charges satisfying this δ_C–q_C relationship reflect, hence, all effects which in usual empirical calculations are itemized as α, β, γ, . . . contributions.

Recent studies[1] have indicated that in acyclic alkanes the carbon-13 nuclear magnetic resonance shifts, δ_C, are linearly related to the carbon net charges, q_C, i.e.,

$$\delta(^{13}C) = -237.1q_C(\text{rel}) + 242.64 \text{ ppm} \qquad (1)$$

from TMS, with a standard error of ∓ 0.3 ppm. The choice of tetramethylsilane as a standard of reference is, in itself, arbitrary and represents purely a matter of practical convenience. In fact, choosing ethane as the reference compound for defining chemical shifts, eq 1 can be written as follows

$$\delta(^{13}C) = -237.1(q_C - 1) \text{ ppm} \qquad (2)$$

from ethane, which in certain cases turns out to be a more practical form than (1). Of course, in these equations q_C is to be expressed in the system of relative units defined by setting the C net charge of ethane equal to 1 arbitrary unit, along the lines described in ref 1–3. The merit of eq 2 is to express clearly that the only empirical parameter arising from the correlation between chemical shifts and carbon net charges is the slope, -237.1 ppm/relative charge unit.

These equations also indicate that ^{13}C chemical shifts are extremely sensitive to small variations in charge. Indeed, a 1% change in q_C corresponds to varying δ_C by ~2.4 ppm. The standard deviation (0.3 ppm) is, therefore, small in comparison with the error in δ_C which would result from a 1% error in the estimate of q_C; the uncertainty in q_C can thus be estimated at ~0.13%. As a consequence of the excellent agreement of eq 1 with experimental δ_C results, this equation can now be used to calculate C net charges (relative to $q_C = 1$ for ethane) when these are not known from previous work. Moreover, these relative net charges can be used for deducing, by means of an easy transformation,[1] the charges which would result from a STO-3G calculation implying full optimization of all (geometry and ζ scale factor) variational parameters, and conversely. In conclusion, ^{13}C chemical shifts not only represent a severe test for the theory[1,2] of charge distributions in alkanes but also represent a powerful means of obtaining C charges which would otherwise imply extremely lengthy optimized STO-3G calculations, often at or beyond the limits of their practical feasibility. These charges can then be used for the study of other molecular properties involving charges, e.g., ionization potentials and ESCA shifts,[4] enthalpies of formation,[5] etc., which is to say that these properties can be deduced from ^{13}C NMR shifts.

Chemical shift is a property of the interaction of the charge density with an external magnetic field. Therefore, it depends not only on the value of the integrated charge density (or "charge") in the neighborhood of a nucleus but also on the magnetic susceptibility of that charge density. This is why the δ_C–q_C correlation (eq 1 and 2) is, in principle, limited to a set of very similar molecules, such as the acyclic alkanes reported in ref 1. The present study contributes to the investigation of what is really meant by "very similar molecules" from the point of view of ^{13}C nuclear magnetic resonance. Indeed, the recent analysis[3] of ab initio charge distributions in cyclohexane and selected methylcyclohexanes indicated no departure from relationship 1 between ^{13}C chemical shifts and C net charges (as determined for the acyclic alkanes); i.e., no special effect seems to contribute significantly to the chemical shift, specifically because of the cyclic structure of cyclohexane. Similar conclusions are no longer true for cyclopropane[3] which, not unexpectedly, fails grossly to verify eq 1.

The successful application of eq 1 to cyclohexanes now suggests the obvious question about the behavior of molecules constructed from several cyclohexane rings, such as adamantane, bicyclo[3.3.1]nonane, etc. This shall be studied here, in order to gain information about the range of validity of eq 1 in cases which are believed to possess appreciable ring strain (e.g., ~6-7 kcal/mol in adamantane[6]) or for molecules containing cyclohexane units in boat conformation, such as iceane. It must also be made clear, however, that any verification of eq 1 does not mean to contradict current arguments in terms of spatial proximity of neighboring atoms on ^{13}C shieldings, gauche γ interactions, etc., but tends to indicate that all these effects are ultimately reflected in the electron populations which, in turn, are simply related to the NMR shifts by the same equation which applies to the acyclic alkanes. Adamantane is an interesting example in that respect, because it fails to obey the customary simple additivity rules for calculating chemical shifts.[7]

Calculations of Charges

The calculations were made using the STO-3G method described in detail by Pople and co-workers.[8] "Standard" calculations imply the use of standard bond lengths, $r(CC) = 1.540$ Å, $r(CH) = 1.091$ Å, and bond angles, 109.47°, as well as the "optimized" set of exponents, i.e., $\zeta_C(s_Lp) = 1.76$, $\zeta_C(s_K) = 5.67$, and $\zeta_H(s) = 1.18$. Optimized STO-3G calculations involve, first, optimization of geometry using the above set of exponents and, second, optimization of the exponents for each different atom, including ζ optimization of the carbon K shell. Now different properties may be more or less sensitive to small changes of the various variational parameters. This means that particular attention must be given to the extent of the dependence of calculated properties upon the increments in the variational parameters. For highly sensitive properties, therefore, the energy minimizations must be carried further than for less sensitive properties. Of course, such an approach implies a large number of calculations for each molecule of interest. This has been shown to be an important aspect in the calculation of charges in acyclic alkanes;[9] it became clear that charge distributions are very sensitive to ζ optimization and, to a somewhat lesser extent, to geometry optimization. Now optimized STO-3G charges have proven to be excellent for comparisons with ^{13}C chemical shifts.[1,10] It appears, therefore, that in view of obtaining charge distributions which are accurate in their relative scaling one should prefer to work at the simple STO-3G level and carry out carefully the optimizations discussed above, rather then attempting calculations involving large Gaussian descriptions without optimizing adequately all the variational parameters.

The ab initio calculations of net charges, $q_C{}^0$ for carbon, and $q_H{}^0$ for hydrogen atoms, were carried out following Mulliken's population analysis,[11] which implies the half-and-half partitioning of all overlap population terms. In the modified population analysis[1] which does not allocate half of the C–H overlap to each carbon and hydrogen, the hydrogen and carbon net charges are

$$q_H = q_H{}^0 - p \tag{3}$$

$$q_C = q_C{}^0 + Np \tag{4}$$

where N is the number of H atoms bonded to C, and p is the departure from the usual halving of the C–H overlap population, for one C–H bond. It has been demonstrated earlier[1,2] that the use of the modified C charges, q_C, is imperative in any comparison of molecular properties with carbon net charges, and expressions for calculating p were given. The p correction term is such that the modified carbon charges comply with the scheme of "most even electron distribution", i.e., with a situation in which the charges of the various C atoms in a variety of alkanes are as similar as possible.[12] Its numerical value depends upon the theoretical method selected for calculating the $q_C{}^0$ charges. When these are derived from Mulliken's scheme using optimized STO-3G calculations, it is

$$p = 30.12 \text{ me} \tag{5}$$

and

$$q_C \text{ (rel units)} = q_C/69.40 \tag{6}$$

where the modified q_C net charges are expressed in millielectron (me) units, and 69.40 (me) is the carbon net charge of ethane in the modified population analysis scale. Comprehensive examples illustrating the calculation of p and of the modified ethane-C charge are given in ref 1 and 3. Of course, these modifications, which shall be used in the present study, are numerically identical with those previously employed for acyclic alkanes and cyclohexanes.

Results

Adamantane (1). For this molecule, the optimization was carried out along the lines indicated earlier for acyclic alkanes[9] and cyclohexane,[3] except for the angles of the carbon skeleton, all of which were kept at 109.47°. Because of its size, preservation of tetrahedral symmetry was required in order to render the calculations possible. A comparison of this assumed CCC angle with electron diffraction and x-ray data (Table I)

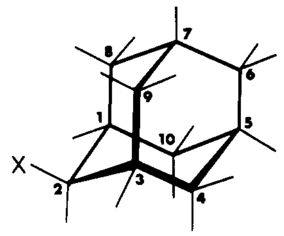
Table I. Calculated and Experimental Geometry of Adamantane

	Calcd				Electron diffraction		X ray	
Parameter	STO-3G	Schleyer[b]	Allinger[a]	Boyd[c]	Hargittai[d]	Nowacki[e]	Nowacki[f]	Nordman[g]
r(CC), Å	1.5312	1.528	1.537	1.544	1.540 ± 0.002	1.54 ± 0.02	1.54 ± 0.01	1.52 ± 0.03
$r(CH_s)$, Å	1.0982				Average 1.112 ± 0.004		Average 1.090[h]	
$r(CH_t)$, Å	1.0956							
$\angle C_tC_sC_t$, deg	109.47[h]	109.2	110.0	109.7	108.8 ± 1.0	109.5[h]	109.5 ± 1.5	
$\angle C_sC_tC_s$, deg	109.47[h]	109.6	109.2	109.3	109.8 ± 0.5	109.5[h]		
$\angle H_sC_sH_s$, deg	107.42				116.9 ± 6.0	109.5[h]	109.5[h]	
$\angle H_sC_sC_t$, deg	111.44							

[a] N. L. Allinger, M. T. Tribble, M. A. Miller, and D. H. Wertz, *J. Am. Chem. Soc.*, **93**, 1637 (1971). [b] E. M. Engler, J. D. Andose, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **95**, 8007 (1973). [c] R. H. Boyd, S. N. Sanwal, S. S. Tehrany, and D. McNally, *J. Chem. Phys.*, **75**, 1264 (1971). [d] I. Hargittai, *Chem. Commun.*, 1499 (1971). [e] W. Nowacki, *Helv. Chim. Acta*, **28**, 1233 (1945). [f] W. Nowacki and K. W. Hedberg, *J. Chem. Phys.*, **70**, 1497 (1948). [g] C. E. Nordman and D. L. Schmitkons, *Acta Crystallogr.*, **18**, 764 (1965). [h] Assumed value.

Table II. Optimized ζ Exponents for Adamantane

Atom	Orbital	ζ
H(sec)	1s	1.1723
H(tert)	1s	1.1736
C(sec)	s_L, p	1.7598
C(sec)	s_K	5.708
C(tert)	s_L, p	1.7596
C(tert)	s_K	5.703



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justifies this assumption. Moreover, it can be inferred from earlier work[3,9] that, within limits, charges are not too sensitive to small errors in angular parameters. In isobutane, for example, a deviation of ±0.6° in the CCC angle about its optimum value distorts the charge on the central C atom by ~0.28 me and has virtually no effect on its neighboring C atoms. Similarly, for the CCC angle in propane, a deviation of ~1° from its optimum value leads to a variation of ~0.06–0.1 me in the charge on the secondary C atom, leaving the charges of the primary C atoms virtually unaltered. By analogy, it can be reasonably inferred from these test calculations that in adamantane any anticipated error in charge is likely to be more important for the tertiary than for the secondary C atom. All other geometry parameters, however, have been optimized, i.e., HCH angles, C–C and C–H distances, using Pople's set[8] of optimum ζ exponents.

Next, the scale factors were optimized using the geometry indicated in Table I, until stable charges were obtained. In this optimization, the total energy drops from −383.532 96 (standard) to −383.544 57 au. The optimized set of exponents is indicated in Table II.

The optimized charges, $q_C{}^0$ and $q_H{}^0$, obtained from Mulliken's population analysis are relatively similar to their "standard" counterparts (Table III). The modified charges, q_C and q_H, calculated from the optimized ones by means of eq 3 and 4, are also indicated. For the carbon atoms, division of these modified charges by 69.40 (eq 6) yields the corresponding quantities in the scale of relative units defined by q_C(ethane) = 1, from which the ^{13}C chemical shifts are deduced by means of eq 1. The calculated shifts are then 38.27 for the secondary and 30.24 ppm from TMS for the tertiary C atoms, which compare favorably with the experimental values reported in Table III.

For the tertiary C atoms, the difference between the calculated and observed shift, 1.49 ppm, is larger than usual. It is not unreasonable to ascribe this divergence to the lack of angle optimization of the carbon skeleton, which is likely to affect mainly the tertiary C atoms. Conversely, a back-calculation of C charges from the observed chemical shifts, by means of eq 1 and 4–6, reveals a difference of 0.44 me between the optimized STO-3G charge and that calculated from the ^{13}C shift in the case of the tertiary C atoms, whereas the agreement between ^{13}C and ab initio charges is virtually perfect for the secondary C atoms. It can, therefore, be concluded with a reasonable degree of confidence that no special effect seems to contribute significantly to the C chemical shifts in adamantane, specifically because of the polycyclic structure of this molecule; the same relation holds between carbon net charges and ^{13}C NMR shifts as that observed for the alkanes.[1] This is to say, speaking now in terms of shifts relative to ethane, and considering eq 2, that the ^{13}C NMR spectrum of adamantane can be deduced from the knowledge of only one al-

Table III. NMR Shifts and Net Charges (me) in Adamantane

Atom	NMR shifts, ppm from TMS	q^0, STO-3G "standard"	q^0, STO-3G "optimized"	Modified charge, q	Net charge $q_C{}^0$ from ^{13}C shift
s-C	38.24[a]	−9.53	−0.42	59.82	−0.41
t-C	28.75[a]	30.08	32.05	62.17	32.49
s-H	1.78[b]	−2.96	−7.06	−37.18	
t-H	1.88[b]	−6.90	−10.26	−40.38	

[a] G. E. Maciel, H. C. Dorn, R. L. Green, W. A. Kleschick, M. R. Peterson, and G. H. Wahl, *Org. Magn. Reson.*, **6**, 178 (1974). [b] R. C. Fort and P. v. R. Schleyer, *J. Org. Chem.*, **30**, 789 (1965).

Table IV. ^{13}C NMR Shifts and Net Charges in Methyladamantanes

		δ_C, ppm from TMS		C net charges (me)	
Molecule	Atom	Lippmaa[a]	Maciel[b]	Standard STO-3G	From ^{13}C[c]
1-MeAd	1	29.9	30.30	65.04	62.15
	2, 8, 10	44.6	45.16	−13.51	−2.44
	3, 5, 7	28.9	29.30	30.13	32.33
	4, 6, 9	36.9	37.43	−9.54	−0.17
	Me-C	31.1		−37.50	−22.44
2-MeAd	1, 3		34.15	24.36	30.91
	2		39.39	27.65	29.37
	4, 10		39.85	−9.29	−0.88
	8, 9		31.76	−12.56	1.49
	5		28.45	30.04	32.57
	6		39.08	−9.39	−0.66
	7		28.76	29.42	32.48
	Me-C			−39.08	

[a] T. Pehk and E. Lippmaa, *Org. Magn. Reson.*, **3,** 783 (1970). [b] G. E. Maciel, H. C. Dorn, R. L. Greene, W. A. Kleschick, M. R. Peterson, and G. H. Wahl, *ibid.*, **6,** 178 (1974). [c] Calculated from ^{13}C data by Maciel et al.,[b] except for the methyl-C atom in 1-MeAd, calculated from Lippmaa's result.[a] These charges, deduced from eq 1 and 4–6, correspond to those which would result from a Mulliken population analysis.

kane ^{13}C shift relative to ethane, e.g., from that of methane, because this alkane shift entirely defines the slope $d\delta/d(q_C - 1) = -237.1$ of eq 2.

Of course, the obvious drawback in this type of approach is that it involves extremely lengthy ab initio calculations, as compared to the usual simple empirical additivity schemes which enable a rapid evaluation of chemical shifts and are, therefore, useful in the elucidation of many problems related to chemical structure. In the case of adamantane, unfortunately, present additivity schemes fail to predict correctly its ^{13}C shifts. For example,[7] the shielding predicted for the bridgehead carbons, using the Savitsky-Namikawa parameters,[13] is 48.2 ppm neglecting contributions by the γ carbons. Inclusion of the γ effects yields 40.7 ppm, in poor agreement with the experimental value, $\delta_C = 28.75$ ppm. For the methylenic carbons, the predicted values are 46.5, viz., 41.5 ppm, where the latter includes γ contribution. It has then been suggested[7] that the fact that shieldings in polycyclic systems are greater than those in more or less comparable positions in acyclic hydrocarbons indicates that there may be an accentuated γ effect due to the rigidity of the carbon skeleton. Now, in view of the present results, it must be considered that a failure of simple additivity is not indicative for the participation of any new particular physical effect, characteristic for polycyclic compounds, which would make the adamantane ^{13}C shifts basically different from that of, say, methane. This, of course, does not preclude the introduction of a new correction parameter for these types of polycyclic compounds, as long as such a correction is made on an empirical basis and no special physical interpretation is attached to its use.

Present results reveal another interesting aspect related to charge distributions. At the level of "modified" population analyses, the effect of methyl substitution for H on a C atom is that the latter becomes less positive (i.e., electron richer) as the number of α-methyl substituents is increased, not because methyl itself pushes electrons toward the central C atom, but because it withdraws less electrons than the H atom which has been replaced by it. For example, $q_C = 63.50$ for C(tert) in isobutane, and 66.19 me for the secondary propane C atom. Now, contrasting with this situation, the adamantane tertiary C atoms are more positive than the secondary ones (Table III). This point can be explained using an analogy with model compounds, i.e., three ethyl groups attached to CH vs. two isopropyl groups attached to CH_2, for the tertiary and secondary C atoms in adamantane. In these models, the observed shift is larger (49.0 ppm) for the secondary than for the tertiary C atom[14] (42.4 ppm), which indicates that two isopropyl groups are better electron donors than three ethyl groups, a situation similar to that encountered in adamantane.

1- and 2-Methyladamantane. For these molecules, geometry and exponent optimizations were not made.[15] The results presented in Table IV are those derived from standard STO-3G calculations using Mulliken's population analysis.

These charges are not suitable for direct comparisons with C NMR shifts, as they are not sufficiently precise for that purpose. Under the following premises, however, it is still possible to extract useful information from standard charge analyses; if the standard geometrical parameters and exponents are not too different from their optimized counterparts, then we can apply in a limited range (which, however, is difficult to define precisely) a Taylor series:

$$q_{\text{opt}} = q_0 + (q_{\text{st}} - q_0)\, dq_{\text{opt}}/dq_{\text{st}} + \tfrac{1}{2}(q_{\text{st}} - q_0)^2\, d^2q_{\text{opt}}/dq_{\text{st}}^2 + \ldots \quad (7)$$

For acyclic alkanes and cyclohexane it was shown[3] that the comparison between standard and optimized C net charges yields a straight line which is better than what would have been hoped for a priori. We now take advantage of this property for studying methyladamantanes. Since it is virtually not feasible to calculate their optimized C charges, these are estimated from carbon-13 NMR shifts by means of eq 1 and 4–6. Clearly, the latter charges are those to be expected from optimized calculations, unless the chemical shifts for methyladamantanes depend also on an effect which is not accounted for in the simple δ_C–q_C relation 1.

The comparison of standard C net charges with charges deduced from NMR shifts indicates (Figure 1) that the same relation holds between these sets of results as between the standard and STO-3G optimized charges calculated for adamantane.

Therefore, within the precision of the present type of analysis, there is no indication that any effect beyond what is accounted for in eq 1 contributes to any significant extent to the ^{13}C NMR shifts of methyladamantanes. This result, which is similar to that obtained for acyclic alkanes and methylcyclohexanes,[3] is not unexpected for methyladamantanes in view of the fact that adamantane itself appears to follow the δ_C–q_C relationship, eq 1. Now it remains to be examined whether this

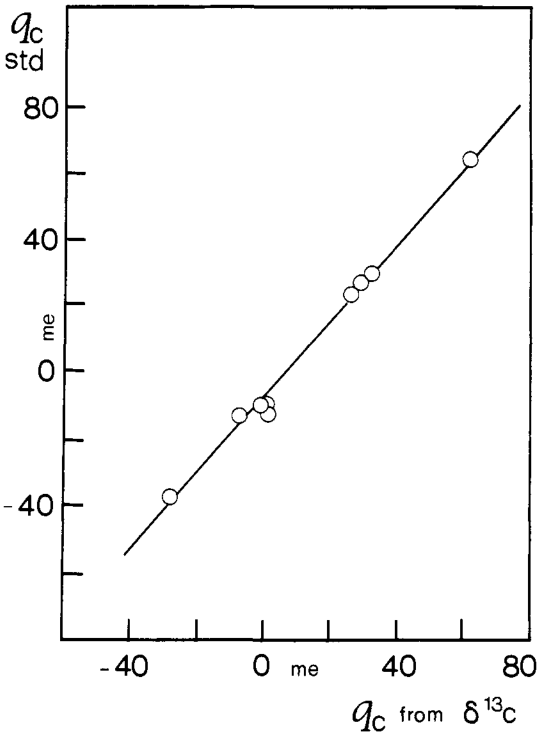
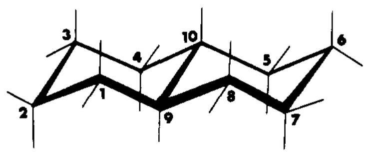


Figure 1. Comparison of standard net C charges (STO-3G) with charges deduced from NMR shifts for methyladamantanes (Table IV).

situation is encountered also with other hydrocarbons consisting of six-membered rings.

Generalization. Molecules consisting of cyclohexane rings in the chair conformation, i.e., *trans*-decalin (**2**), *cis*-decalin (**3**), and bicyclo[3.3.1]nonane (**4**), as well as in boat conformation, i.e., iceane (**5**) and bicyclo[2.2.2]octane (**6**), were selected.

The results derived from standard calculations are presented in Table V, along with the charges deduced from ^{13}C shifts. The atom numbering is that indicated in structures **2–6**.



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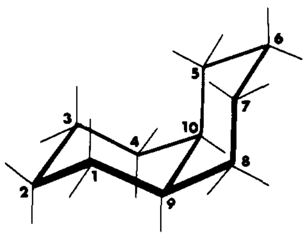

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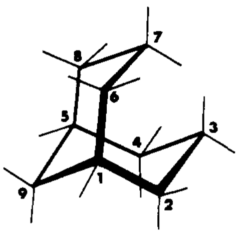

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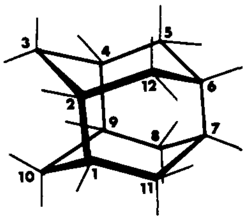

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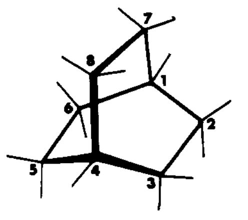

6

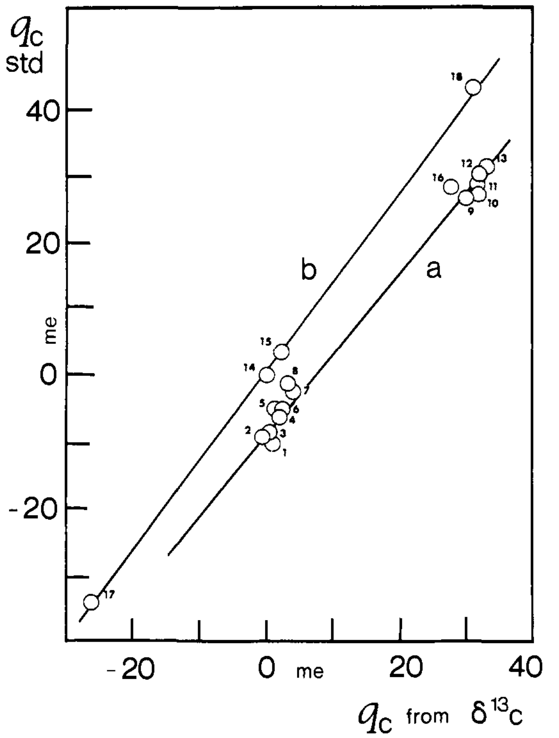

Figure 2. (a) Comparison of standard net C charges (STO-3G) with charges deduced from NMR shifts for compounds **3–6.** Points 8 and 16 are not included in this correlation, which is drawn for adamantane (point 2 = C_{sec}, 12 = C_{tert}). (b) This comparison is for cyclohexanes. The points are: 17 = methyl-C and 18 = C-1 of methylcyclohexane, extracted from ref 3. Points 14 and 15 belong to *trans*-decalin. The point for cyclohexane (not indicated) is very similar to 15.

Table V. ^{13}C NMR Shifts and Net Charges in Selected Polycyclic Molecules

			C net charge (me)	
Molecule	Atom[e]	δ_C, from TMS	STO-3G	From C-13
trans-Decalin[a]	2, 3, 6, 7 (15)	27.17	3.46	2.83
	1, 4, 5, 8 (14)	34.74	−0.69	0.61
	9, 10 (16)	44.22	28.23	27.96
cis-Decalin[a]	2, 3, 6, 7 (8)	24.62	−1.65	3.58
	1, 4, 5, 8 (4)	29.78	−6.55	2.06
	9, 10 (9)	36.93	26.43	30.09
Bicyclo[3.3.1] nonane[b]	1, 5 (13)	27.9	31.05	32.74
	2, 4, 6, 8 (5)	31.6	−5.48	1.53
	3, 7 (7)	22.5	−2.72	4.20
	9 (3)	35.1	−9.02	0.51
Iceane[c]	1, 2, 4, 6, 7, 9 (10)	28.66	26.63	32.51
	3, 5, 8, 10, 11, 12 (1)	31.67	−10.16	1.51
Bicyclo[2.2.2]-octane[d]	1, 4 (11)	24.69	28.10	33.67
	2, 3, 5, 6, 7, 8 (6)	26.81	−5.04	2.93

[a] ^{13}C shifts from D. K. Dalling and D. M. Grant, *J. Am. Chem. Soc.*, **96**, 1827 (1974). [b] ^{13}C shifts from A. Heumann and H. Kolshorn, *Tetrahedron*, **31**, 1571 (1975). [c] ^{13}C shifts from H. Tobler, R. O. Klaus, and C. Ganter, *Helv. Chim. Acta*, **58**, 1455 (1975). [d] ^{13}C shifts from G. E. Maciel and H. C. Dorn, *J. Am. Chem. Soc.*, **93**, 1268 (1971). [e] The numbers in parentheses refer to the points in Figure 2.

Again, use is made of the "linear" relationship between standard and optimized carbon net charges, where the latter are now deduced from ^{13}C NMR shifts. For compounds **3–6,** the correlation (Figure 2a, not including points 8 and 16) is satisfactory, thus suggesting that no major effect in excess over what is included in eq 1 operates in determining the ^{13}C shifts of these compounds. As in Figure 1, the line of reference drawn in Figure 2a is based upon the results obtained for adamantane, whose ab initio optimized charges are those predicted from ^{13}C shifts.

This correlation differs significantly from that drawn for methylcyclohexane and cyclohexane (Figure 2b). Now, for the atoms included in 2a the possible shielding (gauche or eclipsed) γ effects are in excess over what can be anticipated in cyclohexane.[16] This difference between sets 2a and 2b is ignored in standard calculations as far as ζ exponents are concerned,[17] because of the use of constant ζ's. Neglecting this difference also manifests itself in the charges (which are very sensitive to the ζ's) and, therefore, in establishing the correlation (eq 7) which, at best, is expected to hold only for atoms in comparable conditions. Hence it seems reasonable that different lines are obtained, depending upon the amount of contributions which are neglected because of the lack of ζ optimization. In the present case, this suggests that shielding γ effects are of real physical importance. Unfortunately, no direct firm proof to that effect can be extracted from fully optimized calculations; indeed, both cyclohexane and adamantane yield optimized charges satisfying eq 1, notwithstanding the fact that these molecules belong to different correlation lines, which means that γ effects are already included in optimized charges.

These views are confirmed by *trans*-decalin. In this molecule, atoms 1–8 are cyclohexanelike in that each of them experiences only one shielding γ effect: the corresponding points (14 and 15) are, indeed, on the cyclohexane correlation line (b), whereas atoms 9 and 10, each of which experiences two shielding γ effects, tend to correlate with the adamantane line (point 16). Similarly, the four cyclohexanelike atoms (2, 3, 6, 7) of *cis*-decalin approach line b (point 8), whereas the other six atoms of this molecule (points 4 and 9) are adamantanelike. These observations are coherent with the suggestion that shielding γ effects are, indeed, of real physical importance.

Conclusions

The equations relating ^{13}C NMR shifts to carbon net charges which were found to be accurate for acyclic alkanes and cyclohexanes also apply to adamantane, as indicated by its optimized ab initio calculation. In terms of shifts relative to ethane, this means that the ^{13}C NMR spectrum of adamantane can be deduced from the knowledge of only one alkane ^{13}C shift relative to ethane, e.g., from that of methane. The same conclusion is reached for other molecules constructed from several (chair and/or boat) cyclohexane rings, within the limits of precision of the analysis involving standard charges.

While this study suggests that shielding γ interactions are of real physical importance, it also appears that no firm proof for their occurrence can be derived from the δ_C–q_C relationship because, when real, they are already reflected in the carbon charges. Now, of course, the same argument applies also to the other ($\alpha, \beta, \ldots$) effects which are currently used in empirical calculations of carbon chemical shifts; the charges satisfying the δ_C–q_C relationship, and which can be obtained from fully optimized ab initio calculations, appear to reflect the result of all effects which in usual empirical calculations are itemized as $\alpha, \beta, \gamma, \ldots$ contributions.

The value of our correlation probably lies less in its ability to predict chemical shifts accurately than in providing a simple probe into the charge of carbon atoms, whose significance has been discussed elsewhere.[1,2] However, in spite of its demonstrated reliability for saturated hydrocarbons, this correlation should by no means be used to lend unintended support for the growing practice of indiscriminately interpreting ^{13}C shifts in all systems as being strictly linearly related to electron density. The significance or generality of this type of correlation is not known. Recent theoretical progress[18,19] in the calculation of ^{13}C shifts gives some insight into the various contributions that can be related to detailed features of electronic structure. Additional work along these more rigorous approaches will hopefully result in some understanding of charge density–NMR shift correlations and their limitations.

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(10) More precisely, optimized STO-3G were found to be in excellent agreement with the "inductive" charge distributions[2] and the latter, after proper analysis, were found to correlate almost perfectly with ^{13}C shifts.[1]
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(15) A single run on adamantane requires ~20 000 s, using a CDC CYBER 74 computer, and 40 calculations were required for achieving its optimization. Methyladamantanes would require far too many calculations for achieving optimization because of the large number of variational parameters, and each calculation requires ~28 000 s.
(16) The bridgehead atoms in bicyclo[2.2.2]octane (point 11) are included in 2a, although their classification with respect to shielding γ effects is ambiguous.
(17) Shielding γ effects are attributed to particular environmental situations which are absent in molecules for which no such γ effects can be postulated. In optimized calculations, any effect of environment is reflected in the ζ exponents; the ζ parameters are, indeed, incorporated in the description of the orbitals in order to account for the changes in the atomic orbitals due to molecular environment.
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