m/z 144 (M^+, 1), 101 (17), 74 (7), 73 (9), 71 (57), 43 (100). Calcd for $C_7H_{12}O_3$: 144.17. Analytical GLC conditions: column, DB 210, temp 1, 60 °C, time 1, 5 min, rate 20 °C/min, temp 2, 200 °C, time 2, 5 min, injector temp, 250 °C, detector temp, 250 °C, inlet P, 24 psi. Retention times: 3-(acetyloxy)-3-methyl-2-butanone, 8.5 min, 1-(acetyloxy)-3-methyl-2-butanone, 9.2 min, 3-(1-oxo-2-methylpropoxy)-3-methyl-2-butanone, 9.4 min. Preparative GLC conditions: column 5% SE-30 (10 ft × $^3/_8$ in.), column temp, 85 °C, injector temp, 100 °C, detector temp, 100 °C, collector temp, 60 °C, He flow, 45 mL/min, current, 150 mA. Retention times: 3-(acetyloxy)-3-methyl-2-butanone, 7 min, 1-(acetyloxy)-3-methyl-2-butanone, 11 min, 3-(1-oxo-2-methylpropoxy)-3-methyl-2-butanone, 17 min.

Flash Vacuum Pyrolysis of Dimethyldioxirane. A solution of dimethyldioxirane (60 mL, 0.068 M) was placed in a round-bottom flask which was attached to a FVP apparatus. A vacuum (0.2 mmHg) was applied in order to carry the vapors of acetone and **1a** into the pyrolysis zone. The pyrolysis zone consisted of a glass tube packed with glass beads which was enclosed in a tube furnace at 150–180 °C. Vapors leaving the heated zone were condensed by passing them through a double trap (liquid N_2 and dry ice–acetone). A pale yellow condensate was collected and dried with Na_2SO_4. NMR analysis of this material indicated that the major component was methyl acetate. No peaks due to acetol or acetol acetate were present. Amazingly the NMR indicated that some of the dioxirane had survived exposure to the pyrolysis zone.

Treatment of Dimethyldioxirane with BF_3·Etherate. A solution of **1a** (freshly prepared, dried with Na_2SO_4) in acetone (0.5 mL) in an NMR tube was treated with a small drop of BF_3·etherate (3–4 μL). After 15 min the NMR of the solution indicated the presence of acetol (peak at δ 4.16). The peak due to methyl acetate (δ 3.59) was observed to increase while, simultaneously, the absorption due to the methyl groups in **1a** (δ 1.65) was observed to decrease in height. This absorption disappears in 90–100 min while the peaks due to acetol and methyl acetate cease to increase in intensity. At this point the solution was colorless. Repetition of this experiment four times always gave the same results. Upon completion of the experiment the acetone was evaporated off. The residue was dissolved in CH_2Cl_2 and dried with Na_2SO_4. Examination of this solution by NMR indicated that acetol and methyl acetate were present in the ratio of 5:1.

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Registry No. **1a**, 74087-85-7;)1c, 58272-12-1; **1d**, 138629-57-9; **3**, 58272-12-1; **4**, 79-20-9; boron trifluoride etherate, 109-63-7; 2-propanone, 67-64-1; 2-butanone, 78-93-3; 3-pentanone, 96-22-0; 3-methyl-2-butanone, 563-80-4; 3,3-dimethyl-2-butanone, 75-97-8; 2,4-dimethyl-3-pentanone, 565-80-0; 4-methyl-2-pentanone, 108-10-1; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1; 1-(acetyloxy)-2-propanone, 592-20-1; 3-(acetyloxy)-2-butanone, 4906-24-5; 1-(acetyloxy)-2-butanone, 1575-57-1; 4-(acetyloxy)-2-butanone, 10150-87-5; 2-(acetyloxy)-3-pentanone, 2983-05-3; 3-(acetyloxy)-2-pentanone, 20510-66-1; 4-(acetyloxy)-2-pentanone, 55577-75-8; 1-(acetyloxy)-2-pentanone, 7137-27-1; 3-(acetyloxy)-3-methyl-2-butanone, 10235-71-9; 1-(acetyloxy)-3-methyl-2-butanone, 36960-07-3; 1-(acetyloxy)-3,3-dimethyl-2-butanone, 38559-25-0; 4-(acetyloxy)-3,3-dimethyl-2-butanone, 72816-02-5; 2-(acetyloxy)-2,4-dimethyl-3-pentanone, 21980-75-6; 4-(acetyloxy)-4-methyl-2-pentanone, 1637-25-8; 3-(acetyloxy)-4-methyl-2-pentanone, 135274-69-0; 1-(acetyloxy)-4-methyl-2-pentanone, 141665-39-6; 4-hydroxy-4-methyl-2-pentanone, 123-42-2; 2-(acetyloxy)cyclopentanone, 52789-75-0; 2-(acetyloxy)cyclohexanone, 17472-04-7; 3-(1-oxopropoxy)-2-butanone, 141665-40-9; 3-(1-oxo-2-methylpropoxy)-3-methyl-2-butanone, 76777-46-3; oxygen, 7782-44-7; 3-hydroxy-2-butanone, 513-86-0; propionic anhydride, 123-62-6.

Conformational Analysis and Configurational Assignment of 3-(Alkylsulfenyl)-, 3-(Alkylsulfinyl)-, and 3-(Alkylsulfonyl)-*N*-methylpiperidinium Chlorides

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^1H, ^{13}C NMR, DEPT, and two-dimensional ^1H–^{13}C heteronuclear correlation spectra of 3-(alkylsulfenyl)-, 3-(alkylsulfinyl)- (its two epimeric sulfoxides), and 3-(alkylsulfonyl)-*N*-methylpiperidinium chlorides (alkyl = methyl, ethyl, isopropyl) have been recorded and fully interpreted. Magnetic resonance parameters (chemical shifts of ^1H and ^{13}C, and geminal and vicinal coupling constants) of these compounds are described for the first time. Conformational analysis has been carried out on conformations selected by a molecular mechanics force field (MMX). In all compounds there is a single ring conformation, the undistorted chair with *N*-methyl and SO_nR (n = 0, 1, 2; R = Me, Et, Pr^i) in the equatorial orientation. These conclusions are supported by the observed vicinal coupling constants. Configurational assignment of ring nitrogen and carbon C_3 has been carried out from observed vicinal axial–axial coupling constants, and the relative configurations of the diastereomeric sulfoxide pairs have been established from observed ^{13}C chemical shifts for ring carbons C_2 and C_4.

The substitution of a ring methylene unit in cyclohexane by a heteroatom provides a system with a rich variety of conformational properties. Among six-membered saturated heterocycles, the piperidine ring is one of the most important ones because of its occurrence in many alkaloids as well as in compounds of pharmacological importance.[1–4] These piperidyl derivatives have been also widely used in synthesis of metallic complexes,[5–9] which are useful sub-

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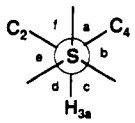
Table I. Calculated Dihedral Angles for Distorted Unstaggered Conformations of Compounds 1-4



dihedral angle	conformation (Me/Et/Pr^i)[a]					
	A	B	D (Et/Pr^i)	F	G	H (Me)
a	36/36/48	93/94/97	44/44	24/29/20	113/105/100	42
b	74/74/63	48/48/44	80/80	98/93/101	14/22/26	76
c	48/54/60	71/71/75	37/38	22/28/18	105/97/94	44
d	63/56/50	39/39/34	88/87	90/85/95	17/25/28	72
e	56/62/67	82/83/86	28/28	28/33/23	102/94/92	45
f	84/78/73	27/26/22	83/83	98/93/102	9/17/20	81

[a] Dihedral angles have been summarized in the order R = Me, Et, Pr^i, except for conformations D (R = Et, Pr^i) and H (R = Me).

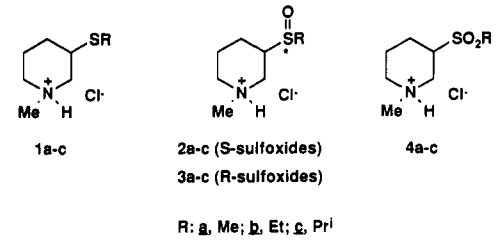


Figure 1.

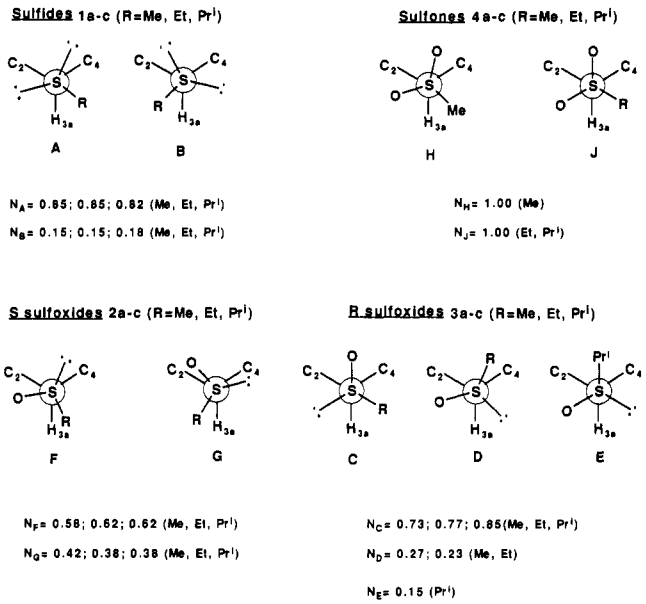


Figure 2.

strates for several organic syntheses. There are many studies about conformational equilibria in piperidines and *N*-alkylpiperidines,[10-15] but there is little information about these compounds with polar substituents. The present work is the first systematic conformational and structural study of 3-substituted *N*-methylpiperidinium chlorides with sulfide, sulfoxide, and sulfone groups. Previous studies of heterocyclic compounds with two heteroatoms in a 1,3-relative position have been confined to 3-substituted thianes,[16] oxanes[17] with polar groups (OR, SMe, SOMe, and SO_2Me), 5-substituted 1,3-dithianes,[18] and 1,3-dioxans[19] with SMe and OMe as polar groups.

In the present work 3-(alkylsulfenyl)-*N*-methylpiperidinium, **1a-c**, 3-(alkylsulfinyl)-*N*-methylpiperidinium, **2a-c** and **3a-c**, and 3-(alkylsulfonyl)-*N*-methylpiperidinium, **4a-c**, chlorides (Figure 1) have been studied. The syntheses of these compounds and the separation of diastereomeric sulfoxides have been previously reported.[20]

The principal tool to elucidate the conformation and configurational assignment have been ^1H and ^{13}C NMR spectroscopy at room temperature. Earlier work on ^1H NMR in piperidines has been carried out by Lambert,[11] Booth,[12] and Robinson,[13] but at present there is not an extended study of proton resonance parameters of the *N*-methylpiperidinium ring. The results reported in this work are the first ones in this field. Earlier work on the ^{13}C NMR of piperidines has been carried out by Jones,[21] Feltkamp,[22] Booth,[23] Duch,[24] Eliel,[14,15] and an extensive review of ^{13}C NMR spectra of saturated heterocycles (including piperidines) has been published.[25]

Results and Discussion

Conformational Analysis. The conformational analysis of the compounds **1a-c**, **2a-c**, **3a-c**, and **4a-c** has been carried out using the molecular mechanics force field (MMX derived from MMP2 program)[26] as the fundamental tool. The significant conformations have been

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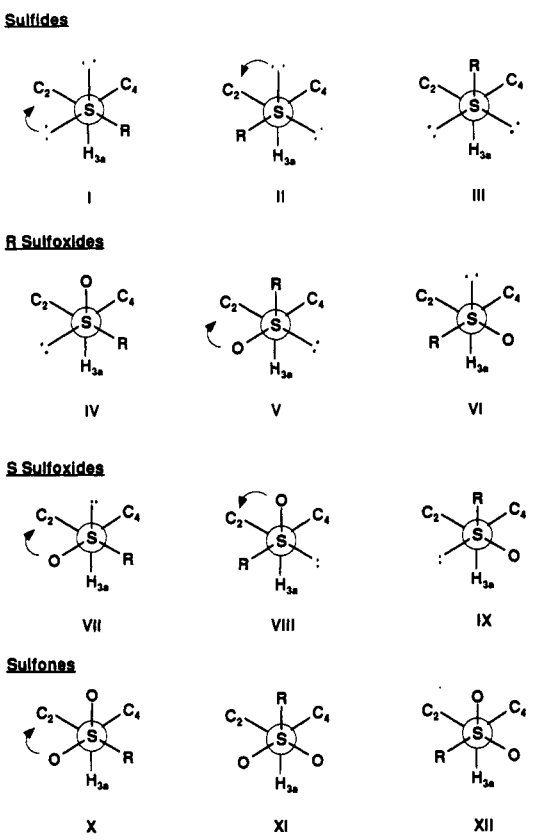

Figure 3.

selected by a careful study of rotational barriers and minimization of all conformations with a relative energy minimum coming from chair inversion of the *N*-methylpiperidinium ring and rotation of the SO_n-alkyl groups in position C_3. The *N*-methylpiperidinium ring adopts in all compounds a single undistorted chair conformation with the *N*-methyl and SO_n-alkyl groups in fixed equatorial orientations. Different conformations have been selected by rotation around C_3–SO_nR and SO_n–R bonds (n = 0, 1, 2). The selected conformations as a result of this energy minimization have been displayed in Figure 2.

The dihedral angles calculated for distorted conformations (conformations A, B, D (R = Pr^i), F, G, and H (R = Me)) have been collected in Table I. Staggered conformations C, E, and J have dihedral angles of 60°.

The results of this energy minimization with the molecular mechanics force field MMX are very reasonable and a qualitative interpretation of them, taking into account steric and polar interactions, can be performed. Ideal staggered conformations for compounds 1–4 deduced by rotation around the C_3–SO_nR (n = 0, 1, 2) bond have been summarized in Figure 3.

The attractive polar interactions that exist in the selected conformations by the molecular mechanics force field MMX can be justified by taking into account the residual charges on ring nitrogen and carbons, calculated by Rescha program.[27] The ring nitrogen and carbons C_2 and C_6 are σ-deficient, and ring carbons C_4 and C_5 are σ-rich. The ring carbon C_3 is σ-rich in sulfides and σ-deficient in sulfoxides and sulfones.

Sulfides. The conformation III for studies **1a–c** (Figure 3) is sterically hindered because it has a larger number of gauche interactions between substituents than conformations I and II. The ideal staggered conformations I and II (Figure 3) evolve to distorted conformations A and B (Figure 2), respectively, as a result of a stabilizing polar interaction that takes place by the proximity of the lone pair of sulfur to the σ-deficient carbon C_2. A is the major conformation because the energy of the 1,2-gauche R/H_{3a} steric interaction for B is higher than A (the dihedral angle R–S–C_3–H_{3a} is larger for conformation A than conformation B, see Table I).

Sulfoxides. A clear predominance of two major conformations has been established for sulfoxides: types IV and V for *R*-sulfoxides (**3a–c**) and VII–VIII for *S*-sulfoxides (**2a–c**). Conformations of types VI and IX are Coulombically unfavored because the σ-deficient C_2 and σ-rich sulfinyl oxygen have an antiperiplanar orientation, in addition the conformation IX has two steric gauche interactions. The staggered conformation of type IV in *R*-sulfoxides is undistorted (conformation C, Figure 2; see Table I) because the proximity of carbon C_2 to the sulfinyl oxygen, Coulombic favored, is hindered by the increase of gauche interaction C_4/R. The ideal staggered conformation of type V (Figure 3) for sulfoxides **3a** and **3b** evolves to conformation D (Figure 2; see Table I) because a polar stabilizing interaction between the sulfinyl oxygen and carbon C_2 is present. The energy of this polar interaction can be estimated as 2.4 kcal/mol (sulfoxides **3a** and **3b**) or 2.1 kcal/mol (sulfoxide **3c**) from the model proposed by Zefirov,[28] the residual charges for the sulfinyl oxygen and carbon C_2 calculated from the Rescha program (see ref 27d), the C_2–O distances deduced from minimization with molecular mechanics force field MMX, and the equation $E_\mu = 332 e_X e_Y / r_{X/Y}$ (kcal/mol) proposed by Abraham.[29] In this equation e_X and e_Y are the residual charges for groups X and Y (as fraction of elemental electric charge) and $r_{X/Y}$ the distance (Å) between groups X and Y. On the other hand, the conformation of type V for sulfoxide **3c** (R = Pr^i) is undistorted (conformation E, Figure 2) because the proximity of carbon C_2 to the sulfinyl oxygen is hindered by the increase of the gauche interaction C_4/R. C is the major conformation because the energy of steric interactions for D and E is higher than C.

The ideal staggered conformations VII and VIII (Figure 3) for *S*-sulfoxides are strongly distorted (conformations F and G, Figure 2). The strong distortion can be easily justified because the increase of the stabilizing polar interaction O/C_2 by the proximity of carbon C_2 to the sulfinyl oxygen is higher than the increase of the destabilizing steric gauche interaction between the group R and hydrogen H_{3a}. The energy of this polar attractive interaction can be estimated as 2.4 kcal/mol (sulfoxides **2a** and **2b**; conformations F and G), or 2.2 kcal/mol (sulfoxide **2c**; conformations F and G) form the Zefirov model[28] and the Abraham equation.[29] The populations of the two significant conformations F and G for sulfoxides **3a–c** have similar values (Figure 2) with a small predominance of conformation F. These results can be easily justified because these two conformations have similar steric and polar interactions.

Sulfones. The sulfones **4a–c** are present in a single

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Table II. ^{1}H Chemical Shifts for Compounds 1a–c, 2a–c, 3a–c, and 4a–c[a] ($CDCl_3$; 25 °C; TMS as Internal Reference)

compd[b]	H_{2e}	H_{2a}	H_{3a}	H_{4e}	H_{4a}	H_{5e}	H_{5a}	H_{6e}	H_{6a}
1a	3.63 (ddd)	2.65 (dt)	3.34 (tt)	2.20 (br d)[c]	1.36 (cd)	1.96 (dq)	2.35 (dtt)	3.50 (dm)	2.71 (tdd)
2a	3.78 (dm)	3.12 (t)	3.50 (tt)[e]	2.17 (br d)	1.81 (cd)	2.07 (dq)	2.44 (dtt)	3.54 (dm)[e]	2.78 (br t)
3a[f]	3.75 (br d)	3.10 (t)	3.46 (br t)[e]	2.06–2.20	1.85 (br c)	2.06–2.20	2.40 (m)	3.55 (br d)[e]	2.90 (m)[g]
4a	3.53 (br d)	2.73 (t)	4.12 (tt)	2.36 (br d)[e]	1.77 (cd)	2.09 (dq)	2.45 (ct)[e]	3.84 (br dt)	2.90 (m)[c,g]
1b	3.61 (br d)	2.74–2.82[g]	3.40 (tt)	2.17 (br d)	1.40 (cd)	1.97 (dq)	2.31 (dtt)	3.49 (br d)	2.74–2.82[g]
2b	3.68 (dm)	3.09 (t)	3.58 (tt)[e]	2.16 (dm)	1.85 (cd)	2.06 (dq)	2.44 (dtt)	3.54 (br d)[e]	2.70–2.98[h]
3b	3.72 (br dd)	3.15 (t)	3.51 (tt)[e]	2.07 (br d)[d]	1.86 (cd)	2.12 (dq)[d]	2.40 (dtt)	3.55 (br d)[e]	2.88–2.94[g]
4b[i]	3.70–3.82[e]	3.08 (t)	3.70–3.82[e]	2.14 (br d)	1.57 (cd)	1.97 (dq)[d]	1.89 (dtt)[d]	3.38 (br d)	2.93 (t)
1c	3.59 (br d)	2.53–2.74[e]	3.45 (tt)[d]	2.17 (br d)	1.35 (cd)	1.94 (dq)	2.36 (dtt)	3.48 (br d)[d]	2.53–2.74[e]
2c	3.61 (br d)[e]	3.08 (t)	3.71 (tt)	2.14 (dm)[d]	1.89 (cd)	2.07 (dq)[d]	2.43 (dtt)	3.55 (br d)[e]	2.81 (br t)
3c[j]	3.54–3.74	3.06 (m)	3.54–3.74	1.78–2.14	1.78–2.14	1.78–2.14	2.46 (dm)	3.50 (br d)	2.78 (m)
4c	3.57 (br d)	3.01 (t)	4.06 (tt)	2.30 (br d)[e]	1.79 (cd)	2.11 (dq)	2.21 (dtt)[e]	3.81 (br d)	2.81 (td)

[a] br, broadened; c, quartet; d, doublet; q, quintuplet, m, multiplet; t, triplet. [b] Other signals: **1a**, 2.18 (s, 3 H, SMe), 2.82 (d, ^3J = 4.8 Hz, 3 H, HN^+Me), 12.38 (br s, 1 H, HN^+Me); **2a**, 2.70 (s, 3 H, SOMe), 2.92 (s, 3 H, HN^+Me), 12.60 (br s, 1 H, HN^+Me); **3a**, 2.64 (s, 3 H, SOMe), 2.91 (s, 3 H, HN^+Me), 12.33 (br s, 1 H, HN^+Me); **4a**, 2.88 (s, 3 H, HN^+Me), 3.00 (s, 3 H, SO_2Me), 13.12 (br s, 1 H, HN^+Me); **1b**, 1.29 (t, ^3J = 7.5 Hz, 3 H, CH_3CH_2), 2.56–2.73 (AB portion of the ABX_3 system, 2 H, δ_A = 2.67 ppm, δ_B = 2.62 ppm, J_{AB} = −12.3 Hz, J_{AX} = J_{BX} = 7.5 Hz, CH_2CH_3), 2.85 (s, 3 H, HN^+Me), 12.18 (br s, 1 H, HN^+Me); **2b**, 1.39 (t, 3 H, ^3J = 7.5 Hz, CH_3CH_2), 2.70–2.98 (m, 2 H, CH_3CH_2), 2.89 (s, 3 H, HN^+Me), 12.56 (br s, 1 H, HN^+Me); **3b**, 1.37 (t, 3 H, ^3J = 7.5 Hz, CH_3CH_2), 2.73 (dc, ^2J = −12.9 Hz, ^3J = 7.5 Hz, 1 H, CH_2CH_3), 2.87 (dc, ^2J = −12.9 Hz, ^3J = 7.5 Hz, 1 H, CH_2CH_3), 2.91 (s, 3 H, HN^+Me), 12.68 (br s, 1 H, HN^+Me); **4b**, 1.25 (t, ^3J = 7.5 Hz, 3 H, CH_3CH_2), 2.78 (s, 3 H, HN^+Me), 3.21 (c, ^3J = 7.5 Hz, 2 H, CH_3CH_2), 11.2 (br s, 1 H, HN^+Me); **1c**, 1.28 (d, ^3J = 6.8 Hz, 3 H, $MeCHMe$), 1.33 (d, ^3J = 6.8 Hz, 3 H, $MeCHMe$), 2.79 (d, ^3J = 4.2 Hz, 3 H, HN^+Me), 3.09 (septuplet, ^3J = 6.8 Hz, $MeCHMe$), 12.47 (br s, 1 H, HN^+Me); **2c**, 1.32 (d, ^3J = 6.9 Hz, 3 H, $MeCHMe$), 1.39 (d, ^3J = 6.9 Hz, 3 H, $MeCHMe$), 2.88 (s, 3 H, HN^+Me), 2.99 (septuplet, ^3J = 6.9 Hz, 1 H, $MeCHMe$), 12.56 (br s, 1 H, HN^+Me); **3c**, 1.20 (d, ^3J = 6.9 Hz, 3 H, $MeCHMe$), 1.37 (d, ^3J = 6.9 Hz, 3 H, $MeCHMe$), 2.83 (s, 3 H, HN^+Me), 2.97 (septuplet, ^3J = 6.9 Hz, 1 H, $MeCHMe$), 12.8 (br s, 1 H, HN^+Me); **4c**, 1.42 (d, ^3J = 6.9 Hz, 3 H, $MeCHMe$), 1.44 (d, ^3J = 6.9 Hz, 3 H, $MeCHMe$), 2.91 (s, 3 H, HN^+Me), 3.22 (septuplet, ^3J = 6.9 Hz, 1 H, $MeCHMe$), 12.00 (br s, 1 H, HN^+Me). [c] Partially overlapped with the signal of group SMe. [d,e] Partially superimposed signals. [f] Together a 33% of diastereomer **2a**. [g] Partially superimposed with the signal of group NH^+Me. [h] The signal for this proton is superimposed with signals of groups NH^+Me and SCH_2CH_3. [i] In DMSO-d_6. [j] Together 10% of diastereomer **2c**.

Table III. ^{13}C Chemical Shifts for Compounds 1a–c, 2a–c, 3a–c, and 4a–c ($CDCl_3$; 25 °C; TMS as Internal Reference)

	carbon					
compd	C2	C3	C4	C5	C6	other signals
1a	57.56	38.17	27.46	22.22	53.03	12.60 (SMe), 42.87 (HN^+Me)
2a	50.70	52.02	23.37	21.75	53.91	36.06 (SOMe), 44.05 (HN^+Me)
3a	53.73	52.32	16.12	20.87	53.67	34.93 (SOMe), 43.62 (HN^+Me)
4a	51.97	55.96	21.15	21.35	54.08	39.75 (SO_2Me), 44.12 (HN^+Me)
1b	58.97	37.19	28.79	22.68	53.70	14.82 (SCH_2CH_3), 24.75 (SCH_2CH_3), 43.38 (HN^+Me)
2b	50.91	49.77	23.35	21.79	53.69	7.23 ($SOCH_2CH_3$), 43.44 ($SOCH_2CH_3$), 43.86 (HN^+Me)
3b	53.90	50.85	16.70	20.97	53.67	7.32 ($SOCH_2CH_3$), 42.79 ($SOCH_2CH_3$), 43.62 (HN^+Me)
4b[a]	50.20	53.61	20.32	20.90	52.28	5.77 ($SO_2CH_2CH_3$), 42.56 ($SO_2CH_2CH_3$), 44.51 (HN^+Me)
1c	58.49	35.87	28.64	22.35	52.81	23.21, 23.02 ($SCHMe_2$), 34.10 ($SCHMe_2$), 42.74 (HN^+Me)
2c	50.58	47.17	23.35	21.54	53.03	15.20, 15.57 ($SOCHMe_2$), 43.27 (HN^+Me), 47.83 ($SOCHMe_2$)
3c	54.84	48.21	16.88	21.17	54.11	15.95, 16.15 ($SOCHMe_2$), 43.98 (HN^+Me), 48.74 ($SOCHMe_2$)
4c	52.77	51.37	20.95	21.51	54.05	14.53, 15.19 (SO_2CHMe_2), 44.22 (HN^+Me), 52.20 (SO_2CHMe_2)

[a] Spectrum recorded in DMSO-d_6.

conformation (conformation X, Figure 3). The conformation XI is sterically very hindered because two gauche interactions CH_2/R are present. The conformation XII is polar unfavored because two repulsive polar interactions between the two sulfonyl oxygens and the σ-rich carbon C_4 and a single attractive gauche interaction C_2/O are present. The conformation of type X (Figure 3) for sulfone **4a** is distorted to conformation H (Figure 2) because a stabilizing gauche interaction between carbon C_2 and the sulfonyl oxygen is involved. The energy of this interaction can be estimated as 2.0 kcal/mol from the Zefirov model[28] and the Abraham equation.[29] However, the ideal staggered conformation X (Figure 3) for sulfones **4b** and **4c** is undistorted (conformation J, Figure 2) because the approach of carbon C_2 to sulfonyl oxygen (polar favored) is sterically hindered by the large increase of the gauche interaction R/H_{3a}.

NMR Spectroscopy. The ^{1}H and ^{13}C NMR spectra of compounds **1a–c**, **2a–c**, **3a–c**, **4a**, and **4c** were measured in $CDCl_3$ (**4b** in DMSO-d_6) at room temperature. ^{1}H and ^{13}C chemical shifts are contained in Tables II and III, respectively, geminal coupling constants in Table IV, and vicinal coupling constants in Table V.

^{1}H NMR. The assignment of the observed signals to hydrogens was made by comparison of chemical shifts with literature values for *N*-methylpiperidinium chloride[12] taking into account the deshielding contributions of groups SR, SOR, and SO_2R (R = Me, Et, Pr^i),[30] by homonuclear decoupling experiments, from observed multiplicity for signals, and by the well-supported hypothesis that an axial

Table IV. Geminal Coupling Constants for Compounds 1a–c, 2a–c, 3a–c, and 4a–c ($CDCl_3$; 25 °C)

compd	$J_{2a,2e}$	$J_{4a,4e}$	$J_{5a,5e}$	$J_{6a,6e}$
1a	−12.1 ± 0.2	−12.8 ± 0.1	−14.4 ± 0.1	−12.3 ± 0.3
2a	−12.0 ± 0.1	−12.8 ± 0.2	−14.7 ± 0.1	−11.8 ± 0.2
3a	−11.8 ± 0.2	−12.6 ± 0.3	–[b]	−11.9 ± 0.5
4a	−12.1 ± 0.2	−13.0 ± 0.2	−14.3 ± 0.4	−12.0 ± 0.3
1b	−12.0 ± 0.3	−13.0 ± 0.1	−14.4 ± 0.1	−12.4 ± 0.7
2b	−11.8 ± 0.2	−13.1 ± 0.1	−14.3 ± 0.1	−12.7 ± 0.7
3b	−11.8 ± 0.1	−12.6 ± 0.4	−14.7 ± 0.3	−12.0 ± 0.2
4b[a]	−12.0 ± 0.3	−12.3 ± 0.3	−14.4 ± 0.1	−12.2 ± 0.2
1c	−12.0 ± 0.3	−13.2 ± 0.1	−14.5 ± 0.2	−12.7 ± 0.4
2c	−11.7 ± 0.2	−13.0 ± 0.1	−14.5 ± 0.1	−12.1 ± 0.3
3c	–[b]	–[b]	−14.4 ± 0.4	−12.0 ± 0.3
4c	−11.5 ± 0.5	−12.6 ● 0.1	−14.6 ± 0.1	−12.0 ± 0.6

[a] In DMSO-d_6. [b] The measure of these coupling constants was unsuccessful on the spectra.

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Table V. Vicinal Coupling Constants for Compounds 1a–c, 2a–c, 3a–c, and 4a–c ($CDCl_3$; 25 °C)[a]

	$^3J_{a,a}$[b]				$^3J_{a,e}$[c]						$^3J_{e,e}$	
compd	$J_{2a,3a}$	$J_{3a,4a}$	$J_{4a,5a}$	$J_{5a,6a}$	$J_{2e,3a}$	$J_{3a,4e}$	$J_{4a,5e}$	$J_{5a,4e}$	$J_{5a,6e}$	$J_{6a,5e}$	$J_{4e,5e}$	$J_{5e,6e}$
1a	12.3 ± 0.1	12.6 ± 0.4	13.0 ± 0.1	12.9 ± 0.3	3.8 ± 0.1	3.9 ± 0.1	3.5 ± 0.1	3.9 ± 0.1	3.9 ± 0.1	3.3 ± 0.1	3.3 ± 0.1	3.3 ± 0.1
2a	12.0 ± 0.1	12.5 ± 0.5	13.5 ± 0.1	12.4 ± 0.5	3.9 ± 0.1	3.9 ± 0.1	3.6 ± 0.3	3.6 ● 0.1	3.6 ± 0.1	3.3 ± 0.1	3.3 ± 0.1	3.3 ± 0.1
3a	12.2 ± 0.2	12.6 ± 0.3	12.6 ± 0.3	–[d]	–[d]	–[d]	–[d]	–[d]	–[d]	–[d]	–[d]	–[d]
4a	12.3 ± 0.1	12.6 ± 0.3	13.3 ± 0.5	12.9 ± 0.9	3.9 ± 0.1	3.9 ± 0.1	3.6 ± 0.3	3.9 ● 0.1	3.6 ± 0.3	3.3 ± 0.1	3.3 ± 0.1	3.3 ± 0.1
1b	12.3 ± 0.1	12.7 ± 0.4	13.2 ± 0.1	12.4 ± 0.7	3.9 ± 0.1	3.9 ± 0.1	3.6 ± 0.3	3.9 ± 0.1	3.9 ± 0.1	3.3 ± 0.1	3.3 ● 0.1	3.3 ± 0.1
2b	11.9 ± 0.2	12.5 ± 0.5	13.3 ± 0.2	12.7 ± 0.7	3.9 ± 0.1	3.9 ± 0.1	3.5 ± 0.5	3.6 ± 0.1	3.6 ± 0.1	2.8 ± 0.2	2.8 ± 0.2	2.8 ± 0.2
3b	12.0 ± 0.3	12.6 ± 0.4	12.9 ± 0.2	12.9 ± 0.2	3.8 ± 0.1	3.9 ± 0.1	3.9 ± 0.1	3.6 ± 0.1	3.6 ± 0.1	2.9 ± 0.2	2.7 ± 0.3	3.2 ● 0.5
4b	12.0 ± 0.3	12.0 ± 0.3	12.0 ± 0.3	12.0 ± 0.3	–[d]	–[d]	3.9 ± 0.5	3.6 ± 0.1	3.6 ± 0.1	3.3 ± 0.2	3.3 ± 0.2	3.3 ± 0.2
1c	12.0 ± 0.3	12.7 ± 0.4	13.2 ± 0.1	12.7 ± 0.4	3.9 ± 0.1	3.9 ± 0.1	3.6 ± 0.3	3.6 ± 0.3	3.9 ± 0.1	3.3 ± 0.1	3.3 ± 0.1	3.3 ● 0.1
2c	11.9 ± 0.4	12.6 ± 0.3	13.1 ± 0.1	12.6 ± 0.5	3.9 ± 0.1	3.9 ± 0.1	3.6 ± 0.3	3.9 ± 0.1	3.9 ± 0.1	3.3 ± 0.1	3.3 ± 0.1	3.3 ± 0.1
3c[d]	–	–	–	–	–	–	–	–	–	–	–	–
4c	12.2 ± 0.2	12.5 ± 0.2	13.0 ± 0.3	12.9 ± 0.3	3.6 ± 0.1	3.6 ± 0.1	3.6 ± 0.3	3.3 ± 0.3	3.3 ± 0.3	3.2 ± 0.1	3.2 ± 0.1	3.2 ± 0.1

[a] In $CDCl_3$, except 4b in DMSO-d_6 at room temperature. [b] Other vicinal axial–axial couplings: 1a, $^3J_{1a,2a}$ = 9.6 ± 0.3 Hz, $^3J_{1a,6a}$ = 9.6 ± 0.3 Hz. [c] Other vicinal axial–equatorial couplings: 1a, $^3J_{1a,2e}$ = 1.8 ± 0.2 Hz. [d] The measure of these coupling constants was unsuccessful on the spectra.

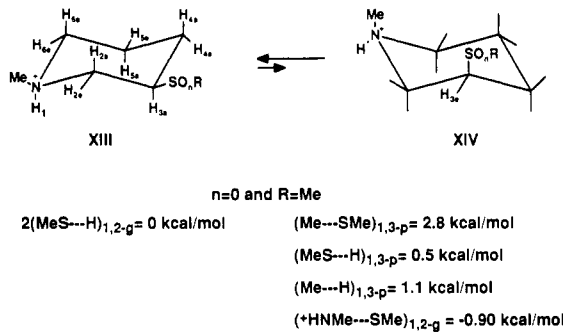

Figure 4.

proton is more shielded than an equatorial one.[31]

The observed multiplicity for protons has been able to be justified by a first-order analysis, which has been summarized in Table II. The vicinal coupling constants between axial NH^+ and $MeNH^+$ has been observed for sulfides 1a and 1c. The values collected in Table V for vicinal coupling constants are midway (i.e., the arithmetic mean of) between the measured values for all constants on multiplets of the usual spectra and spectra recorded with homonuclear decoupling of each one of the protons.

Analysis of Coupling Constants. The observed geminal coupling constants have been gathered in Table IV. Generally, the order (in absolute value) $^2J_{6a,6e} \leq {}^2J_{2a,2e} < {}^2J_{4a,4e} < {}^2J_{5a,5e}$ has been observed. This order is in agreement with the hypothesis well established in the literature[33] that substituents with an inductive effect $-I$ make geminal coupling constants more positive. Thus, the most negative geminal coupling constant corresponds to the ring methylene at position 5, and the most positive value corresponds to ring methylene groups at positions 2 and 6.

The equilibrium between the two alternative chair conformations XIII and XIV is the only equilibrium taken into account to discuss the conformational analysis of piperidinium ring because nitrogen inversion for these compounds is locked[12] (Figure 4). The observed values for vicinal coupling constants[32] (see Table V) prove that the *N*-methylpiperidinium ring adopts a single undistorted chair conformation.

In all cases, the signal of the proton attached to carbon C_3 appears as a triplet of triplets with vicinal coupling constants according to a fixed antiperiplanar orientation of the hydrogen H_3 with H_{2a} and H_{4a}, indicating that the major conformer has an axial H_3, hence the SO_nR group is equatorial. On the other hand, in the spectrum of the compound 1a, the measured values for vicinal coupling constants for NH^+ with the protons H_{2a} and H_{6a} (9.6 Hz) are in agreement with an axial arrangement for the proton attached to the nitrogen. These facts indicate that the conformational equilibrium is fully shifted toward conformation XIII (Figure 4) with groups *N*-methyl and SO_nR in equatorial position. Thus, compounds 1–4 are monoconformational at room temperature, and the observed magnetic resonance parameters are the values of those for conformation XIII.

A semiquantitative evaluation of the equilibrium constant and conformational populations of the two chair conformations XIII and XIV for 1a has been carried out from literature data described for free conformational energies of groups Me and SMe on methylpiperidinium and cyclohexane systems, respectively (Figure 4).

The conformational free energies described in the literature are the following: $\Delta G°_{SMe}$ = 1.0 kcal/mol (ring cyclohexane);[36] $\Delta G°_{Me}$ = 2.2 kcal/mol (at position 3 of a ring of *N*-methylpiperidinium),[15] and the energy of a gauche interaction SMe/H is zero.[37] The free energies for 1,3-parallel interactions SMe/H and Me/H can be estimated as 0.5 and 1.1 kcal/mol, respectively, from the well-known relationship between the free conformational energy of a group X and the energy of a 1,3-parallel interaction X/H.[38] A minimum value for the free energy of a 1,3-parallel interaction Me/SMe can be estimated as 2.8 kcal/mol.[39] The energy of the polar gauche interaction between a ring nitrogen and SMe can be calculated as –0.9 kcal/mol from the empirical equation proposed by Zefirov,[28] the residual charges for ring nitrogen and sulfur calculated by the Rescha program,[27] and the distances between nitrogen and sulfur calculated by minimization with the molecular mechanic force field MMX program.[26] From these values and computing the differential inter-

(31) Reference 30, p 72.
(32) The observed values for axial–axial vicinal coupling constants correspond to an antiperiplanar orientation of the protons (dihedral angles of 180°), and the values of axial–equatorial and equatorial–equatorial couplings correspond to a 1,2-synclinal orientation of the protons. See ref 12.
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(39) The empirical relationship $(X - Y)_{1,3\text{-}p} < 0.87(\Delta G°_X + \Delta G°_Y)$, proposed in the literature,[40] allows the estimation of a minimum value for 1,3-parallel interaction between two groups X and Y for the free conformational energies for groups X and Y.
(40) (a) Fernández-González, F.; Pérez-Ossorio, R.; Rico-Sarompas, M. *An. Quím.* **1974**, *70*, 524. (b) Fernández-González, F.; Pérez-Ossorio, R. *Ibid.* **1973**, *69*, 101.

actions that are present in conformations XIII and XIV, a value of ~300 can be calculated for the equilibrium constant of interconversion XIV ⇄ XIII.

The C_3–C_4–C_5–C_6 and C_4–C_5–C_6–N dihedral angles calculated from the experimental coupling constants by the use of empirical equations proposed by Lambert[34] and Buys[35] and the values displayed for these dihedral angles by the MMX program[26] are in a very good agreement (supplementary material, Table S1). These facts support the validation of the structural minimization carried out by the MMX program and the hypothesis of the monoconformational nature of all compounds studied.

The application of empirical equations of the Karplus type proposed by Altona[41] and Osawa[42] to calculate vicinal coupling constants in an ethane fragment ratifies the same conclusions. The vicinal coupling constants have been calculated from the geometrical parameters (dihedral angles and distances) provided by program MMX and the electronegativities proposed by Huggins[43] (Altona equation) and Mullays[44] (Osawa equation). These calculated vicinal coupling constants for compounds **1a–4a** together with the observed vicinal coupling constants and correlation coefficients of linear regressions between calculated and observed vicinal coupling constants are included in the supplementary material (Table S2). The results for compounds **1b–4b** and **1c–4c** have to be fully analogous because the optimized geometry for the *N*-methylpiperidinium ring by the molecular mechanics force field MMX is identical for all compounds.

The agreement between the observed and calculated vicinal coupling constants from the Altona and Osawa equations is excellent. The linear regression coefficients of the two empirical equations were almost identical. However, axial–equatorial and equatorial–equatorial vicinal coupling constants calculated from the Altona equation were better than those from the Osawa equation. Thus, the observed vicinal coupling constants for compounds 1–4 can be proposed as model values for the conformational analysis of cyclic and acyclic compounds conformationally heterogeneous and structurally related to compounds 1–4.[45]

^{13}C Chemical Shifts. The observed ^{13}C chemical shifts at room temperature for compounds 1–4 have been summarized in Table III. The only available literature data for related compounds were the data described by Eliel[15] for 1-methyl-, 1,2-dimethyl-, 1,3-dimethyl-, and 1,4-dimethylpiperidinium chlorides. The assignment of observed signals to carbons has been carried out from DEPT spectra[46] and two-dimensional ^{1}H–^{13}C heteronuclear correlation spectra.[47] The proposed assignment is fully unequivocal and is in agreement with the described values for *N*-methylpiperidinium chloride[15] taking into account the contributions of groups SMe, SOMe, and SO_2Me in a cyclohexane system.[36]

The contributions of equatorial groups SR, SOR, and SO_2R (R = Me, Et, Pr^i) in a ring *N*-methylpiperidinium, and a ring quaternary nitrogen in a (methylsulfenyl)-, (methylsulfinyl)-, and (methylsulfonyl)cyclohexane have been calculated from ^{13}C chemical shifts described for *N*-methylpiperidinium chloride,[15] thiosubstituted cyclohexanes,[36] and the experimental data described in this work (supplementary material, Tables S3 and S4).

The ^{13}C experimental chemical shifts for compounds **1–4** can be used as model values for the conformational analysis of acyclic and cyclic compounds structurally related to compounds **1–4**.

Configurational Assignment. The configurational assignment of the quaternary nitrogen and ring carbon C_3 for compounds **1–4** is unequivocal and immediate from observed values for vicinal axial–axial coupling constants $^3J_{1a,2a}$, $^3J_{1a,6a}$, $^3J_{2a,3a}$, and $^3J_{3a,4a}$ (see Table V). In all compounds the observed values for these coupling constants agree with an antiperiplanar orientation for hydrogens that are unequivocally axial. Thus, the configurational assignment of these two asymmetric centers was established as (1*S*,3*R*, 1*R*,3*S*).

The configurational assignment of the sulfinyl sulfur for sulfoxides **2a–c** and **3a–c** was less direct. The proton magnetic parameters (chemical shifts and coupling constants) for each pair of diastereomeric sulfoxides **2a/3a**, **2b/3b**, and **2c/3c** were very similar. For this reason, the criteria well established in the literature[48] from geminal coupling constants,[48] chemical shifts of α-protons from sulfinyl sulfur,[48] the syn-axial effect,[49] induced chemical shifts by aromatic solvents,[50] or induced chemical shifts by lanthanide reagents,[50b,c,51] have not been able to be applied. Then, the configurational assignment of the sulfinyl sulfur for sulfoxides **2a/3a**, **2b/3b**, and **2c/3c** has been supported by observed ^{13}C chemical shifts for carbons C_2 and C_4 (see Table III) because these were the only magnetic resonance parameters substantially different for each pair of diasteromeric sulfoxides.

Observed Chemical Shifts for Carbon C_2. The dihedral angle O–S–C_3–C_2 for two major conformations of *S*-sulfoxides (Figure 2, conformations F and G) was significantly less than 60° (28° and 9°, respectively; see Table I). For this reason, carbon C_2 is shielded by the proximity of the σ-rich sulfinyl oxygen. This situation was not present in the major conformation for the *R*-sulfoxides (Figure 2, conformation C). The geometry of this conformation is staggered and carbon C_2 has a gauche orientation relative to the sulfinyl oxygen and the lone pair of sulfur. Thus, the chemical shift observed for carbon C_2 on *S*-sulfoxides has to be less than for *R*-sulfoxides. Then, the configuration *S* of the sulfinyl sulfur can be assigned to sulfoxides **2a**, **2b**, and **2c**, and the configuration *R* to sulfoxides **3a**, **3b**, and **3c**.

On the other hand, the chemical shift for carbon C_2 on *R*-sulfoxides must have an intermediate value between the observed chemical shifts for carbon C_2 on the sulfides and sulfones, because the situation of carbon C_2 in the major conformation of *R*-sulfoxides (Figure 2, conformation C) is halfway between the arrangement of this carbon on the sulfides (conformation A) and sulfones (conformation H or J). Thus, the configuration *R* again can be assigned to sulfoxides **3a**, **3b**, and **3c**.

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Observed Chemical Shift for Carbon C_4. The relative arrangement of the lone pair of the sulfinyl sulfur and carbon C_4 is antiperiplanar in the major conformation for *R*-sulfoxides (conformation C, Figure 2). However, the relative arrangement of the lone pair and carbon C_4 is gauche in major conformations for *S*-sulfoxides (conformations F and G, Figure 2). From the well-known fact that the shielding effect of a lone pair on a carbon chemical shift is greater for a relative antiperiplanar arrangement than for a gauche arrangement,[52] it can be established that the chemical shifts observed for carbon C_4 have to be less in *R*-sulfoxides than *S*-sulfoxides. Thus, the relative configuration *R* is supported for sulfoxides **3a**, **3b**, and **3c**, and the configuration *S* for sulfoxides **2a**, **2b**, and **2c**.

A semiquantitative configurational assignment for the sulfinyl sulfur on the diastereomeric sulfoxide pairs **2a/3a**, **2b/3b**, and **2c/3c** has been carried out by solving eqs 1 and 2[53]

$$\delta^{obs}_{Cj} = \sum N_i \delta^i_{Cj} \quad (1)$$

$$\sum N_i = 1 \quad (2)$$

where δ^{obs}_{Cj} is the chemical shift observed for carbon C_j, δ^i_{Cj} is the chemical shift for carbon C_j in the conformation *i*, and N_i the population of conformation *i*.

The application of these two equations by using the observed chemical shifts for carbons C_2 and C_4 and taking into account the conformations C and D (or E) (Figure 2) for *R*-sulfoxides, and conformations F and G for *S*-sulfoxides (Figure 2), gives rise to a sytem of 6 equations with 12 unknown parameters. In order to reduce the number of these parameters, we can consider that (a) the chemical shifts for carbon C_2 in conformations C and F are practically identical because the relative arrangement of carbon C_2 and the lone pair is gauche and the arrangement of carbon C_2 and group R is antiperiplanar in these two conformations; (b) the chemical shifts for carbon C_2 in conformations D (or E) and G have to be practically identical because carbon C_2 has a gauche arrangement with the sulfinyl oxygen and group R and an antiperiplanar arrangement with the sulfur lone pair; (c) the chemical shifts for carbon C_4 in conformations D (or E) and F have to be identical because in these conformations carbon C_4 has a relative gauche arrangement with the sulfur lone pair and group R and an antiperiplanar arrangement with the sulfinyl oxygen; (d) the chemical shift for carbon C_4 in conformation G (δ^G_{C4}), and the chemical shift for carbon C_2 in conformation F (δ^F_{C2}), can be related as $\delta^G_{C4} = \delta^G_{C2} - 33.4$ ppm, the value of 33.4 ppm being the difference between the chemical shifts observed for carbons C_2 and C_4 of *N*-methylpiperidinium chloride.[15]

Considering all combinations of values for populations of major conformations between zero and one for the two alternative configurational assignments, a set of solutions are obtained. The valid solutions can be selected taking into account that the following conditions have to be satisfied simultaneously:

$$\delta^F_{C2} > \delta^F_{C4};\ \delta^C_{C2} > \delta^{D(or\ E)}_{C4};\ \delta^F_{C2} > \delta^C_{C4};\ \delta^G_{C2} > \delta^{D(or\ E)}_{C4};\ \delta^F_{C2} > \delta^G_{C2};\ N_C > N_F$$

These conditions are very reasonable according to the influences of the sulfur lone pair and the sulfinyl oxygen on chemical shifts for carbons C_2 and C_4. In all solutions selected the chemical shifts for carbons C_2 and C_4 of sulfoxide **2a**, **2b**, and **2c** correspond to *S*-sulfoxides, and the chemical shifts for these carbons of sulfoxides **3a**, **3b**, and **3c** correspond to *R*-sulfoxides. Furthermore, the calculated unknown parameters taking into account all logical solutions have a small variation and are very reasonable.

Sulfoxides **2a/3a**: $0.2 \le N_F \le 1.0$; $0.6 \le N_c \le 1.0$; $38 \le \delta^G_{C2} \le \delta^{D(orE)}_{C2} \le 50$ ppm; $54 \le \delta^F_{C2} = \delta^C_{C2} \le 57$ ppm; $23 \le \delta^F_{C4} = \delta^{D(orE)}_{C4} \le 35$ ppm; $14 \le \delta^C_{C4} \le 16$ ppm.

Sulfoxides **2b/3b**: $0.2 \le N_F \le 1.0$; $0.6 \le N_C \le 1.0$; $39 \le \delta^G_{C2} = \delta^{D(orE)}_{C2} \le 50$ ppm; $54 \le \delta^F_{C2} = \delta^C_{C2} \le 57$ ppm; $19 \le \delta^F_{C4} = \delta^{D(orE)}_{C4} \le 35$ ppm; $13 \le \delta^C_{C4} \le 17$ ppm.

Sulfoxides **2c/3c**: $0.2 \le N_F \le 1.0$; $0.6 \le N_C \le 1.0$; $33 \le \delta^G_{C2} = \delta^{D(orE)}_{C2} \le 50$ ppm; $54 \le \delta^F_{C2} = \delta^C_{C2} \le 64$ ppm; $21 \le \delta^F_{C4} = \delta^{D(orE)}_{C4} \le 35$ ppm; $15 \le \delta^C_{C4} \le 19$ ppm.

The calculated values for conformational populations N_C and N_F by this procedure are very analogous with the calculated populations from relative energies established from the molecular mechanics force field MMX (see Figure 2). Likewise, the calculated range of variation for the chemical shifts of carbons C_2 and C_4 in the major conformations of *R*- and *S*-sulfoxides is in good agreement with chemical shifts observed for these carbons (see Table III).

A full spectroscopic study (^1H and ^{13}C NMR) of 3-(alkylsulfenyl)-, 3-(alkylsulfinyl)-, and 3-(alkylsulfonyl)-*N*-methylpiperidines is in progress.

In summary, then, 3-(alkylsulfenyl)-, 3-(alkylsulfinyl)-, and 3-(alkylsulfonyl)-*N*-methylpiperidinium chlorides (alkyl = Me, Et, Pri) have been studied for the first time to evaluate the importance of polar interactions between a quaternary nitrogen and a sulfur (sulfide, sulfoxide, or sulfone) in relative positions 1,3. The application of molecular mechanics force field MMX has made it possible to perform a correct analysis of conformational equilibria for all compounds. The *N*-methylpiperidinium ring for all compounds adopts a single undistorted chair conformation with the groups *N*-methyl and SO_nR in fixed equatorial positions. The conformational differences between different compounds come from rotation around the bond C_3–SO_nR. The results can be rationalized by taking into account the steric interactions and attractive or repulsive polar interactions between the σ-deficient and σ-rich ring carbons C_2 and C_4, the lone pair of sulfur, and the σ-rich oxygen of the sulfoxide and sulfone groups. The residual charges for all atoms have been computed with the Rescha program.

Likewise, the magnetic resonance parameters (^1H and ^{13}C NMR chemical shifts and geminal and vicinal coupling constants) have been described for the first time for these compounds. The assignment of signals has been carried out from observed chemical shifts, homonuclear decoupling experiments, DEPT spectra, and two-dimensional ^1H–^{13}C heteronuclear correlation spectra. The observed axial–axial vicinal coupling constants establish that the *N*-methylpiperidinium ring for all compounds adopts a single undistorted chair conformation. The configurational assignment of ring quaternary nitrogen and ring carbon C_3 has been carried out from vicinal axial–axial coupling constants observed for protons H_{1a} and H_{3a}. The configurational assignment of sulfinyl sulfur in the diastereomeric sulfoxide pairs has been carried out from the differences observed for chemical shifts of carbons C_2 and C_4.

Experimental Section

The synthesis of compounds **1ac**, **2a–c**, **3a–c**, and **4a–c** and the separation of diastereomeric sulfoxides **2a–c/3a–c** have been previously described.[20] Proton (300 MHz) and ^{13}C NMR (75 MHz) one- and two-dimensional spectra were recorded at 25 °C on a

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Varian VXR 300S instrument operated in the pulsed Fourier transform mode and locked on solvent deuterium. Samples were prepared as 10–15% solutions in $CDCl_3$ (**4b** in DMSO-d_6) with 0.1% of TMS as internal reference in 5-mm-o.d. tubes.

One- and two-dimensional spectra were recorded under the following conditions. ^1H NMR: spectral width, 7500 Hz; acquisition time, 3.742 s; number of scans, 16/32/128; pulse width, 7 μs (35°); weighting function, line broadening of 0.8–1.0 Hz and gaussian apodization of 0.543 s; zero filling of 64 K; digital resolution, 0.23 Hz/point. ^{13}C NMR: spectral width, 16500 Hz, acquisition time, 0.8 s; delay time between pulses, 1 s; pulse width, 4 μs (30°); number of scans, 1024–4096; weighting function, line broadening of 0.6–1.0 Hz; decoupler, Waltz-16 modulated; zero filling of 64 K; digital resolution, 0.5 Hz/point. DEPT spectra: spectral width, 3614 Hz; acquisition time, 0.8 s; delay time between pulses, 1.5 s; pulse width, 12 μs (90°); pulse width of decoupler, 18 μs (90°); number of scans, 128/256/512; decoupler, Waltz-16 modulated; weighting function, line broadening of 1.0 Hz. Two-dimensional ^1H–^{13}C heteronuclear correlation spectra, ^{13}C dimension: spectral width, 3766 Hz; acquisition time, 0.8 s; pulse width, 12 μs (90°); delay time between pulses, 1.5–2.0 s; number of scans, 512/1024; number of increments; 32/64. ^1H dimension: pulse width, 18 μs (90°); decoupler gated on during acquisition and off during delay; decoupler, Waltz-16 modulated. Data processing, zero filling: ^1H dimension, 2 K and ^{13}C dimension, 0.5 K. Weighting functions: ^1H dimension, sine bell of 0.034 s, and ^{13}C dimension, sine bell of 0.020 s.

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Registry No. **1a**·HCl, 135625-93-3; **1b**·HCl, 135625-94-4; **1c**·HCl, 135625-95-5; (*R,S*)-**2a**·HCl, 135625-96-6; (*R,S*)-**2b**·HCl, 135625-97-7; (*R,S*)-**2c**·HCl, 135625-98-8; (*R,R*)-**3a**·HCl, 135626-02-7; (*R,R*)-**3b**·HCl, 135626-03-8; (*R,R*)-**3c**·HCl, 135626-04-9; **4a**·HCl, 135625-99-9; **4b**·HCl, 135626-00-5; **4c**·HCl, 135626-01-6.

Supplementary Material Available: Tables S1 (dihedral angles), S2 (calculated vicinal coupling constants for compounds **1a–4a** from the Altona and Osawa equations), S3 (^{13}C equatorial substituent parameters in 3-(alkylthio)-substituted *N*-methylpiperidinium chlorides), and S4 (^{13}C induced shift contributions of a ring quaternary nitrogen in substituted cyclohexanes) (4 pages). Ordering information is given on any current masthead page.

Systematic Substitution on the Cubane Nucleus: Steric and Electronic Effects

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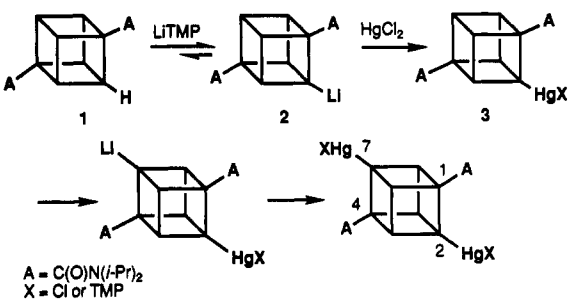
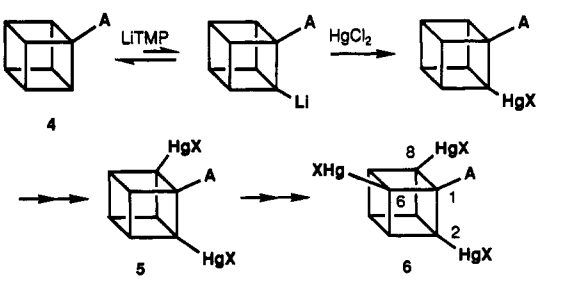
Effective methodology for the synthesis of cubanes with novel substitution patterns is presented. The use of an electron-withdrawing group to accelerate ortho-metalation of amide-activated cubanes is described, as is the effect of the steric bulk of the activating group on the degree of ortho-metalation.

In previous work from this laboratory it was shown that the ortho-metalation process so well-known in aromatic chemistry could be extended to certain strained, saturated systems like cubane and cyclopropane.[1] This discovery has led to novel and useful methodology for systematic substitution on such compounds. For example (Scheme I), the activation provided by the *N,N*-diisopropylcarbamoyl groups on the 1,4-disubstituted cubane **1** permits a strong base like lithium tetramethylpiperidide (LiTMP) to remove a proton ortho to one amide group, giving the lithiated cubane **2**. When there are no amide groups (cubane itself) only very little deprotonation occurs.[1a] The amide adjacent to the lithiated position assists ortho-metalation, presumably as it does in aromatic cases.[2] The remote amide group (position 4) stabilizes the lithiated cubane significantly via its general electron-withdrawing inductive effect; without it the equilibrium is much less (about $^1/_{25}$) to the right.[1a] The reaction can be drawn

Scheme I



Scheme II



completely over to a metalated species by coupling the first equilibrium step with a transmetalation process in which the cubyl lithium is converted into a far less polar and

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