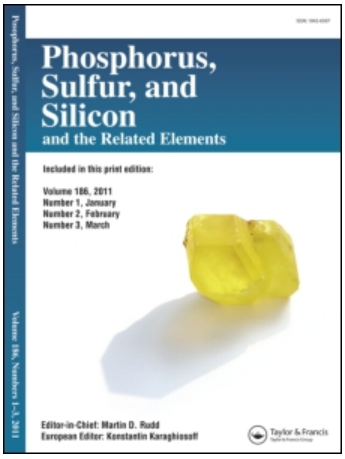

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GEOMETRICAL OPTIMIZATIONS, NMR ANALYSES, AND NOVEL CRYSTAL STRUCTURES OF 3-OXA-7-BENZYL-7-AZABICYCLO[3.3.1]-NONAN-9-ONE AND 3-THIA-7-BENZYL-7-AZABICYCLO[3.3.1]-NONAN-9-ONE; STRUCTURAL ANALYSIS OF THE CORRESPONDING 3,7-DIHETERABICYCLO[3.3.l]NONANE HYDROPERCHLORATES

K. DARRELL Berlin[a]; Sameer Tyagi[a]; Asif Rahaman[a]; Feng Qiu[a]; Lionel M. Raff[a]; Lalitha Venkatramani[b]; M. A. Khan[b]; Dick Van Der Helm[b]; Valentina Yu[c]; K. D. Praliev[c]
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GEOMETRICAL OPTIMIZATIONS, NMR ANALYSES, AND NOVEL CRYSTAL STRUCTURES OF 3-OXA-7-BENZYL-7-AZABICYCLO[3.3.1]-NONAN-9-ONE AND 3-THIA-7-BENZYL-7-AZABICYCLO[3.3.1]-NONAN-9-ONE; STRUCTURAL ANALYSIS OF THE CORRESPONDING 3,7-DIHETERABICYCLO[3.3.1]NONANE HYDROPERCHLORATES

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An investigation has been made of the structures of the title compounds via theoretical calculations, high resolution NMR analysis, and X-ray diffraction analysis. Conformational analyses of these compounds in the gas phase were performed using *ab inito* methods with GAUSSIAN 94. Single point calculations at the MP4/6–31G level for 3-oxa-7-azabicyclo[3.3.1]nonan-9-one revealed an energy difference of only $\Delta E = 1.497$ kcal/mole between the chair-chair (CC) and boat-chair (BC) conformers. Full geometry optimization of the oxygen-containing ketone at the Hartree-Fock (HF) level using a 6–31G basis set indicated only a negligible variation in interatomic distances in the equilibrium geometry when the phenyl group was included in the calculation versus when the phenyl group was replaced by hydrogen. Full geometry optimization for the sulfur-containing ketone (phenyl replaced by a hydrogen) at the HF level using the 6–31G basis set again demonstrated that the BC form was

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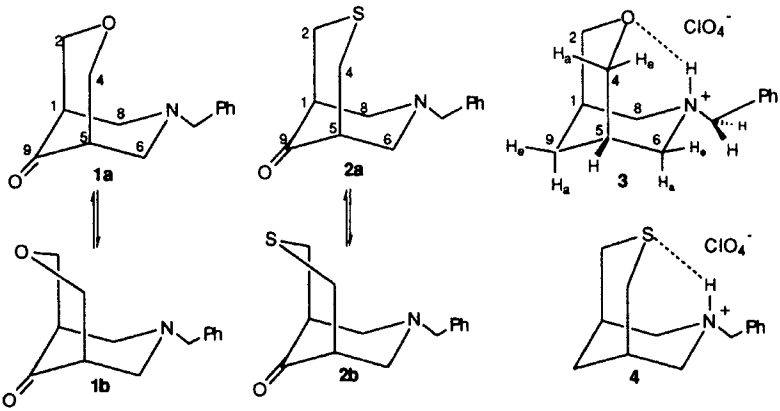
slightly more stable than the CC form, identical to that found with the oxygen counterpart. Full geometry optimization of the two hydroperchlorates (phenyl replaced by hydrogen) resulted in the CC form being suggested as the more stable with H-bonding between the hydrogen on nitrogen and the respective heteroatom, a situation which likely enhances stability. Proton NMR analyses of both compounds using NOESY techniques strongly supported a predominance of the BC form in solution for the oxygen-containing ketone. Severe signal overlap in the sulfur ketone (even at 600 MHz) prevented in depth analysis of the structure. Using NOESY, DQCOSY, and HMBC techniques, NMR analyses of the corresponding hydroperchlorates implied CC forms for each in solution. The X-ray diffraction analysis of the oxygen-containing ketone revealed a CC in the solid state.

Keywords: 3-Oxa- and 3-thia-7-benzyl-7-azabicyclo[3.3.1]nonan-9-ones; corresponding 3,7-diheterabicyclo-[3.3.1]nonane hydroperchlorates; NMR analyses; theoretical calculations; X-ray diffraction

INTRODUCTION

The dynamics of 3,7-diheterabicyclo[3.3.1]nonanes (DHBCNs) and 3,7-diheterabicyclo[3.3.1]nonan-9-ones (DHBCNONs) are not completely understood, especially in solution.[1,2] Some preliminary work has appeared in this area,[2,3] but no detailed theoretical and structural analyses have been described. In view of the potential utility of the DHBCNONs as synthons, a rigorous examination is worthwhile of the dynamics and structures of the two related title ketones, along with their respective reduced systems in the form of hydroperchlorates. Moreover, such latter salts have exhibited strong antiarrhythmic activity in animal models.[2,3] The structures under consideration are **1–4**.



We report herein the use of theoretical calculations, 2D NMR measurements with NOESY, DQCOSY, and HMBC experiments, and X-ray diffraction analysis of **1.** We have reported the solid state analysis of **2** and **4** earlier.[2b] The NMR data proved extremely useful in diagnosing preferred conformations of the compounds in solution with the theroretical data being supportive.

RESULTS AND DISCUSSION

Initially, we elected to examine the ^1H NMR spectra of **3** and **4** at 400 MHz using NOESY. Since both rings in each of the four systems can be considered as having axial and equatorial positions, we have labeled specific positions as shown in the drawing. This is an arbitrary assignment to avoid confusion about the identity of a specific proton at a position. To clearly distinguish signals from H(2,4,6,8), an entry point of δ 4.22 (methylene protons of the benzyl group) was chosen for the NOESY experiment for **3** (Figure 1). Crosspeaks were observed for these methylene protons and the signals at δ 3.24 and δ 3.40. Since $H(6,8)_{ae}$ are closer in space than are $H(2,4)_{ae}$ to the H_2CPh group, it was concluded that the signals at δ 3.24 and δ 3.40 were from $H(6,8)_{ae}$. This is somewhat contrary to what might be expected since signals for $H(6,8)_{ae}$[adjacent to HN^+] are at higher field than those for $H(2,4)_{ae}$ [adjacent to oxygen]. Crosspeaks were observed between δ 3.40 with HN(7) [δ 8.65] and with the benzylic protons CH_2Ph (δ 4.22). Since $H(6,8)_e$ is closer in space to HN(7) than is $H(6,8)_a$, the signal at δ 3.40 is due to $H(6,8)_e$ and hence the signal at 6 3.24 can be assigned to H(6,8)a. A crosspeak occurred between δ 3.24 [$H(6,8)_a$] and that at δ 1.81, and thus the latter was assigned to $H(9)_a$ since it was closer. The signal at δ 1.91 was then assigned to $H(9)_e$. From this observation, it was reasonable to conclude that $H(6,8)_{ae}$ signals were more upfield than those for $H(2,4)_{a,e}$. Signals at δ 3.67 and δ 3.93 were assigned to $H(2,4)_{ae}$. In view of the crosspeak between the signal at δ 3.67 and that for $H(9)_e$ at δ 1.81, the former was designated for $H(2,4)_a$ thereby leaving the signal at δ 3.93 for $H(2,4)_e$. A crosspeak was also observed for $H(2,4)_e$ and $H(6,8)_e$. Both observations support **3a** as the major conformer. Thus, in summary, it appears that **3** exists, on the average, in solution as a CC conformer based on crosspeaks between $H(2,4)_e$-$H(6,8)_e$, $H(2,4)_a$-$H(9)_e$, and $H(6,8)_a$-$H(9)_a$. Note that $H(2,4)_a$ and $H(2,4)_e$ are pseudo axial and equatorial in BC **3b**.

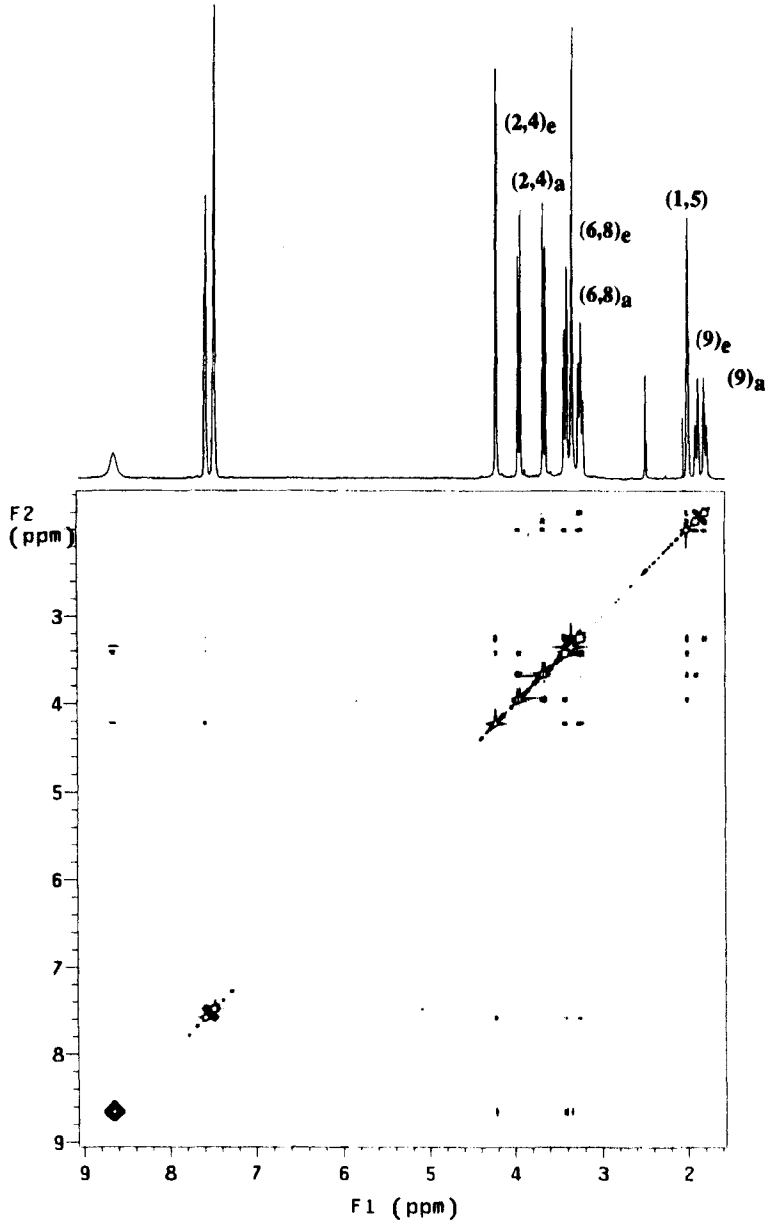
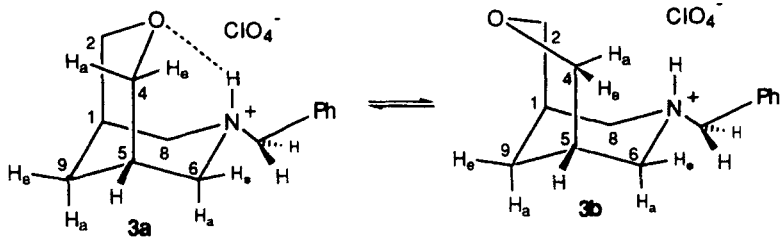


FIGURE 1 NOESY NMR spectrum of **3**



The DQCOSY spectrum (Figure 2) displayed several long range "W" patterns (4-bond couplings).[4] Some dominant 4-bond couplings are visible between $H(9)_a$-$H(2,4)_e$, $H(9)_e$-$H(6,8)_e$, and $H(6,8)_a$-$H(2,4)_a$. This type of coupling is believed to occur when the tails of the orbitals of the first and fourth bond overlap. With **3**, this is only possible when both rings are in chair conformations in a CC form. As an example, such overlap is clearly feasible between the tails of $H(2,4)_a$ and $H(6,8)_a$ when the rings are in chair conformations in **3**. In contrast, such overlap is not possible in the BC conformer **3b**. This observation also supports a CC conformation **3a**.

Similar to **3**, the point of entry in the NOESY spectrum for **4** (Figure 3) was chosen as δ 4.28 which is the signal for the methylene protons of the benzyl group. Crosspeaks were noted between the latter signal and those at δ 3.33 and δ 3.55. These signals were assigned to $H(6,8)_{ae}$ since the protons are closer to H_2CPh than is $H(2,4)_{ae}$. A crosspeak between the signal at δ 3.55 and that at δ 9.25 [HN(7)] confirmed the former as that for $H(6,8)_e$, and, hence, the signal at δ 3.33 was due to $H(6,8)_a$. Another crosspeak between the signal at δ 3.33 and that at δ 1.84 confirmed the latter to be that for $H(9)_a$ and that at δ 1.79 had to be for $H(9)_e$. A crosspeak between the signal at δ 1.79 [$H(9)_e$] and that at δ 3.10 supported the latter to be for $H(2,4)_a$. Thus, the signal at δ 2.69 was attributed to $H(2,4)_e$ This is somewhat contrary to what has commonly been accepted in cyclohexyl systems where axial protons appear more upfield than equatorial protons.[5] A cross peak was also observed between $H(6,8)_e$ and $H(2,4)_e$. Note again that $H(2,4)_a$ and $H(2,4)_e$ are pseudo axial and pseudo equatorial, respectively, in **4b**. Thus, crosspeaks between $H(2,4)_e$-$H(6,8)_e$, $H(2,4)_a$-$H(9)_a$, and $H(6,8)_a$-$H(9)_a$ are confirmatory for the CC conformer **4a** as dominant in solution. This conclusion is identical to that for this sul-

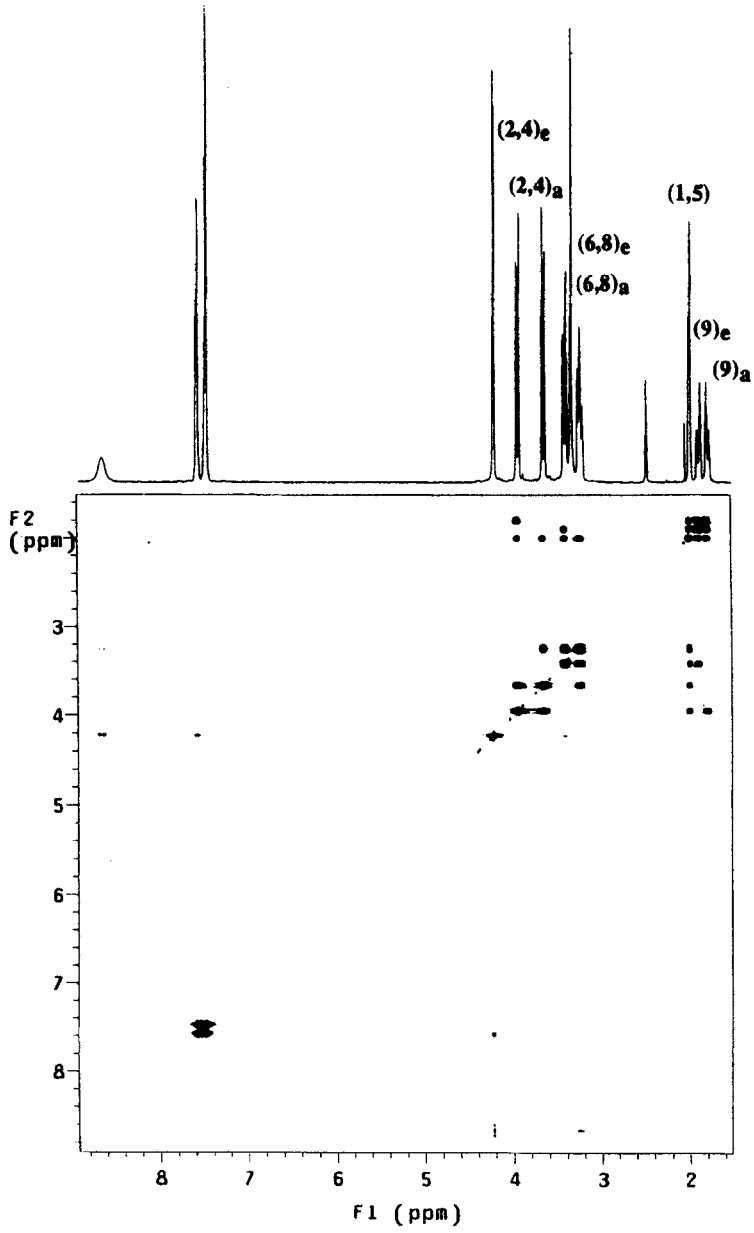
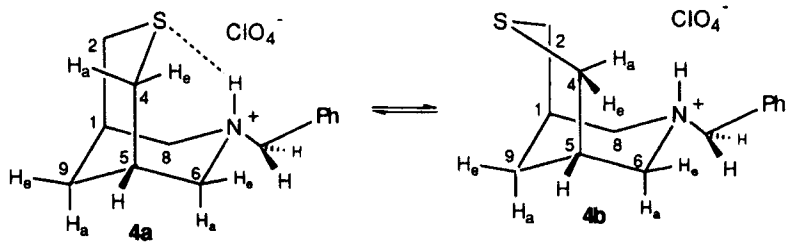


FIGURE 2 DOCOSY NMR spectrum of **3**

fur compound whose X-ray diffraction analysis of a single crystal revealed the CC form **4a**.[2b]



The DQCOSY spectrum (Figure 4) of **4a** was informative in that "W" couplings were observed between $H(9)_a$-$H(2,4)_e$, $H(9)_e$-$H(6,8)_e$, and $H(6,8)_a$-$H(2,4)_a$ which is supportive of the CC form. Interestingly, long range, 3-bond couplings between protons and carbons were noted in the HMBC spectrum (not shown). Prominent examples include $H(9)_{ae}$-C(6,8), $H(2,4)_e$-C(9), $H(2,4)_a$-C(6,8), $H(6,8)_a$-C(2,4), $H(6,8)_e$-C(9), and benzyl protons $H_2CC_6H_5$-C(6,8).

In the ketones **1** and **2,** one might expect greater conformational mobility in terms of ring reversal as compared to salts **3** and **4** where intramolecular H-bonding surely occurs between HN(7) and the heteroatom O or S.[2] In addition, repulsion of the nonbonded electron pairs on the heteroatoms in the ketones could reduce the energy barrier to ring reversal, thereby making possible a rapid equilibrium of CC⇄BC at room temperature.[6] An ^{17}O NMR investigation of **1a**⇄**1b** in D_3CCN/H_3CCN was best defended by assuming such an equilibrium with possibly the **1b** (BC form) predominating.[2a] Although based upon comparisons with reasonable model systems, none of this earlier work was definitive, however.

In the case of ketone **1**, homonucelar NOESY and DQCOSY experiments were not informative. However, a heteronuclear NOESY (HOESY)[7] and coupling constant analysis proved useful. In an ^1H-^{13}C HOESY experiment (Figure 5) a significant proton-carbon correlation was detected for H(2,4) and C(6,8). This was manifested in a crosspeak between the signal at δ 3.87 [$H(2,4)_e$] and that observed for C(6,8). Since the distance between $H(2,4)_e$ to C(6), for example, is greater in **1a** than is the distance between $H(2,4)_a$ and C(6) in **1b** (as found via *ab initio* calculations), it is tentatively concluded that such evidence supports the BC

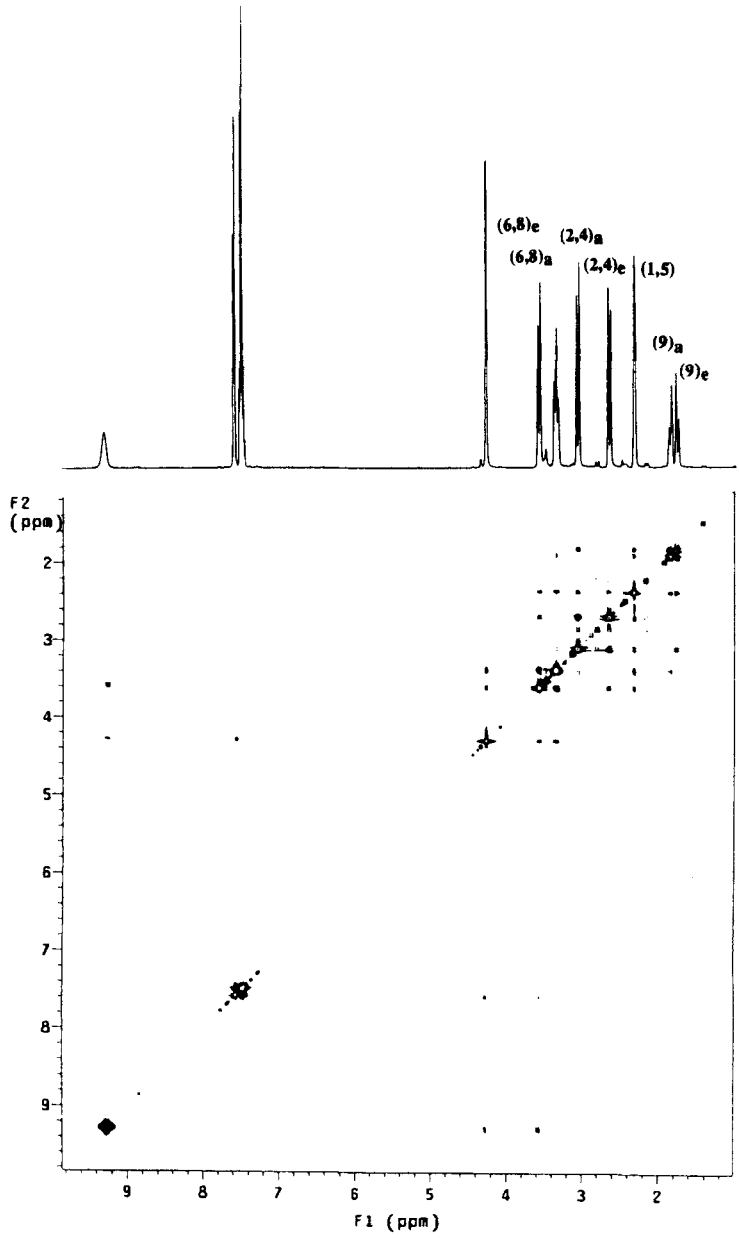


FIGURE 3 NOESY NMR spectrum of **4**

form **1b** in $DCCl_3$. The calculations for these distances are not given but have the values of 2.777 Å and 2.543 Å for $H(2)_e$-C(6) in **1a** and $H(2)_a$-C(6) in **1b,** respectively. Note the $H(2,4)_e$ in **1a** refers to the same hydrogen atoms in **1b** but the latter are designated $H(2,4)_a$ (pseudo axial) because of the BC conformation. The ^2J and ^3J coupling constants in Table I are also best rationalized by assuming the BC form **1b** is preferred. In the BC conformer **1b,** the angle between $H(2,4)_a$ and H(1,5) approaches 90° while the angle between $H(2,4)_e$ and H(1,5) is closer to 0°. Thus, a small vicinal ^3J coupling is expected for the former case and a larger ^3J coupling for the latter case. These couplings were observed, and we tentatively suggest a predominance of the BC form **1b** as present in solution. This agrees with the former ^{17}O NMR study.[2a]

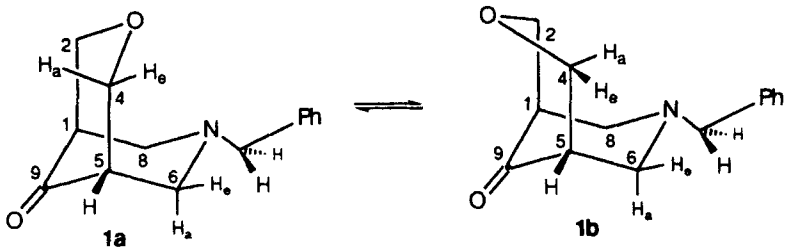
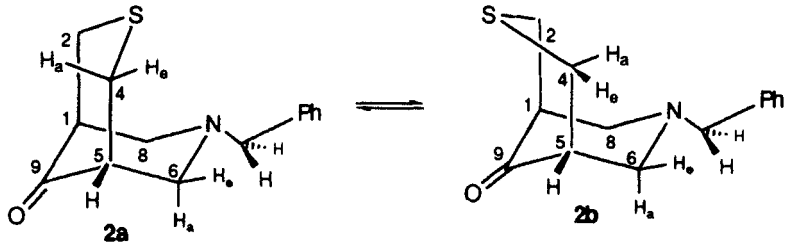


TABLE I ^1H NMR chemical shifts (δ), multiplicities, and coupling constants for **1**

proton	δ *values*	*J values*
H(1,5)	2.53	
$H(2,4)_a$	4.21 (d)	$^2J = 10.98$
$H(2,4)_e$	3.87 (dd)	$^2J = 11.17, ^3J = 2.74$
$H(6,8)_a$	2.93 (dd)	$^2J = 11.17, ^3J = 6.04$
$H(6,8)_e$	3,11 (dd)	$^2J = 10.98, ^3J = 2.56$

With the sulfur ketone **2,** overlap of the signals for methylene protons was extensive at 400 MHz. Examples were the signals for $H(2,4)_a$ and $H(6,8)_e$ which overlapped and appeared as a multiplet at δ 3.08 as shown in Table II. Spectral analysis of **1** and **2** even at 600 MHz spectrometer was confirming for the former, with respect to the signals for $H(2,4)_a$ and



$H(6,8)_e$ which appeared as a multiplet at δ 3.08, but was still not resolved for **2**, especially in the range of δ 3.07–3.13. Although several doublets were visible in this range, resolution was not sufficiently inadequate to allow assignment of the signals. At this point, it is tempting to speculate that BC **2b** predominates in solution as was found in the solid state.[2b] However, X-ray diffraction data to be discussed below for the oxygen-containing ketone clearly shows the solid conformer as the CC form **1a**. In view of these observations, we elected to perform *ab initio* calculations.

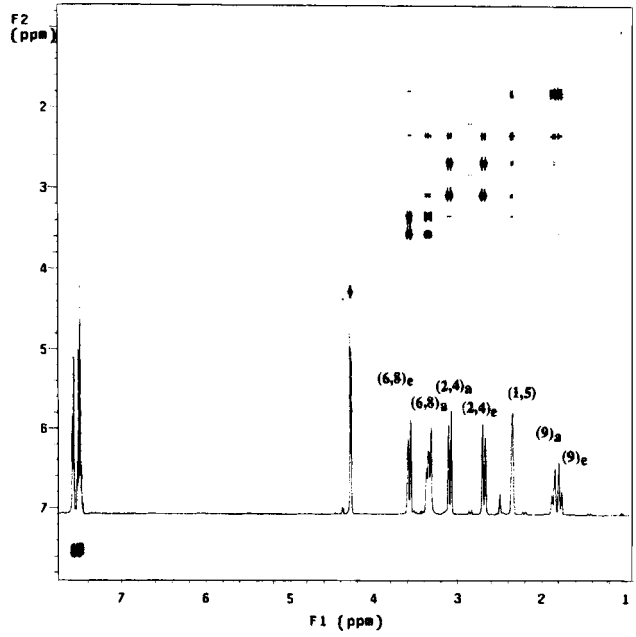


FIGURE 4 DOCOSY NMR spectrum of **4**

TABLE II ^{1}H NMR chemical shifts (δ), multiplicities, and coupling constants for **2**

proton	δ *values*	*J values*
H(1,5)	2.70	
$H(2,4)_a$	3.08 (m)	
$H(2,4)_e$	3.25 (dd)	$^2J = 13.68$, $^3J = 3.80$
$H(6,8)_a$	2.64 (dd)	$^2J = 11.35$, $^3J = 4.80$
$H(6,8)_e$	3.08 (m)	

TABLE III Minimum potential energy (kcal/mole) calculations for ketones **1a⇄1b** and **2a⇄2b**

System	*Theory level/Basis set*	*CC*	*BC*	*ΔE*
1a/1b (O)	HF/6–31G	-322803.7043	-322804.2484	0.544
2a/2b (S)	HF/6–31G	-525278.5930	-525279.4852	0.892

In an effort to determine the relative conformer stabilities of **1–4**, *ab initio* methods with GAUSSIAN 94[7] were employed. The results of the calculations for ketones **1** and **2** are tabulated in Table III. The goal was to ascertain the most stable conformation and to determine interatomic distances between $H(2,4)_a$-C(9), $H(2,4)_e$- C(9), and $H(6,8)_a$-C(9) in systems **1–4**. To reduce computational time, the phenyl (Ph) group was replaced by hydrogen (H) in all calculations except one. The above geometries were fully optimized at the Hartree-Fock (HF) level of theory with different basis sets. With a minimal STO-3G basis set, the CC form **1a** is more stable than the BC form **1b**. With more extended basis sets (3–21G onward), the order of stability reversed, i.e. the BC form **1b** was the more stable conformer. Repulsion between the lone electron pairs on N(7) and the lone pairs on oxygen destabilized the CC form **1a** compared to the BC form **1b** where repulsion was reduced.

To examine the effect of substitution of hydrogen for the phenyl (Ph) group, a full geometry optimization for the BC form **1b** was performed at the HF level of theory using a 6–31G basis set. Only a negligible variation was found in the interatomic distances in the equilibrium geometery for **1a⇄1b and 2a⇄2b**. Thus, it appears that the replacement of H on N(7) by a phenyl group does not produce spurious effects on the results.

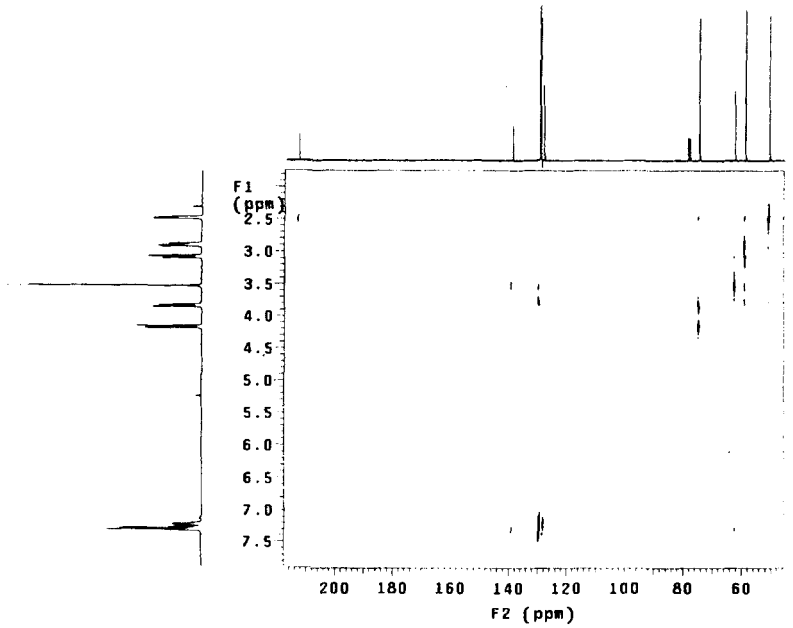


FIGURE 5 HOESY NMR spectrum of **1**

To gain insight as to the population of conformers **1a** and **1b** as a function of temperature, the energy difference (ΔE) between the CC and BC conformers was determined in the gas phase. A single-point calculation was carried out for each conformer at the MP2/6–31G level using the optimized geometry obtained at the HF level of theory with a 6–31G basis set. The energy difference (ΔE) between the CC (**1a**) and BC (**1b**) conformations is given in Table IV. It is clear that this difference is very small. Thus, the energy gain in the conversion of one conformer to the other in the equilibrium **1a**⇄**1b** is probably quite small.

TABLE IV Energy difference between the CC and BC conformations of **1a**⇄**1b**

Theory Basis Set	*ΔE (Hartrees)*	*ΔE (Kcal/mole)*
MP2/6–31G	2.1865E-3	1.3720
MP4/631-G	2.3857E-3	1.4970

Full geometry optimization for the sulfur-containing **2a⇄2b** system was performed at the HF level with different basis sets. These results appear in Table V. The data show similar trends as in the **1a⇄1b** system with the BC form being favored, but only slightly.

TABLE V Minimum potential energy (kcal/mole) calculations for ketones **3a⇄3b** and **4a⇄4b**

System	*Theory level/Basis set*	*CC*	*BC*	ΔE
3a/3b (O)	HF/6–31G	-276843.1707	-276827.7789	15.39
4a/4b (S)	HF/6–31G	-479314.1682	-479302.6091	11.55

Full geometry optimizations were carried out for the oxygen salt **3a⇄3b** and the sulfur salt **4a⇄4b** at the HF level. In these calculations, an H replaced the phenyl group to reduce computation time. Results are shown in Table V. In both cases the CC form was the more stable than the BC form, an opposite effect from that noted in the ketones **1a/1b** and **2a/2b.** It is assumed that H-bonding between the proton on N(7) and the oxygen atom in **3a** and the sulfur atom in **4a** contribute significantly to the stabilization of the CC conformers.

Interatomic distances were calculated (Table VI) for **1–4** as a measure of closeness of certain protons to C(9) and the differences in these distances with the level of the theory employed for both the CC and BC forms. It is clear from the data in Table VI that very little deviation occurs in the various distances as the level of sophistication increases in terms of the basis sets utilized. Consequently, there is confidence in the values of the distances to represent the CC and BC conformers of **1–4**. In the CC forms **1a**, **2a**, **3a**, and **4a** there is remarkable consistency in the distance of $H(2,4)_e$-C(9) which implies there is little distortion in the various sets of rings in spite of slight flattening expected in the CC ketones **1a** and **2a** versus the CC salts **3a**, and **4a**. The maximum deviation is only 0.04 Å for this distance which is striking as well. The deviation is slightly greater (0.09 Å) in the distance of $H(2,4)_e$-C(9), suggestive of some slight ring deformation. In the ring containing N(7), the $H(6,8)_a$ deviation is less than 0.02 Å, suggesting that the nitrogen-containing ring is not altered geometrically to any appreciable extent. These data are consistent with the oxygen- and sulfur-containing rings experiencing some alteration from a cyclohexyl type system due to internal repulsion between the heteroatoms.

TABLE VI Interatomic distances (Å) of selected protons to C(9) for **1–4** at different basis sets (NH replaced NPh)

Compd	*Form*	*Basis Sets*	$H(2,4)_a$	$H(2,4)_e$	$H(6,8)_a$	$H(2,4)_{pa}$	$H(2,4)_{pe}$	$H(6,8)_a$
1a	CC	HF/STO-3G	2.7503	3.4556	2.7509			
	CC	HF/3–21G	2.7460	3.4130	2.7437			
	CC	HF/6–21G	2.7525	3.4163	2.7534			
	CC	HF/6–31G	2.7588	3.4064	2.7567			
1b	BC	HF/STO-3G				3.2223	3.2630	2.7428
	BC	HF/3–21G				3.1708	3.2174	2.7401
	BC	HF/6–21G				3.1703	3.2271	2.7483
	BC	HF/6–31G				3.1606	3.2447	2.7331
2a	CC	HF/STO-3G	2.7639	3.4675	2.7745			
	CC	HF/3–21G	2.7637	3.4375	2.7854			
	CC	HF/6–21G	2.7764	3.4411	2.7915			
	CC	HF/6–31G	2.7752	3.4314	2.7926			
2b	BC	HF/STO-3G				3.2919	3.2741	2.7486
	BC	HF/3–21G				3.3059	3.2181	2.7170
	BC	HF/6–21G				3.3016	3.2320	2.7253
	BC	HF/6–31G				3.2714	3.2504	2.7259
3a	CC	HF/STO-3G	2.7748	3.4922	2.7769			
	CC	HF/3–21G	2.7514	3.4689	2.7519			
	CC	HF/6–21G	2.7577	3.4722	2.7584			
	CC	HF/6–31G	2.7613	3.4666	2.7597			
3b	BC	HF/STO-3G				3.2189	3.3175	2.7741
	BC	HF/3–21G				3.1781	3.3139	2.7513
	BC	HF/6–21G				3.1774	3.3139	2.7587
	BC	HF/6–31G				3.1587	3.3366	2.7590

Compd	*Form*	*Basis Sets*	$H(2,4)_a$	$H(2,4)_e$	$H(6,8)_a$	$H(2,4)_{pa}$	$H(2,4)_{pe}$	$H(6,8)_a$
4a	CC	HF/STO-3G	2.7723	3.4975	2.7877			
	CC	HF/3–21G	2.7793	3.4925	2.7725			
	CC	HF/6–21G	2.7846	3.4950	2.7794			
	CC	HF/6–31G	2.7835	3.4898	2.7797			
4b	BC	HF/STO-3G				3.2905	3.3394	2.7695
	BC	HF/3–21G				3.2660	3.3660	2.7487
	BC	HF/6–21G				3.2547	3.3809	2.7568
	BC	HF/6–31G				3.232	3.3908	2.7613

[a]Axial H; [e]Equatorial H; [pa]Pseudo Axial H; [pe]Pseudo equatorial H.

In the BC ketones **1b** and **2b** and the BC salts **3b** and **4b,** considerable variation in the distance for the selected protons to C(9) is obvious. This was not unexpected since repulsion between C(2,4)-H bonds and C(1,5)-C(6,8) bonds was anticipated, especially with the $C(2,4)_a$-H bonds in the BC form. The remaining data are reasonable.

For the sake of completeness, an X-ray diffraction analysis was performed on a single crystal of **1** which was shown to have the CC conformation **1a**. Crystal data are given in Table VII. The CC form is in striking contrast to the crystal structure of **2a** which is a BC form.[2b] Ketone **1a** crystallizes with two moleules in the asymmetric unit. The structure of one of the molecules is shown in Figure 6. The bond distances are very similar for both molecules. However, there is significant difference in the conformational angles for C(6)-C(7) which are −53.6° (3) in molecule I and −21.1° (3) in molecule II. Angles for C(7)-N(1) are 171.3° (2) and 162.5° (2) in I and II, respectively. The tricyclic systems in both molecules are in CC conformations. The conformation for related bonds in I and II differ by 1.6° or less. Most of the puckering occurs around bonds C(9)-C(10) and C(10)-C(11) with average conformational angles of 64° and the least occurs for the N(1)-C(12) and N(1)-C(8) angles (53°) as well as for O(2)-C(13) and O(2)-C(14) (54°). Numbers for the atoms in this instance are only those in Figure 6.

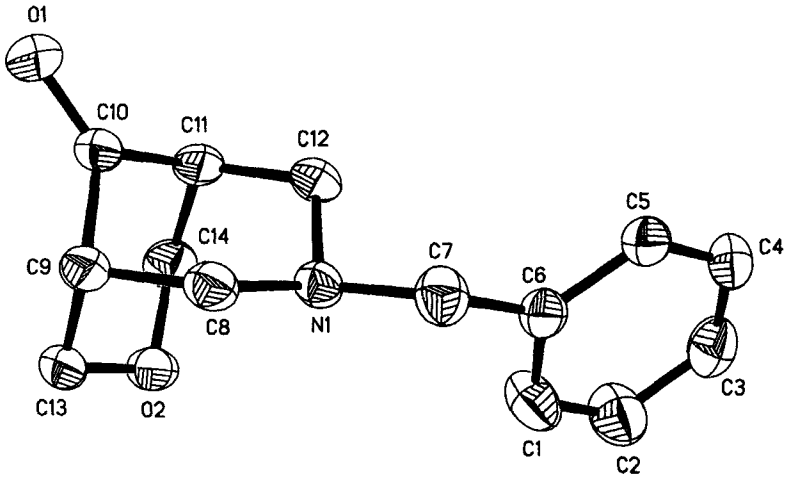


FIGURE 6 3D structure of **1a**

TABLE VII Crystal data and structure refinement for **1a**

Emperical formula:	$C_{14}H_{17}NO_2$	
Formula weight:	231.29	
Temperature:	173(2) K	
Wavelength:	0.71073 Å	
Crystal system:	Triclinic	
Space group:	P_T	
Unit cell dimensions:	a = 9.776(1) Å b=11.236(1) Å c = 11.676(1) Å	alpha = 105.26(1)d beta = 94.97(1)d gamma = 95.39(1)d
Volume, Z:	1123.5(2) $Å^3$, 4	
Density (calculated):	1.256 Mg/m^3	
Absorption coefficient:	0.084 mm^{-1}	
F(000):	496	
Crystal size:	0.12 × 0.46 × 0.28 mm	
Theta range for data collection:	1.89 to 24.99 deg.	
Limiting indices:	$0 \le h \le 11, -12 \le k \le 12, -13 \le 1 \le 13$	
Reflections collected:	4518	
Independent reflections:	4248 [R (int) = 0.0172]	
Absorption correction:	None	
Refinement method:	Full-matrix least-squares on F^2	
Data/restraints/parameters:	4246/0/308	
Goodness-of-fit on F^2:	1.069	
Final R indices [I>2 sigma(I)]:	R1 = 0.0465, wR2 = 0.1126	
R indices (all data):	R1 = 0.0666, wR2 = 0.1257	
Extinction coefficient:	0.0072(14)	
Largest diff. peak and hole:	0.235 and –0.197 $e.Å^{-3}$	

In conclusion, both experimental and theoretical evidence suggest that the stable forms of ketones **1** and **2** in solution favor, on the average, conformers **1b** and **2b**, respectively. However, the energy difference between the CC and BC forms is relatively small, suggesting an equilibrium is

highly possible at ambient temperatures. An X-ray diffraction analysis of the ketone **1** revealed the solid conformer to be the CC form **1a**. This contrasts with the known BC form for the sulfur ketone **2b**.[2b] Interestingly, hydroperchlorates **3** and **4** appear to favor CC conformers **3a** and **4a**, respectively, in solution, and **4a** is known to be a CC form in the solid state.[2b] Hydrogen bonding between the heteroatom and the hydrogen on N(7) is a compelling reason for the stability of the conformers. These experimental and theoretical results provide a basis for future work, especially with DHBCNONs.

EXPERIMENTAL

Ketones **1**[3b] and **2**[2b] were prepared as described in the literature. Hydroperchlorates **3**[3b] and **4**[2b] were also obtained from known routes. Most NMR spectra were recorded mostly on a Varian Unity Inova-400 MHz spectrometer, operating at 399.925 MHz, with a few spectra being recorded on a Varian Unity Inova-600 MHz unit, operating at 598.724 MHz (not included). Chemical shifts were reported as δ values downfield from TMS [$(H_3C)_4Si$]. Spectra for **1** and **2** were obtained on solutions in $DCCl_3$ while spectra of **3** and **4** were on solutions in DMSO-d_6, all taken at 22 °C. All 2D NMR experiments were performed with a Varian Unity Inova 400 MHz spectrometer. The NOESY spectra were collected with a spectral width of 3827.8 Hz in both dimensions. The data were collected as an array of 2K × 400 points, which, after linear prediction and zero filling in the t_1 dimension, produced a data matrix with 2K × 4K points. A mixing time of 150 ms and a relaxation delay of 1.5 s were used.

The DQCOSY data were acquired with a spectral width of 3827.8 Hz in both dimensions. The data were also collected as an array of 2K × 600 points, which, after linear prediction and zero filling in the t_1 dimension, produced a data matrix with 2K × 4K pionts.

The heteronuclear NOESY (HOESY) experiments were performed with a spectral width of 3825.4 Hz for ^1H and 21499.6 Hz for ^{13}C, respectively. The data were collected as an array of 4K × 128 points, which, after linear prediction and zero filling in the t_1 dimension, produced a matrix with 4K × 4K points. A mixing time of 2 s and a relaxation delay of 7 s were used.

Data for the X-ray diffraction analysis for **1a** were collected at −100 °C on a Bruker P4 diffractometer using MoKα (λ = 0.71073 Å) radiation. The data were corrected for Lorentz and polarization effect; absorption correction was not applied since it was judged to be insignificant. The structure was solved by direct methods using the SHELXTL (Bruker) system and was refined by full-matrix least squares of F^2 using all reflections. Hydrogen atoms were included in the refinement with idealized parameters.[9] Intensity statistics suggested the centric space group $P\bar{1}$, and the successful refinement confirmed this choice. There are four molecules in the unit cell, and hence, the asymmetric unit contains two independent molecules. Final R1 = 0.047 is based on 3290 "observed reflections" [$I \geq 2\sigma(I)$]. Details of the crystal data and refinement are given in Table VII.*

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* Full lists of crystallographic data for **1a**, including tables of crystal data, atomic coordinates, bond lengths and bond angles, anisotropic displacement parameters, and hydrogen coordinates and isotropic displacement parameters, are deposited with the Cambridge Crystallographic Data Center, 12 Union Road, CB2 1EZ Cambridge, UK.

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