Boat-Chair Equilibria in Free-Base and Protonated 2,3-Dihydro-1*H*-1,4-benzodiazepines. A PM3-Quantum-Mechanical Study

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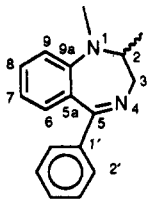
Optimized structures and energies obtained on the semiempirical PM3 level are reported for derivatives of 2,3-dihydro-1*H*-1,4-benzodiazepines both as free bases and in their protonated forms. The structures are built up stepwise from their simplest progenitor, 1,3-cycloheptadiene, by aza substitution and benzannelation. Special attention is paid to the boat and different half-chair conformations of the seven-membered ring. For sterically congested derivatives the boat form turns out to be the most stable conformation, an effect that is attenuated by hydrogen bonding with an appropriate side chain. Chiral discrimination by substituents in the C2-position is probed, and a relationship between the helicity of the chromophore and the absolute configuration at C2 is developed.

Introduction

Among the derivatives of 2,3-dihydro-5-aryl-1*H*-1,4-benzodiazepines many examples of therapeutically highly active derivatives can be found. From a theoretical point of view these compounds deserve special interest because they combine in their molecular structure several unique features. The C=N double bond (C=NH$^+$ in the protonated form) of the seven-membered ring is in formal conjugation with two aryl rings, one annelated and the other one rotating rather freely. The ring nitrogen N1



must be viewed at the same time as part of the diazepine ring and as an alkylamino substituent of the annelated aromatic ring with far-ranging electronic consequences, especially in the acidic form. Steric and torsional effects, on the other hand, govern the conformation of the saturated C2-C3 bridge and at least partially the relative orientation of the two aryl rings. A proper description of this molecular system has to take both these steric and electronic effects into account.

In view of the importance the 1,4-benzodiazepines have attained commercially, it is surprising how little is known about the conformations available to these systems in solution. Most studies have been concerned with lactam-type derivatives. A nonplanar rapidly (on the NMR time scale) inverting boat-like structure of the seven-membered ring was established for these compounds[1] much like the one found in several X-ray analyses,[2] with a barrier to inversion of around 17 kcal/mol depending on the substitution of the molecule. Likewise, NMR spectroscopy has been employed to show that ortho-substituted aryl groups at C5 can assume two stable conformations differing by ca. 180° with respect to the torsion angle along the C1'-C5 bond and with a barrier to rotation which permits rapid equilibration at room temperature.[3] Possible electronic interaction of the imine bond with the two aromates and between the aromates was probed with UV[4] and photoelectron spectroscopy,[5] but a quantitative description of this complicated chromophoric system is still missing. CD spectroscopy has been employed to deduce the absolute configuration of the inherently chiral diazepine ring and the type of electronic transitions involved.[6]

Rigorous ab initio calculations are still out of the question for systems as large as the benzodiazepines; force-field calculations on the other hand cannot do justice to the complex electronic interactions governing the conjugated imine chromophore, and if semiempirical methods are up to this task remains to be seen. Still, there have been several attempts to gain theoretical insight into the benzodiazepine structure by applying approximate methods, such as CNDO,[7] EHT and HAM/3,[5] or MNDO.[8]

We have recently reported[9] the CD spectra of several chirally substituted 2,3-dihydro-1*H*-1,4-benzodiazepines and the unexpected finding that change from a protic to a nonprotic solvent suffices to induce a more or less complete inversion of the spectra of the protonated species. We interpret these spectral results as indicative of the inversion of the 7-membered ring including a change of helicity of the inherently twisted chromophore. For a detailed analysis of the structural changes which the diazepines undergo as a function of their substitution pattern and their surrounding, we found it necessary to perform a rigorous conformational analysis using the recently developed semiempirical schemes PM3 with its very efficient geometry optimization algorithm. The study encompasses both the free base and the protonated benzodiazepines since under physiological conditions these

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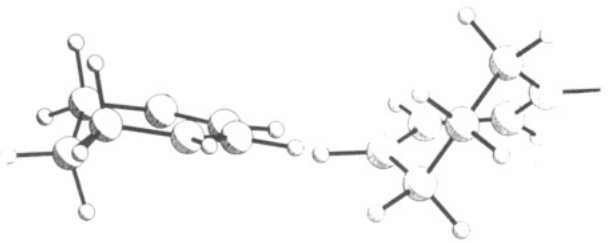


Figure 1. Half-chair (left) and boat conformation (right) of 1,3-cycloheptadiene. In the half-chair, the view is across the mirror plane, in the boat it is along the C_2-axis.

systems act as strong proton acceptors.

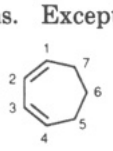
Computational Details

Starting geometries for the quantum-mechanical calculations were obtained with PCMODEL.[10] All PM3 calculations[11] were performed without geometry restrictions except where noted, and the PRECISE option with its strong convergence criteria was employed throughout. PM3 which is an extensively reparametrized version of MNDO is known to yield fairly reliable heats of formation and molecular geometries.[12] Care must be exercised as always when using parametrized methods. We have found e.g. that under certain conditions PM3 may lead to false minima which are characterized by very close hydrogen contacts.[13] We have encountered such structures in the present study resulting among others from rotation of the C5 aryl group and interaction between the C6 and C6′ hydrogens. These structures had to be discarded. Also, there are methods at the semiempirical level of PM3 that are more suitable to describe hydrogen bonding. In the series of closely related structures, however, such as **9–11**, the PM3-calculated data appear to bear relevancy.

Results and Discussion

The substituted benzodiazepines that form the basis of our present study are extremely complex and rather flexible systems. A complete geometry search covering the more than 100 internal coordinates of these compounds is impossible to perform, even with an approximate method and employing a high-speed computer.[14] To keep the problem manageable we have built up the complete structure from simple progenitors that we try to describe in as much detail as possible both to understand the structures involved and to test the applicability of the method employed.

1,3-Cycloheptadiene (1). This hydrocarbon whose structure has been the subject of several experimental and theoretical investigations forms a natural point of departure for our calculations. Except for the structure with



1,3-cycloheptadiene, 1

all carbon atoms in one plane (point group C_{2v}) which can be safely neglected, there are two possible symmetric conformations this compound can assume, one with a C_2-axis passing through atom C6 and the midpoint of the C2–C3 bond, the other with a mirror plane instead. (Figure

Table I. Comparison of Experimentally Determined Geometry of 1,3-Cycloheptadiene with PM3 and ab Initio Calculated Results (Bond Lengths in pm, Angles in deg)

	electron diffraction[a]	PM3		ab initio[b]	
		half-chair	boat	half-chair	boat
		Bond Lengths			
C1–C2	134.65	133.7	133.8	132.3	132.3
C2–C3	144.98	144.7	145.6	146.7	147.9
C4–C5	150.92	148.2	148.9	150.6	151.3
C5–C6	152.18	151.7	152.4	153.8	154.9
		Bond Angles			
C1–C2–C3	129.1	129.6	122.4	130.2	121.4
C3–C4–C5	129.1	128.2	122.6	128.4	121.7
C4–C5–C6	114.0	114.6	114.6	115.5	113.7
C5–C6–C7	113.0	112.7	115.1	114.1	111.7
		Dihedral Angles			
C1–C2–C3–C4	0.0	−0.3	43.6	0.0	46.4
C2–C3–C4–C5	0.0	0.6	−3.6	1.4	3.2
C3–C4–C5–C6	33.1	32.9	67.4	30.4	71.4
C4–C5–C6–C7	−74.6	−74.5	−38.8	70.5	40.6

[a] Hagen, K.; Traetteberg, M. *Acta Chem. Scand.* **1972**, *26*, 3643. [b] Saebo, S.; Boggs, J. E. *J. Mol. Struct.* **1982**, *87*, 365. No signs for dihedral angles are provided in this work, but the agreement with experiment and with out calculations is obvious.

1) In the first which is also called the boat form (chiral point group C_2), the saturated three-carbon chain connects the ends of a twisted diene system; in the latter so-called half-chair (symmetry C_s), the double bonds are necessarily coplanar. Models indicate both conformers to be fairly flexible and interconvertible via C_1 intermediates which is also born out by calculations (vide infra).

According to two electron diffraction studies[15] and an analysis of its microwave spectrum,[16] 1,3-cycloheptadiene has C_s symmetry. In the microwave study, moreover, a strong case is made against the existence of a second conformation, possibly of C_2 symmetry, in contrast to NMR measurements[17] which favor a distorted boat conformation. Calculations render both conformations energetically feasible. We are aware of just one semiempirical study on 1,3-cycloheptadiene in which, moreover, the somewhat out-moded MINDO/2 method has been utilized.[18] On the basis of force-field and quantum-mechanical models the C_s form is calculated slightly more stable than the C_2 conformation (MMP2, 2.1 kcal/mol,[19] ab initio of double-ζ quality, 2.5 kcal/mol[20]). The calculated geometries agree satisfactorily with experiment, especially with respect to the dihedral angles along the C4–C5 and the C5–C6 bonds (+30 and −70.5°,[19] +33 and −74.4°[15]). However, distorted conformations resulting from twisting the double bonds against each other have been found with different force fields.[19,21] According to Allinger, these may even represent the lowest-energy conformations of the compound.

With PM3 we find the stable conformation to be of C_s symmetry, 1.6 kcal/mol lower in energy than C_2. Calculated geometrical parameters for both conformations are given in Table I together with experimental results. The agreement between the calculated half-chair and the electron diffraction study is very good, especially with

(10) Serena, Software, Box 3076, Bloomington, IN 47402-3076.
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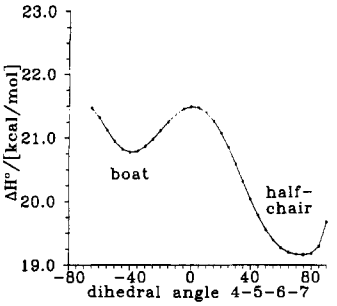
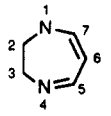


Figure 2. Potential energy curve of 1,3-cycloheptadiene as a function of the dihedral angle C4–C5–C6–C7. Each point represents the energy of a completely optimized structure the only restriction being the dihedral which is fixed at the value indicated. For the shape of certain structures on this curve, see Figure 3.

respect to bond angles and the dihedrals. Angle strain is significant in both calculated structures; in the boat form it is found mainly in the saturated carbon chain that has to connect the ends of the twisted double bonds, while in the half-chair form the ethylenic angles are appreciably widened, a consequence of the planar arrangement of carbon atoms C1 to C5 and C7. For comparison we include the results of an ab initio calculation. While the two models agree closely with respect to the C_s form (and with experiment), they differ significantly in their description of the less stable C_2 conformer.

The torsional potential around the bond connecting the double bonds is much more shallow for the C_s than for the C_2 conformation. A 25° twist from the equilibrium geometry increases the energy of the half-chair by only 0.35 kcal/mol, while the same twist in the boat form (from 43.5 to 18.5°) requires almost 2 kcal/mol. The dihedral angles along the CH_2–CH_2 bonds[22] have the same sign in the boat (C_2) and opposite signs in the half chair form (C_s symmetry). Consequently, upon interconversion of the two conformers either of these bonds has to go through an eclipsed *cis*-butane like conformation which is responsible for the barrier separating these two forms. More specifically, it is the bond that stays on the same side of the diene plane when the half-chair form is converted to the boat form that has to go through this unfavorable arrangement. To a certain degree the molecule can avoid this eclipsing by adopting a twisted conformation. In Figure 2 the calculated energy is plotted as a function of this dihedral angle. The conformers corresponding to the two minima, the transition state and one of the many twisted structures, are shown, together with dihedral angles determining the geometries, in Figure 3.

2,3-Dihydro-1,4-1*H*-diazepine (2). No experimental information is available for the structure of this compound which forms the backbone of the benzodiazepines and derives from 1,3-cycloheptadiene formally by substitution of the two CH groups at positions 1 and 5 by nitrogen.



2,3-dihydro-1*H*-1,4-diazepine, **2**

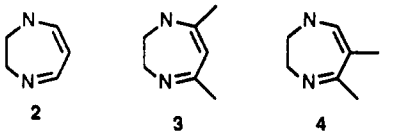
The maximum symmetry is C_s which is reduced to C_1 in any nonplanar conformation. The calculated minimum energy structure is half-chair, though distorted because of the missing symmetry, with a dihedral angle between the two double bonds of about 9° (Figure 4). In principal this distortion can occur in either of two directions leading to opposite dihedral angles along the C5–C6 bond. In the one which is realized according to the calculations, N1 moves toward the out-of-plane carbon C2 (up in Figure 4) while C3 moves down. As a consequence, the dihedral angle along the N1–C7 bond is smaller than that along the C3–N4 bond, allowing for more conjugation of the N1 electron lone pair with the double bonds. Also, by following this torsional mode the unfavorable C–C eclipsing which separates boat and half-chair in 1,3-cycloheptadiene can be avoided. For the same reason diazepine **2** cannot assume a stable boat-like conformation. C–C eclipsing, present in the transition state for the conversion of the C_s to the C_2 form in **1**, is replaced in **2** by C–N eclipsing which is much less costly, so there is no barrier separating the two conformations.

A consequence of this biased distortion is that the sign of the dihedral angle between the two double bonds determines the side toward which the carbon bridge is flipped, a positive diene twist resulting in a positive C2–C3 dihedral angle.

Methyl substitution in the 5-, 6-, or 7-position does not affect the conformational flexibility of the diazepine ring in a significant way; disubstitution, however, as in **3** and **4**, increases the twist between the double bonds (see the parameters of the optimized structures in Table II). As a consequence, N1 inverts completely, which is evident from the sign change of the dihedral angles C5–C6–C7–N1 and C6–C7–N1–C2. This inversion leaves the electron free pair almost perpendicular to the plane of the C6–C7 double bond, a prerequisite for good π-conjugation. The relationship between the dihedrals noted above is not changed by inversion of the nitrogen atom.

Table II. Selected Dihedral Angles (deg) and Bond Lengths (pm) of the Diazepines 2–4

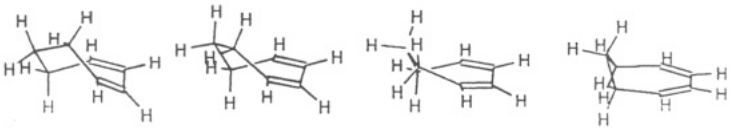
	2	3	4
	Dihedral Angles		
N1–C2–C3–N4	75.4	80.1	79.3
C2–C3–N4–C5	-38.6	-48.9	-55.0
C3–N4–C5–C6	-1.5	-3.1	-3.7
N4–C5–C6–C7	8.8	16.4	24.0
C5–C6–C7–N1	-3.3	9.6	7.9
C6–C7–N1–C2	29.1	-1.5	-10.9
C7–N1–C2–C3	-68.3	-47.7	-37.7
	Bond Lengths		
N4–C5	129	130	130
C5–C6	145	146	147
C6–C7	135	135	135
C7–N1	141	143	141



2 **3** **4**

Protonated 2,3-Dihydro-1*H*-1,4-diazepines. The consequences of protonation at nitrogen atom N4 are fundamental. While the free base is characterized by highly localized double bonds, protonation results in a cyanine-type electronic structure in which an even number of π-electrons (i.e. 6) is distributed over an odd number of π-centers (5) with the well-known consequence of loss of double bond fixation. Optimized geometries for the parent compound $\mathbf{2H^+}$ and the two dimethyl derivatives $\mathbf{3H^+}$ and $\mathbf{4H^+}$ are given in Table III together with the X-ray structure results of the *p*-tosyl salt of **3**. The agreement is satisfactory, especially with respect to dihe-

(22) We are aware of the fact that in order to define a dihedral angle properly four atoms must be indicated that form a contiguous set of three bonds. In cyclic structures a shorthand notion may be employed by which only the central of these bonds is indicated. The other two are then understood to be the bonds along the cycle.



	boat	transition state	twisted	half-chair
dihedral [deg]				
C1–C2–C3–C4	−43.6	−38.9	−26.9	0
C4–C5–C6–C7	−38.8	0	+40.0	+74.5
C1–C7–C6–C5	−38.8	−66.7	−82.4	−74.5
energy [kcal/mol]	1.6	2.25	-	0

Figure 3. 1,3-Cycloheptadiene. Plot of minimum-energy and transition-state structures and of one of the twisted forms on the potential energy curve of Figure 2, together with a list of important dihedral angles and relative energies.

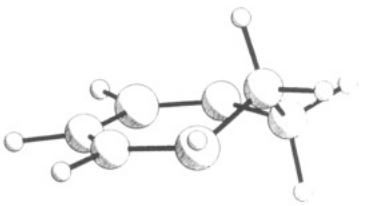


Figure 4. Minimum-energy conformation of 2,3-dihydro-1*H*-1,4-diazepine. The conformation shown corresponds to positive dihedral angles both along the C5–C6 and the C2–C3 bonds.

Table III. Calculated Structures of Protonated Diazepines $2H^+$–$4H^+$ and X-ray Structure of $3H^+$

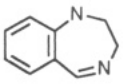
	$2H^+$	$3H^+$	$3H^+$[a]	$4H^+$
	Dihedral Angles			
N1–C2–C3–N4	−75.6	−78.4	−78.6	−77.4
C2–C3–N4–C5	50.9	49.5	52.4	53.4
C3–N4–C5–C6	−4.2	−0.7	−1.8	−1.4
N4–C5–C6–C7	−9.1	−11.4	−15.2	−14.9
C5–C6–C7–N1	−9.5	−9.7	−6.1	−8.7
C6–C7–N1–C2	−3.0	−3.0	−2.3	−2.3
C7–N1–C2–C3	49.7	51.5	48.6	45.3
	Bond Lengths			
N4–C5	135	136	131.5	136
C5–C6	139	139	138.5	141
C6–C7	139	140	139.6	139
C7–N1	135	136	132.0	135

[a] Ferguson, G.; Marsh, W. C.; Lloyd, D.; Marshall, D. R. *J. Chem. Soc., Perkin Trans. 2* **1980**, 74.

dral angles, although experimental N–C bond lengths are somewhat shorter than the calculated ones.

The structure adopted by the unsubstituted diazepinium ion is almost symmetric (C_2), with a close to planar geometry of the cyanine chain and a zig–zag arrangement of the saturated C2–C3 bridge. Methyl substitution increases the dihedral angle at C5–C6 (and C6–C7) with a concomitant loss of symmetry in $\mathbf{4H^+}$ and a more nearly planar arrangement of the C–N termini of the cyanine. The computed minimum energy conformation of $\mathbf{3H^+}$ is depicted in Figure 5.

2,3-Dihydro-1*H*-1,4-benzodiazepine (5). As a consequence of the annelation of a benzene ring three different stable conformations (Figure 6) are obtained for the 7-membered ring in the benzodiazepine **5** which are characterized by different combinations of the dihedrals along the ring (see Table IV). In conformations **5a** and **5b** the



2,3-dihydro-1*H*-1,4-benzodiazepine, **5**

arrangement between the "exocyclic" double bond N4–C5 and the plane of the benzene ring is close to planar (di-

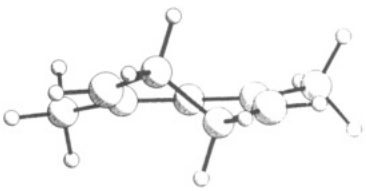


Figure 5. Minimum-energy conformation of N4-protonated 2,3-dihydro-1*H*-1,4-diazepine. The view is along the C_2-axis.

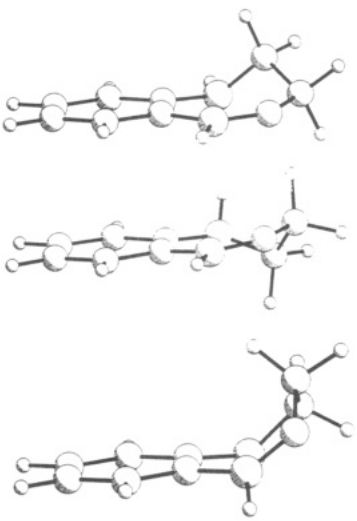


Figure 6. Minimum energy conformations of benzodiazepine **5** showing (from top) the two half-chairs **a** and **b** and the boat form **c**.

Table IV. Heats of Formation (kcal/mol), Dihedral Angles (deg), and Bond Lengths (pm) of the Two Half-Chairs a and b and the Boat Conformation c of Benzodiazepine 5

	a	b	c
$\Delta H°$	43.395	44.590	45.411
	Dihedral Angles		
N1–C2–C3–N4	−61.9	76.9	51.9
C2–C3–N4–C5	17.9	−36.9	−66.4
C3–N4–C5–C5a	−1.2	−4.4	−0.7
N4–C5–C5a–C9a	13.3	6.8	40.6
C5–C5a–C9a–N1	0.5	7.7	8.0
C5a–C9a–N1–C2	−51.0	16.2	−59.8
C5a–C9a–N1–1H	−177.8	−115.0	172.1
C9a–N1–C2–C3	86.0	−64.1	24.3
	Bond Lengths		
N4–C5	129	129	129
C5–C5a	147	147	147
C5a–C9a	140	140	141
C9a–N1	144	144	144

hedral angles 13 and 7°, respectively), while in **5c** this angle is increased to 40°. In keeping with our nomenclature, we call the former half-chairs, the latter boat. The difference

between the two half-chair forms is best expressed in the dihedral angle N1–C2–C3–N4 which is negative in **5a** and positive in **5b**, indicating that the latter corresponds to the conformation found before in the parent diazepine ring. This is confirmed by a detailed comparison of calculated structural parameters of **5b** and **2** which reveals just one major deviation which concerns bond N1–C9a (this is N1–C7 in **2**). The dihedral along this bond is only 16° (vs 29° in **2**), obviously on account of increased conjugation between the aromatic ring and the amine substituent.

The inverted chair **5a** with oppositely signed dihedral angles along C2–C3 and C5–C5a is not stable in the unsubstituted diazepine **2**, and neither is the boat form **5c**. In all three conformations N1 has an almost tetrahedral configuration, a fact that may in part be attributable to the tendency of PM3 to pyramidalize nitrogen atoms.[23] Maximum conjugation between the N1 lone pair and the aromatic π-system is achieved for **5a** and **5c** which may be the reason that these structures are calculated as stable at all.

Only one conformation, **5c**, results from a search of the benzodiazepine boat structures, since for steric reasons the C2–C3 and the C5–C5a dihedral angles have to be of equal signs. Inversion of the ring can only be achieved if it involves inversion of the dihedrals at both bonds. The stereochemistry at the C2–C3 bond is important in so far as coupling between the hydrogens at this bond can be determined by ^{1}H NMR spectroscopy leading to one of the possible experimental entries into benzodiazepine conformations.[24]

Protonated 2,3-Dihydro-1*H*-1,4-benzodiazepine (5H$^+$). As in the case of the diazepine itself there are two positions where protonation can occur in this compound, either at the amine nitrogen N1 or the imine nitrogen N4. Protonation of N4 is 7 kcal/mol less costly than protonation of N1, in agreement with experiment.[25] Formation of a cyanine type electronic structure is evident again from calculated structural data but is dependent on a close to planar arrangement of the atomic centers involved. As a consequence, the two half-chairs found in **5** coalesce into a single conformation, **5bH$^+$**, but the boat form, **5cH$^+$**, is still present (Table V), with a slightly increased energy difference compared to the unprotonated forms.

Not unexpectedly, the benzene ring resists, at least partly, formation of the cyanine structure which involves loss of aromaticity. This fact is apparent from the calculated bond lengths which show more bond length alternation and also leaves the two nitrogens which are identical in **2H$^+$** very much different. The N4–C5 bond is only 133 pm, while the C9a–N1 bond is 141 pm (corresponding value in **2H$^+$**: 135 pm), indicating that cyanine resonance is not very effective here. On the other hand, conjugation of N1 with the aromatic ring is stronger than in the parent base. Inspection of the calculated data reveals that both with respect to planarization of N1 and conjugation of the N1 lone pair with the π-system the boat form is disfavored relative to the half-chair which may account for the increased destabilization of this conformation compared to the free bases.

Alkyl-Substituted 2,3-Dihydro-1*H*-1,4-benzodiazepines. In order to determine the extent to which calculated geometries and energies are affected by steric interactions, derivatives of **5** were optimized with methyl substituents in the 1-, 5-, 6-, and 9-positions. In addition, the 5-phenyl-substituted derivative was considered which forms the prototype of many pharmacologically active benzodiazepines. Substitutents in these positions will destabilize conformations with small dihedrals along C5–C5a and C9a–N1 which is of advantage to the boat conformation **c** and the half-chair **a**. In Table VI geometries and energy differences between the boat and the more stable of the two chair forms are given.

Table V. Heats of Formation (kcal/mol) and Structural Data (Lengths in pm, Angles in deg) of the Two Protonated Conformations of 5

	5bH$^+$	5cH$^+$
$\Delta H°$	194.357	197.225
Dihedral Angles		
N1–C2–C3–N4	75.4	50.5
C2–C3–N4–C5	−33.8	−69.5
C3–N4–C5–C5a	−3.5	4.2
N4–C5–C5a–C9a	4.4	36.9
C5–C5a–C9a–N1	0.4	8.5
C5a–C9a–N1–C2	33.1	−62.1
C5a–C9a–N1–1H	173.3	166.6
C9a–N1–C2–C3	−77.4	26.1
Bond Lengths		
N4–C5	133	132
C5–C5a	142	144
C5a–C9a	142	142
C9a–N1	141	143

In all derivatives of **5** the half-chair **a** is more stable than half-chair **b** even in the protonated forms. Without exception methyl substitution stabilizes the boat form relative to the chair forms, the largest effect being observed for the 5-position where the stability is even inverted and the boat results as the preferred conformation. A methyl group exerts the least influence in the 9- and the 6-positions, with *N*1-methyl ranging in between. The results for the bases and the protonated species run completely parallel, indicating that the effects are probably steric and not electronic in nature.

While the chair conformations (within the constraint noted above) show a large variation of angles, the boat conformations appear to be rather rigid. In the protonated forms, for example, the range of the two angles is 3.3 and 4.7°, respectively; in the chair forms the corresponding values are 20.5 an 17.5°. This different flexibility of the two conformations was pointed out already in the case of 1,3-cycloheptadiene. We note also that for large values of the C5–C5a dihedral (brought about, for example, by 5-substitution) the boat form becomes progressively more stable relative to the half-chair form.

The crystal structures for medazepam, which is 5-phenyl-7-chloro-5,[26] and for medazepam hydrochloride[27] have been reported. As expected, the 7-membered ring in the free base adopts a twisted-boat conformation which is flattened somewhat, but not as much as we calculate as a consequence of protonation.[28]

C2 Substitution and Chiral Discrimination. All the structures considered so far are chiral (point group C_2 or C_1). In the absence of discriminating agents this chirality is not manifest, with inversion of the 7-membered ring affording nonseparable mirror images. Suitable substitution should lead to diastereomeric invertomers with dif-

(23) This was pointed out by one of the referees.
(24) Finner, E.; Zeugner, H.; Milkowski, W. *Arch. Pharm. (Weinheim)* **1985**, *318*, 1135.
(25) Barrett, J.; Franklin-Smyth, W.; Davidson, I. E. *J. Pharm. Pharmacol.* **1973**, *25*, 387.
(26) Gilli, G.; Bertolasi, V.; Sacerdoti, M.; Borea, P. A. *Acta Crystallogr.* **1978**, *B34*, 3793.
(27) Chananont, P.; Hamor, T. A. *Acta Crystallogr.* **1980**, *B36*, 898.
(28) As judged by the value of the N1–C2–C3–N4 dihedral angle. Experimental values for medazepam base are −59.5 and 56.4° (two independent molecules in the unit cell) while for the hydrochloride salt it is −49.1°.

Table VI. Relative Heats of Formation (kcal/mol) and Dihedral Angles (deg) of Boat and Stable Half-Chair Conformations of Free-Base and Protonated Derivatives of 5

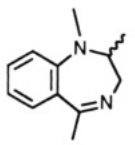
	conformation c		conformation a		
	N4–5–5a–9a	N1–2–3–N4	N4–5–5a–9a	N1–2–3–N4	$\Delta H°_{rel}$[a]
5H⁺	36.9	50.5	4.4[b]	75.4[b]	2.87
5	40.6	51.9	13.3	−61.9	2.02
1-methyl-**5H⁺**	40.2	40.2	13.3	−65.0	1.75
1-methyl-**5**	42.1	42.6	19.0	−57.4	1.59
5-methyl-**5H⁺**	42.2	44.9	24.9	−54.2	−1.33
5-methyl-**5**	42.2	52.6	26.3	−49.4	−0.32
5-phenyl-**5H⁺**	42.8	43.5	18.3	−60.0	−1.26
5-phenyl-**5**	42.9	47.9	21.9	−54.7	−0.18
6-methyl-**5H⁺**	39.5	43.3	11.6	−66.1	1.86
6-methyl-**5**	40.2	49.3	20.2	−55.8	1.62
9-methyl-**5H⁺**	41.4	41.2	4.4	−71.7	2.41
9-methyl-**5**	42.6	46.0	18.4	−59.0	1.85

[a] Calculated energy difference between boat **c** and lowest half-chair conformation **a**. [b] Conformation **b**.

Table VII. Heats and Relative Heats of Formation (kcal/mol) and Selected Dihedral Angles (deg) of Different Conformations of 6

	$\Delta H°$	$\Delta H°_{rel}$	N4–5–5a–9a	N1–2–3–N4	5a–9a–N1–2
			Free Base **6**		
S-**a**	33.13	1.39	29.0	−39.3	−64.8
R-**a**	33.77	2.04	28.8	−49.3	−64.2
S-**b**	34.12	2.38	38.7	81.0	−13.6
R-**b**	35.49	3.75	33.2	82.8	0.7
S-**c**	31.74	0.00	45.4	39.0	−72.2
R-**c**	32.46	0.72	43.7	46.1	−70.6
			Protonated **6H⁺**		
S-**a**	180.08	2.96	28.4	−41.7	−64.8
R-**a**	180.42	3.30	28.2	−49.9	−64.7
S-**b**	181.88	4.76	37.0	80.5	−16.5
R-**b**	181.63	4.51	28.0	81.1	10.3
S-**c**	177.12	0.0	49.3	38.2	−76.3
R-**c**	177.82	0.70	44.6	43.3	−75.1

ferent geometries and energies. To clarify these relationships we have optimized the geometry of chiral **6**. As a



6

consequence of substitution in the 1- and 5-position we hoped to obtain stable boat and half-chair conformations, with the 2-methyl group discriminating between the invertomers. For this compound we find, not surprisingly, six different conformations resulting from a doubling of the three conformations expected for the achiral progenitor.

Calculated heats of formation and the relevant dihedral angles for all calculated structures of free base and protonated **6** are summarized in Table VII. The structures are pairwise epimeric, i.e. they differ in the absolute configuration of one center (C2); the different energies and geometries are thus an indication of the ability of the chiral center to differentiate between otherwise enantiomeric structures.

As a result of the disubstitution at N1 and C5 and the concomitant nonplanarity we expect, and find, the boat conformation to be more stable than both chair conformations, the difference being larger in the case of the protonated forms. The chiral discrimination by the 2-methyl group amounts to from 0.7 kcal/mol (in the boat form, both protonated and unprotonated) to 1.4 kcal/mol for the free base chair form **b**. The different structures resulting from the 2-substituted *S*- and *R*-forms are depicted in Figure 7. In this case, as in all the other of Table VII, the preferred configuration at C2 is *S*, with the methyl substituent in the sterically less hindered pseudoequatorial position.[29]

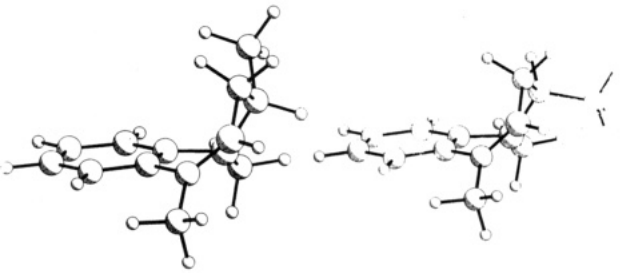
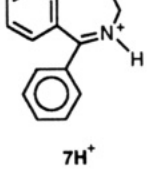


Figure 7. Plot of the two boat conformations calculated for **6H⁺**. The left one which is more stable has the *S*-configuration at C2, and the methyl group is quasi-equatorial. In the right one, the configuration is *R* and the substituent is quasi-axial. The twist of the C=N⁺ double bond with respect to the benzene ring is *P* in both cases.

The global minimum of compound **6** with a 2*S*-configuration is a *P*-helical boat conformation with the methyl group in 2-position occupying the pseudoequatorial position. Its mirror image is the inverted boat with *M*-helicity and has a 2*R*-configuration. The epimeric compound with the methyl group pseudoaxially positioned is less stable by 0.72 (free base) or 0.70 kcal/mol (protonated species).

Derivatives of Protonated 2,3-Dihydro-1,2-dimethyl-5-phenyl-1*H*-1,4-benzodiazepine. Since all compounds we have investigated experimentally carry an aryl substituent at C5 and methyl at N1 we consider from now on only structures of this type. Also, we will retain methyl substitution at C2 to study the effect of chiral discrimination. Calculated minimum energy structures and heats of formation of the simplest member of this series, **7H⁺**, and of several derivatives are given in Table VIII.



7H⁺

(29) For the pseudoaxial and -equatorial designation to be used, a reference plane, viz. N1–C2–C3, has to be imagined and the position of the C2 substituent with respect to that plane. Another possibility to describe the overall conformation of the 7-membered ring is by indicating the helicity of the twisted double bond C5–N4 with respect to the plane of the aromatic ring as either *P* or *M*. For *P*-helical conformations the dihedral angle N4–C5–C5a–C9a is positive; for *M*-helicity, it is negative.

Table VIII. Heats and Relative Heats of Formation (kcal/mol) and Selected Dihedral Angles (deg) of 7 and Derivatives

compound	N4–5–5a–9a	N4–5–1′–2′	$\Delta H°$	$\Delta H°_{rel}$
6H⁺, *S*-**c**	43.9		177.12	0
R-**a**	28.4		180.08	2.96
R-**c**	44.6		177.82	0.70
7H⁺, *S*-**c**	45.9	38.0	209.07	0
R-**a**	24.6	66.4	212.26	3.19
R-**c**	44.8	39.4	209.75	0.68
8-F-**7H⁺**, *S*-**c**	45.8	38.4	168.03	0
R-**a**	24.5	67.0	171.10	3.07
R-**c**	44.6	38.3	168.74	0.71
8-Me-**7H⁺**, *S*-**c**	45.8	39.0	198.58	0
R-**a**	25.4	67.0	201.59	3.01
R-**c**	44.7	40.0	199.29	0.71
8-MeO-**7H⁺**, *S*-**c**	44.4	40.6	168.81	0
R-**a**	24.4	68.6	171.56	2.75
R-**c**	44.3	38.8	169.33	0.52
6,8-$(Me)_2$-**7H⁺**, *S*-**c**	49.7	40.6	191.38	0
R-**a**	36.4	58.1	196.70	5.32
R-**c**	59.4	41.5	192.14	0.76
7-Br-**7H⁺**, *S*-**c**	44.9	39.0	218.84	0
R-**a**	25.1	66.3	222.03	3.19
R-**c**	44.9	38.2	219.57	0.73
2′-Cl-**7H⁺**, syn, *S*-**c**	46.0	42.6	204.64	0
anti, *S*-**c**	43.7	53.3[a]	206.24	1.60
syn, *S*-**a**	24.6	65.6	207.94	3.30
anti, *S*-**a**	24.8	79.1[a]	208.34	3.40
syn, *R*-**c**	45.3	41.6	205.32	0.68
anti, *R*-**c**	43.7	50.3[a]	206.96	2.32
2′-F-**7H⁺**, syn, *S*-**c**	44.4	45.1	167.49	0
anti, *S*-**c**	43.7	55.0[a]	169.71	2.22
syn, *S*-**a**	23.9	60.2	170.87	3.38
anti, *S*-**a**	25.7	88.6[a]	171.95	4.46
syn, *R*-**c**	44.4	44.1	168.19	0.70
anti, *R*-**c**	43.6	54.3[a]	170.45	2.96
2′-Me-**7H⁺**, syn, *S*-**c**	43.8	52.3	201.62	0.12
anti, *S*-**c**	42.2	64.9[a]	201.50	0
syn, *S*-**a**	23.7	83.8	203.82	2.32
anti, *S*-**a**	24.2	79.0[a]	203.82	2.32
syn, *R*-**c**	44.5	56.3	202.30	0.80
anti, *R*-**c**	42.6	63.4[a]	202.20	0.70

[a] Dihedral angle C4–C5–C1′–C6′.

Turning to **7H⁺** first, we note that phenyl substitution at C5 leaves the relative energies virtually unchanged, the energy minimum still corresponding to the boat conformation, with the pseudoequatorial position occupied at C2. Geometry changes are observed only for the more flexible half-chair the twist of the C=N double bond being reduced from 28 to 24°.

The dihedral angle N4–C5–C1′–C2′ is used to characterize the orientation of the aryl substituent with respect to the rest of the molecule. In **7H⁺** this angle is 38° (boat form **c**) and 66° (half-chair **a**). We note that in all boat conformations this angle is equal (or close to equal) to the dihedral angle N4–C5–C5a–C9a. This is evidence of the fact that the two aromatic rings have a propeller-like geometry with a close to C_2 local symmetry about the C=N double bond. Only as a result of substitution at C6 and/or C2′ does this situation change significantly. In the half-chair conformations the out-of-plane twist of the phenyl ring at C5 is always much larger, leading to an almost perpendicular arrangement of the ring with respect to the C=N bond. This is a direct consequence of the small dihedral angle N4–C5–C5a–C9a in this conformation and the resulting increased repulsion between the hydrogens at C6 and C6′.

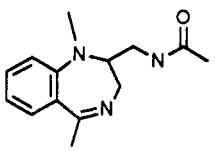
Substitution at C8, either by alkyl, methoxy, or halogen, has only minor consequences for relative energies and geometries and the same is true for the 7-bromo derivative. Electronic effects appear to be of minor importance in this respect. Dimethyl substitution at C6 and C8 increases the energy of the half-chair relative to the boat, as found earlier.

Table IX. Heats and Relative Heats of Formation (kcal/mol) and Selected Dihedral Angles (deg) of Different Conformations of 8

	$\Delta H°$	$\Delta H°_{rel}$	N4–5–5a–9a	N1–2–3–N4	5a–9a–N1–2
			Free Base **8**		
S-**a**	−3.89	3.33	24.6	−45.5	−62.3
R-**a**	−3.34	3.88	27.5	−51.6	−64.1
S-**b**	−3.79	3.43	39.4	84.8	−13.7
R-**b**	−2.87	4.35	35.2	84.5	1.1
S-**c**	−5.78	1.44	44.6	37.2	−73.3
R-**c**	−7.22	0	47.3	47.1	−71.1
			Protonated **8H⁺**		
S-**a**	138.48	1.74	19.2	−57.9	−60.1
R-**a**	141.82	5.08	26.5	−50.7	−64.6
S-**b**	142.71	5.97	22.0	90.3	10.2
R-**b**	137.84	1.10	37.7	83.1	−7.8
S-**c**	137.33	0.59	43.5	21.3	−77.9
R-**c**	136.74	0	44.7	44.4	−73.9

With a substituent at the C2′ position a 180° rotation of the phenyl group yields two different conformations, syn and anti. In the former, the substituent is located on the side of the C=N double bond (dihedral angle N4–C5–C1′–C2′ between +90 and −90°); in the latter this substituent ends up closer to the face of the annelated benzene ring. Methyl substitution favors, however slightly, the anti conformation; halogen on the other hand prefers the syn geometry. If dispersion terms are added,[30] interaction between the aromatic systems and the heavy atom shifts the equilbrium toward anti. The twist angles of the anti geometries are significantly larger than those of the syn forms, which results in a decrease of the dihedral angles N4–C5–C5a–C9a and a stabilization of the half-chair forms relative to the boat conformations.

C2 Side Chain with Hydrogen Bonding Capability. Substituting the methyl group at C2 by a CH_2–NH–CO–CH_3 side chain as in **8** affords the possibility of intramolecular hydrogen bond formation. In the free base this



8

involves the amide proton and N4 leading to a CO—N-H···N=C bridge in a 6-membered ring; in the protonated form a bridge of the type NH—CO···HN=C and formation of an 8-membered ring seems conceivable. The conformation of the side chain was optimized first without taking recourse to possible hydrogen bond formation. For the amide group a trans-planar arrangement of the NH and C=O bonds was assumed as the starting geometry together with all possible combinations of staggered conformations for the remaining dihedral angles N1–C2–C1′–N2′ and C2–C1′–N2′–C3′.

Hydrogen bonding affects both calculated geometries and energies (Table IX). The data for compound **6** (Table VII) should be consulted for comparison. The minimum energy conformation of the free base is the boat form with *R*-configuration in contrast to **6** where it was *S*. For the half-chair geometries, *S* remains the more stable epimer; however, all chair forms are destabilized relative to the boat.

The protonated derivatives behave completely analogously. The difference between conformations that can establish hydrogen bonds and those that for steric reasons

(30) Buss, V.; Messinger, J. *Tetrahedron* **1990**, *46*, 423.

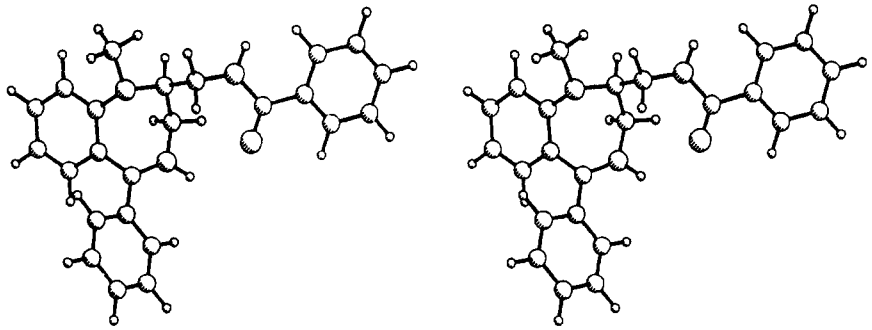


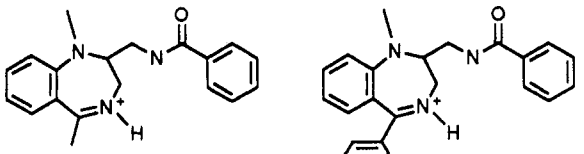
Figure 8. Stereoplot of the minimum-energy boat conformation of **10H**$^+$. The helicity of the N4–C5–C5a–C9a fragment is *M*. The configuration at C2 is *S*, and the substituent occupies a pseudo-axial position.

Table X. Heats and Relative Heats of Formation (kcal/mol) and Selected Dihedral Angles (deg) of Different Conformations of Protonated 9–11

	$\Delta H°$	$\Delta H°_{rel}$	N4–5–5a–9a	N1–2–3–N4	5a–9a–N1–2
9H$^+$, *S*-**a**	172.73	3.74	23.5	−54.8	59.1
R-**b**	171.58	2.59	36.6	83.2	−7.2
S-**c**	171.39	2.40	42.5	37.7	−77.0
R-**c**	168.99	0	42.3	51.6	−71.5
10H$^+$, *S*-**a**	204.61	3.06	16.6	−58.6	−57.6
R-**b**	205.20	3.65	40.4	81.8	−15.0
S-**c**	203.58	2.03	44.2	38.3	−77.2
R-**c**	201.55	0	44.9	51.1	−72.3
11H$^+$, *S*-**a**	170.53	3.12	16.9	−57.8	−58.7
R-**b**	171.46	4.05	39.9	82.3	−12.8
S-**c**	169.26	1.85	44.4	38.3	−77.2
R-**c**	167.41	0	44.8	51.8	−72.4

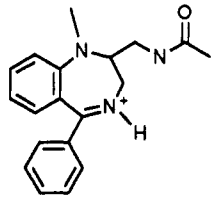
cannot is most clearly seen in the two half-chair forms *S*-**a** and *R*-**b** which are stabilized by 3.3 and 4.8 kcal/mol compared to their respective epimers. Also, as a result of hydrogen bonding, the stabilities of the two boat conformations **c** are reversed, leaving as in the case of the free bases the *R*-configurated diastereomer the global minimum.

Substitution by additional phenyl groups in the side chain and at the ring position C5 affords compounds **9H**$^+$ to **11H**$^+$. Calculated energies and geometrical data for



9H$^+$

10H$^+$



11H$^+$

these structures are given in Table X. In addition, relevant data from Table IX has been included.

The main inferences that can be drawn are the following. For each compound the 2*R*-configurated *P*-helical boat form represents the most stable conformation. The calculated minimum-energy structures are all very similar (including **8H**$^+$), the most prominent feature being the carbonyl group which is rotated toward the imine nitrogen with a resulting distance between the amide oxygen and the N4 hydrogen of 246 ± 3 pm. This affords a strong hydrogen bond which is the main single stabilizing factor for these conformations. The minimum energy conformation of **10H**$^+$ which shows this proper alignment of the amide carbonyl and the iminium proton is presented in Figure 8.

Solvent-induced conformational changes in 2-substituted chiral benzodiazepines have been investigated by us[9] and interpreted as inversion of the 7-membered ring initiated by intramolecular hydrogen bond formation. This followed a proposal put forward by Milkowski and Finner[31] who suggested the possibility of intramolecular folding of these molecules with concomitant $\pi\pi$-stacking of the unsaturated side chain and the C5-phenyl group. The counterion and solvent-mediated interaction between the carboximide nitrogen and N4 can be found in the crystal structures of tifluadom[32] both as a salt[33] and as a hydrate.[34]

Summary

The dominant feature of the benzodiazepine conformations in this study is the dynamical equilibrium between the boat and different half-chair conformations of the 7-membered ring. This equilibrium is a sensitive function of the substitution pattern of the compound being shifted, in the free base and the protonated form alike, by substituents in the 5- and/or 6-position toward the boat which eventually becomes the most stable form.

Chiral discrimination at C2 yields six different conformations for the 7-membered ring of which the two boat forms that differ in their configuration at C2 turn out to be more stable than the half-chair forms. In the most stable conformation the substituent at C2 occupies a pseudoequatorial position which minimizes steric interaction with other substituents. The absolute configuration at C2 in turn determines the absolute conformation of the benzodiazepine as expressed by the dihedral angle N4–C5–C5a–C9a, *S*-C2 correlating with a positive, *R*-C2 with a negative twist along the C5–C5a bond.

When a C2 side chain with hydrogen bonding capabilities, such as an (acylamino)methyl group, is present, the boat forms are still the most stable, but the preferred arrangement of the substituent is pseudoaxial. The driving force for this geometry is the hydrogen bond between N4 and the side-chain N–H in the free bases and between N4–H and the acyl oxygen in the protonated species.

Acknowledgment. Our work has benefited greatly from numerous discussions with Drs. E. Finner and M.

(31) Milkowski, W.; Finner, E. quoted in ref 33. Finner, E., private communication.

(32) Tifluadom is **10** with a fluoro substituent in the 2′-position and a 3-thiophene group instead of the benzene ring in the side chain.

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Zeugner regarding the boat-half-chair equilibria and side-chain orientation in 1,4-benzodiazepines. Part of this work was supported by KaliChemie, Hannover.

Registry No. 1, 4054-38-0; 2, 21908-58-7; **2H**$^+$, 21995-42-6; 3, 3187-88-0; **3H**$^+$, 21995-41-5; 4, 45673-88-9; **4H**$^+$, 140927-32-8; 5, 5945-91-5; **5H**$^+$, 140927-33-9; 1-Me-**5H**$^+$, 140927-34-0; 1-Me-5, 140927-35-1; 5-Me-**5H**$^+$, 140927-36-2; 5-Me-5, 140927-37-3; 5-Ph-**5H**$^+$, 140927-38-4; 5-Ph-5, 2898-20-6; 6-Me-**5H**$^+$, 140927-39-5; 6-Me-5, 140927-40-8; 9-Me-**5H**$^+$, 140927-41-9; 9-Me-5, 140927-42-0; *S*-6, 141017-65-4; *R*-6, 140927-43-1; *S*-**6H**$^+$, 140927-44-2; *R*-**6H**$^+$, 140927-45-3; *S*-**7H**$^+$, 125228-22-0; *R*-**7H**$^+$, 140927-46-4; *S*-8-F-**7H**$^+$, 140927-47-5; *R*-8-F-**7H**$^+$, 140927-48-6; *S*-8-Me-**7H**$^+$, 140927-49-7; *R*-8-Me-**7H**$^+$, 140927-50-0; *S*-8-MeO-**7H**$^+$, 140927-51-1; *R*-8-MeO-**7H**$^+$, 140927-52-2; *S*-6,8-(Me)$_2$-**7H**$^+$, 140927-53-3; *R*-6,8-(Me)$_2$-**7H**$^+$, 140927-54-4; *S*-7-Br-**7H**$^+$, 140927-55-5; *R*-7-Br-**7H**$^+$, 140927-56-6; *S*-2′-Cl-**7H**$^+$, 140927-57-7; *R*-2′-Cl-**7H**$^+$, 140927-58-8; *S*-2′-F-**7H**$^+$, 140927-59-9; *R*-2′-F-**7H**$^+$, 140927-60-2; *S*-2′-Me-**7H**$^+$, 140927-61-3; *R*-2′-Me-**7H**$^+$, 140927-62-4; *S*-8, 140927-63-5; *R*-8, 140927-64-6; *S*-**8H**$^+$, 140927-65-7; *R*-**8H**$^+$, 140927-66-8; *S*-**9H**$^+$, 140927-67-9; *R*-**9H**$^+$, 140927-68-0; *S*-**10H**$^+$, 140927-69-1; *R*-**10H**$^+$, 140927-70-4; *S*-**11H**$^+$, 140927-71-5; *R*-**11H**$^+$, 140927-72-6.

Synthesis of Pyrrolidines and Pyrrolidinones by the Rhodium Complex Catalyzed Cyclization of Unsaturated Amines

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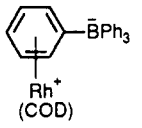
N-Allylic arylamines react with carbon monoxide, sodium borohydride, 2-propanol, and catalytic amounts of the zwitterionic complex η^6-$C_6H_6BPh_3^-Rh(COD)^+$ (1), to form pyrrolidines as the main products in most cases. Pyrrolidinones result from N-allylic alkylamines. An alternate route to the lactams from N-allylic alkylamines involves synthesis gas instead of $CO/NaBH_4$, together with the dual catalytic system $1/[Ru(CO)_3Cl_2]_2$. Complementary to the N-allylic arylamine route to pyrrolidines with $NaBH_4$ and 1 is the use of synthesis gas, 1, and 1,4-bis(diphenylphosphino)butane.

The zwitterionic rhodium complex 1 is a useful catalyst for the hydroformylation (CO/H_2) of a variety of simple and functionalized olefins. The process is highly regios-



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elective, and regiospecific in some instances, with steric effects playing a role in this reaction. For example, branched-chain aldehydes were obtained as the predominant or only products when monosubstituted styrenes were used as reactants, while terminal aldehydes were favored when bulky alkyl substituents were attached to the double bond (e.g., 3,3-dimethyl-1-hexene) or when the olefin was a 1,1-disubstituted one.[1] One can also realize the direct, regioselective preparation of alcohols from olefins by use of carbon monoxide and sodium borohydride (eq 1).[2]

$$RCH{=}CH_2 + CO + NaBH_4 \xrightarrow[500\ psi,\ 100\ °C]{i\text{-}PrOH,\ 1,\ CH_2Cl_2} R(CH_3)CHCH_2OH + R(CH_2)_3OH \quad (1)$$

The metal-catalyzed hydroformylation of allylamine usually results in the formation of 2-pyrrolidinone. Both cobalt carbonyl and chlorocarbonylbis(triphenylphosphine)rhodium catalyze the reaction under rather stringent conditions [e.g. $Co_2(CO)_8$, 125–250 °C and 60–300 atm; $Rh(CO)Cl(PPh_3)_2$, 150 °C and 136 atm].[3-7] It was also observed that use of hydridocarbonyltris(triphenylphosphine)rhodium as the catalyst, with excess triphenylphosphine, gave 1-pyrroline and 2-pyrrolidinone, the product distribution being sensitive to the nature of the solvent.[8] However, it should be noted that treatment of allylamine with rhodium acetate and triphenylphosphine [4:1 ratio of $PPh_3/Rh_2(OAc)_4$] and 1:1 CO/H_2 in benzene (28 atm, 70 °C) gave the lactam in 86% yield.[9] Also, use of rhodium complexes, containing or lacking phosphine ligands, as catalysts for the carbonylation of *N*-allylalkylamines at 65–90 atm, produced *N*-alkyl-2-pyrrolidinones and other products in variable yields.[10] We now report that the carbonylation of allylic amines, catalyzed, under relatively mild conditions, by 1 in the presence of sodium borohydride, selectively affords pyrrolidines or pyrrolidinones in good yields. Both types of products were also obtained in selective hydroformylation reactions catalyzed by 1.

Results and Discussion

Reaction of allyl amine with 1, carbon monoxide, sodium borohydride, and 2-propanol in methylene chloride for 30 h at 100 °C and 34.5 atm gave numerous products, each of which was formed in low yield. However, use of *N*-allylaniline (2, Ar = Ph) as the reactant afforded 1-phenylpyrrolidine (3, Ar = Ph) in 31% isolated yield, to-

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