the calculated electrostatic properties of free CO. In Figure 1 we have also included LiCO\(^+\) (22) and Cl\(_2\)ScHCO\(^-\). In LiCO\(^+\) the binding clearly is electrostatic, with no opportunity for back-donation. The possibility of a donation is also very remote. In Cl\(_2\)ScHCO the Cl substituents remove electrons from Sc giving it considerable Sc\(^+\) character. The calculated 23 ScCO bond length and bond energy (2.406 Å and 16.4 kcal/mol) are consistent with those calculated for the transition metal monocarbonyl cations. (c) The Mulliken population analysis results indicate that very little charge transfer takes place. Notwithstanding the well-known pitfalls of the method, 20 the trends are rather clear. The question naturally arises as to why the bonding is totally different between MCO and MCO\(^+\)? The \(\sigma-d\) view is a synergistic one: the \(\sigma\) ligand donation assists the \(d\) back-donation and vice versa. If the one cannot take place, the effect of the other is also greatly diminished. For the ionic systems the \(d\) metal back-donation does not occur mainly for energetic reasons. Electron transfer out of the M\(^+\) ion is prohibitively costly in light of the values of the second IE of the metals. The second IE's for Sc\(^+\), Ti\(^+\), V\(^+\), and Cr\(^+\) are 12.9, 13.6, 14.2, and 16.5 eV, respectively, as opposed to \(\sim 6.7\) eV on the average for the first IE of the metal atoms. The gain in energy due to covalent binding, if charge is transferred from M\(^+\) to CO, cannot compensate for the cost of that transfer and therefore the electrostatic interaction dominates.

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**Registry No. Sc\(^+\),** 14336-93-7; Ti\(^+\), 14067-04-0; V\(^+\), 14782-33-3; Cr\(^+\), 14067-03-9.

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**Stereochemical Studies on Protonated Bridgehead Amines.**

**\(^1\)H NMR Determination of Cis and Trans B-C Ring-Fused Structures for Salts of Hexahydropyrrolo[2,1-a]isoquinolines and Related C Ring Homologues.** Capture of Unstable Ring-Fused Structures in the Solid State†

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**Abstract:** Acid-addition salts of tricyclic isoquinolines 2a/b, 3a/b, 4a–4c, 5, 6a/b, 7, 8a/b, 9a/b, and 17a/b were studied by high-field \(^1\)H NMR in CDC\(_3\) solution. Cis (e.g., 14 and 15 in Figure 1) and trans (e.g., 13) B–C ring-fused structures were identified by using the vicinal \(J(CH-\text{NH})\) coupling constants, which demonstrate a Karplus-like behavior. In some cases, we initially observed a trans form, which converted to a cis A form by NH proton exchange. For 4c-HBr, the exchange process was slowed by addition of trifluoroacetic acid. In many cases, cis A and cis B structures were preferred in solution. The pendant phenyl group exerted a strong influence on the preferred solution structure. Observation of the initial, unstable trans-fused structures was related to their capture in the solid state and release intact on dissolution. X-ray diffraction was performed on the HBr salts of 2a (B–C cis), 2b (B–C cis), and 4c (B–C trans). The result for 4c-HBr confirmed the connection between the initial trans form in solution and the solid state. For 17b-HCl two conformers, associated with hindered rotation about the bond connecting the 2,6-disubstituted phenyl group to the tricyclic array, were detected at ambient probe temperature; however, rotamers were not observed for either of the two forms (trans and cis A) of 17a-HBr. Two conformers were also found for 16b-HBr. Temperature-dependent behavior was recorded in the \(^1\)H NMR spectra of 17b-HBr and 16b-HBr; the activation free energy for interconversion of conformers was estimated to be in the vicinity of 17 kcal/mol for the former and 14–15 kcal/mol for the latter. The \(^1\)H NMR spectrum of butalamol hydrochloride (20-HCl), a potent neuroleptic agent, in Me\(_2\)SO-d\(_6\) revealed two species in a ratio of 81:19, which were assigned as trans and cis A forms, respectively. \(^1\)H NMR data for various free bases are also presented and discussed. Empirical force field calculations on three model hydrocarbons are discussed from a perspective of finding an explanation for the configurational/conformational behavior of the bridgehead ammonium salts. Diverse literature examples of structures for protonated bridgehead amines are also discussed. Tentative rationales are suggested for the preference of cis A forms in some protonated tetrahydroisoquinoline derivatives.

Although substantial information has been acquired on the structural and conformational properties of alicyclic amines with nitrogen at the bridgehead position, such as bicyclic \([m.n.0]\) compounds where \(m\) and \(n\) = 3 or 4, the corresponding protonated species (i.e., acid-addition salts) have been largely ignored.\(^1\) Since this type of molecular framework is part and parcel of a wide variety of alkaloid structures,\(^2\) as well as several biologically active compounds,\(^2,5\) further study of acid-addition salts would be useful.

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2. This paper was presented in part in the "Symposium on Heterocyclic Chemistry" at the 19th Middle Atlantic Regional Meeting of the American Chemical Society, Newark, NJ, May 1984; paper ORGN-246. It was also presented at the 194th National Meeting of the American Chemical Society, New Orleans, LA, Sept 1987; paper ORGN-122.


4. The Pennsylvania State University.

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This paper deals in detail with the solution and solid-state structural properties of protonated tricyclic compounds containing a tetrahydroisoquinoline nucleus, which have been of special interest to us because they comprise our hexahydropyrrolo[2,1-a]isoquinoline series of inhibitors of the uptake of biogenic amine neurotransmitters (potential antidepressant agents).4a

Results and Discussion

In the course of our research on N-acyliminium cyclizations leading to polycyclic isoquinoline derivatives,4 we encountered 1 as a 55:45 mixture of diastereomers 1a and 1b. After isomer separation, attempted assignment of stereochemistry by 1H and 13C NMR was problematic. The quaternary center at C6 obviated a convenient 1H NMR paradigm that we had employed for many similar compounds.5 Although 1H and 13C NMR spectra for the corresponding amines 2a and 2b, or their HBr salts, were quite distinctive, no convincing stereochemical assignments could be made from these data. A tentative designation of structure 1a to the major diastereomer was ultimately made from 1H NMR LIS data for 1a and 1b [Eu(fod)], however, we wanted unequivocal evidence.

A single-crystal X-ray analysis on the hydrobromide salt of the minor isomer (higher melting salt) verified structure 2b. It was intriguing to us that 2b.HBr possesses a cis fusion between rings B and C. Therefore, we also performed an X-ray study on the major isomer, 2a.HBr (lower melting salt). Since it too was found to adopt a cis-fused structure in the crystal, we sought to establish the existence of such cis structures in solution by 1H NMR. The NMR studies on 2a.HBr and 2b.HBr at 200 or 360 MHz, in CDCl3 or CD3OD between +25 and -60 °C or in Me2SO-d6, proved uninformative because of broadness of the resonance lines and some N-H exchange (the importance of having relatively slow N-H exchange is discussed later). Thus, we turned to the investigation of other molecules in the pyrrolo[2,1-a]isoquinoline series, such as 3a/b, 4a-4c, and 5. By using high-field 1H NMR, we were able to characterize cis- and trans-indolizidine structures (the three species are shown in Figure 1) for various amine salts.

Chemical Synthesis. A 55:45 mixture of lactams 1a and 1b was produced via N-acyliminium ion cyclization of 5-ethoxy-5-oxopyrrolidin-2-one 10, obtained from succinic anhydride and 2,2-dimethylbutanamide. Additionally, we have investigated several homologues having 6-, 7-, and 4-membered C rings: 7-phenylhexahydrobenzo[a]quinolizines 6a/b and desphenyl analogue 7, 8-phenylhexahydropyrrolo[2,1-a]isoquinolines 8a/b, and 5-phenyltetrahydroazepino[2,1-a]isoquinolines 9a/b, respectively.

The syntheses of compounds 3a/b, 5, 6a/b, 8a/b, 9a/b, 16b, and 17a/b have already been reported by us.6a,6b For the synthesis of 4a-4c, the lactam (3-one) precursor was obtained by cyclization of 11 (from Ph2CHCH(Me)NH2 and

Figure 1. Trans, cis A, and cis B ring-fused structures illustrated for the pyrrolo[2,1-a]isoquinoline system.
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Figure 2. Molecular structure of 2a-HBr from X-ray analysis (ORTEP drawing).

Figure 3. Molecular structure of 2b-HBr from X-ray analysis (ORTEP drawing).

succinic anhydride) in polyphosphoric acid (PPA) at 100 °C (Scheme 1). Three diastereomeric lactams, 12a–12c, were produced in a 4:2:1 ratio; the fourth possible diastereomer was absent. The compounds were separated by preparative HPLC to minor lactam 12c, which corresponds to cis lactam 12a and amine salt 4eHBr (vide infra), which corresponds to minor lactam 12c, established the respective stereochemistry.

Known2 compound 7 was prepared by the N-acyliminium sequence on 1-(2-phenethyl)glutarimide, followed by borane reduction.

Stereochemical Background. There are three possible arrangements for the B–C ring fusion in the tricycles of interest here: one trans and two cis forms, the latter of which we designate cis A and cis B. These structures are depicted for the pyrroloisoquinoline class by structures 13–15, respectively (Figure 1). The two cis-fused structures represent true conformations, which are in dynamic equilibrium in solution at normal temperatures because of rapid bond rotation that interconverts the two tetrahydroisoquinoline half-chair conformers; thus, the free amines truly represent three conformations for the B-C ring fusion has the cis B arrangement (viz. 15). The phenyl substituent in 2a-HBr is oriented axially with its face directed toward the midpoint of the C10b–N bond, while the phenyl group in 2b-HBr is equatorial and orthogonal to the plane of the tetrahydroisoquinoline system. So, the cis B conformation in the solid state is independent of the positioning of the C6 substituents.

Compounds 16b-HBr, which lacks the 6-methyl group, also possesses the same gross structure in the solid state: a half-chair tetrahydroisoquinoline conformation, a cis B ring fusion, and an equatorial 2-chlorophenyl group (skewed ca. 30° from orthogonality).46

The HBr salt of 4c was found to have a half-chair tetrahydroisoquinoline system with equatorial methyl and phenyl groups and axial NH and H10b groups. The molecular structure is displayed in Figure 4. Although this salt adopts a trans B–C ring junction, that arrangement is probably imposed by crystal packing forces. As discussed below, dissolution of 4c-HBr involves transformation of this trans form to a more stable cis A form. In fact, the X-ray analysis of 4c-HBr was originally carried out to support interpretation of its unusual NMR behavior (vide infra).

Figure 4. Molecular structure of 4c-HBr from X-ray analysis (ORTEP drawing showing the atom numbering scheme).

Figure 5. Angular dependence of $\frac{1}{3}J(\text{CH-NH})$ values from ref 10.

Selected 'H NMR parameters for these salts, deduced with the aid of 2D homonuclear COSY and/or homonuclear decoupling, are collected in Table I. The NH resonances and the vicinal 3J(CH-NH) coupling constants were generally recorded in their entirety. Selected 1H NMR parameters for these salts, deduced with the aid of 2D homonuclear COSY and/or homonuclear decoupling, are collected in Table I. The COSY technique was particularly useful in analyzing mixtures of two isomeric species. Selected 1H NMR data for some corresponding free bases and lactams (including 18a and 18b for reference purposes) appear in Table II; selected 13C NMR data appear in Table III.

The key to understanding the stereochemical behavior of the amine salts in solution rests with the 1J(CH-NH) values. Al-

(7) The relative amount of these lactams is likely determined by a complex balance of various steric interactions.3 The fourth possible lactam, which was not produced, would have developed adverse A(1,3) strain due to an equatorial 5-methyl group and adverse 1,3 syn-axial interactions in the intermediate arenium ion due to an axial 6-phenyl group. For the minor product 12c, the cyclization would experience adverse A(1,3) strain due to the 5-methyl group. The preference for 12a over 12b is difficult to explain, but it may involve buttressing between the methyl and phenyl substituents and steric interaction between the phenyl group and H7.

(8) Details of this X-ray analysis are presented in the Experimental Section and the supplementary material.24

though this parameter has received just scant attention in the literature, a sufficient foundation has been established to allow stereochemical assignments to be inferred. The important work of Fraser and Crowley has provided the necessary information for describing the angular dependence of $J(CH-NH)$ in amine salts. As indicated in Figure 5, a Karplus-like relationship, analogous to that associated with $J(HC-CH)$, is manifest by $J(CH-NH)$. Fortuitously, each conformation possesses a unique set of $J(CH-NH)$ values, which exquisitely defines the structure. This can be illustrated for the pyrroloisoquinoline salts (Figure 1) by the following values for J(5a,NH) and J(10b,NH): (1) in the trans form both of these will be large (10–12 Hz); (2) in the cis A form J(5a,NH) will be small (ca. 3 Hz) and J(10b,NH) will be moderate (ca. 6 Hz); (3) in the cis B form J(5a,NH) will be large (10–12 Hz) and J(10b,NH) will be moderate (ca. 6 Hz). This paradigm will carry over, more or less, to the other ring systems. Certain other parameters can also be of value. Since there is a chair piperidine in the benzoquinoline system there is a high intrinsic propensity to adopt the cis A conformation and definitely disfavors the trans form. In the case of 3a-HBr, the cis A form is presumably favored for two reasons: (1) in order to escape the disfavored trans form and (2) because the cis B form would dispose the 6-phenyl group axially. Salts 4a–4c, which have two biasing substituents, were also studied. Salt 4d-HBr was particularly interesting. After dissolution of 4c-HBr in CDCl$_3$, the $^1$H NMR spectrum showed trans and cis A forms in a 90:10 ratio, both with a half-chair tetrahydroisoquinoline ring (Table I). The cis A form predominated, as judged by the $J(CH-NH)$ values. Some cis B form also contributed to the conformational profile since $J(5,4a)$ is somewhat large and J(5,6a) is somewhat small, indicating that averaging is taking place. This indicates that the protonated hexahydropyrroloisoquinoline ring system has a high intrinsic propensity to adopt the cis A conformation and definitely disfavors the trans form. In the case of 3a-HBr, the cis A form is presumably favored for two reasons: (1) in order to escape the disfavored trans form and (2) because the cis B form would dispose the 6-phenyl group axially.
in the latter. Without \( J(CH-NH) \) values, we tentatively make this assignment on the basis of the chemical shifts for H7 and H10b. Although these assignments must be regarded as tentative at this time, it is interesting to note that the cis B structures are manifested in the solid state (vide supra).

We also studied salts of 17a and 17b, which possess a bulky 2,6-disubstituted C6 aryl group (Table I). The 360-MHz \(^1\)H NMR spectrum of 17a-HBr first showed a trans B-C ring-fused structure to the extent of ca. 90%, as would be expected. However, the tetrahydroisoquinoline moiety does not assume the usual half-chair conformation; rather it exists predominantly in a boat-type conformation (Figure 6). This boat form is characterized chiefly by three features: (1) the \( J(4,5a) \) value of 6.6 Hz, instead of ca. 10 Hz; (2) the J(5,6) values of 10.5 (quasi-5a-6a) and 8.3 (quasi-5e-6a) Hz, instead of ca. 11 and 6-7 Hz; and (3) failure of H7 to resonate upfield of 7.0 ppm. Presumably, the bulky 2,6-disubstituted phenyl group suffers severe steric interactions in the equatorial orientation, such as an A(1,3) interaction with H7, causing this portion of the molecule to adopt a boat arrangement, wherein the phenyl group is removed from the plane of the tricyclic array (Figure 6). Over several hours, the trans form disappeared and the usual cis A form arose; the cis A form accounted for ca. 90% of the mixture at the end point of isomerization (presumably equilibrium). The 360-MHz \(^1\)H NMR spectrum of 17b-HCl displayed two cis B structures in a persistent ratio of 77:23 at ambient probe temperature (ca. 20 °C). The NMR parameters for these two species are closely parallel (Table I), consistent with an assignment of these as rotamers by virtue of hindered rotation about the bond connecting the 2,6-disubstituted phenyl group to the tricyclic network (Figure 6). Although it is not possible to assign which rotamer is which, given the data at hand, we tentatively suggest the structures depicted in Figure 6 for the major and minor forms. For 17b-HCl, changing the probe temperature from 20 to 60 °C resulted in coalescence of H7 (\( \Delta \rho = 10 \) Hz at -20 and +20 °C) with a coalescence temperature (\( T_c \)) of ca. 60 °C (other signals, such as those for H5e and H4, were also shifted). This coalescence data can be used to approximate a rotational barrier of 17 kcal/mol, by employing \( \Delta G^\ddagger = 4.57T_0(10.02 + \log (T_c/K_B)) \) with \( K_B = 2.2 \times 10^{-21} \).

The free bases 17a and 17b exist mainly as trans and cis B forms, respectively, in chloroform solution. Compound 17b is anomalous not only for favoring a cis B form but also because it exists as two rotamers (ca. 3:1) in the 360-MHz \(^1\)H NMR spectrum, in analogy with its HCl salt. Hallmark parameters in support of this assignment for 17b are the following: the absence of Bohlmann bands, in contrast to 17a (IR bands at 2816 and 2745 cm\(^{-1}\); 4% wt/vol in CHCl\(_3\)), the presence of two H7 resonances upfield of \( \delta 7.0 \) (ca. 6.73 ppm) and two H10b resonances at a position substantially downfield relative to 17a (major at \( \delta 4.02 \) and minor at \( \delta 4.07 \); also, H6 occurred as a major dd at \( \delta 5.02 (J = \text{ca. 5, 10 Hz}) \) and a minor dd at \( \delta 5.06 (J = \text{ca. 5, 11 Hz}) \) indicative of an equatorial aryl group. For 17b the bulky 2,6-disubstituted phenyl group is presumably favored when axially disposed in the trans form; thus, the cis B form with an equatorial aryl group is favored. In this case, a boat-type form is not prevalent, possibly because an unfavorable geometry would have to be adopted by the cis-fused pyrroloisoquinoline system. In connection with this view, one should note that the aforementioned boat structure for 17a-HBr was observed only for the trans form of this compound, not for the cis A form. \(^1\)H NMR data for 17a indicate that it has a trans B-C ring junction and that it may adopt a boat form to some degree in combination with a half-chair form (H10b, dd at 3.52 ppm with \( J = 8, 8 \) Hz; H6, dd at 5.14 ppm with \( J = \text{ca. 7, 9 Hz} \); H7, d at 6.75 ppm with \( J = 7.6 \) Hz).

After recording the rotamers for 17b-HCl, we examined 2-chloro derivative 16b-HBr (McN-5707-14). The 360-MHz \(^1\)H NMR spectrum of this compound at ambient probe temperature showed broad envelopes for most of the signals instead of sharp resonances. We suspected that this was caused by slow interconversion of two rotamers, as discussed above, rather than by an N-H exchange process. Indeed, an NMR spectrum at \(-20 \) °C exhibited sharp signals for two species in a 55:45 ratio (integration of the NH resonances at \( \delta 12.38 \) and 12.22, respectively), and a spectrum at 60 °C exhibited a single set of sharp signals, an NMR time-averaged situation. At the low temperature, the chemical shift difference between the signals for H7 in the two species of 16b-HBr is 20 Hz (\( \Delta \rho \)). Given a coalescence temperature of ca. 0 °C for the two H7 signals, the activation free energy for this two-site exchange is in the range of 14–15 kcal/mol.\(^{15}\)

Benzo[a]quinolizidines 6a and 6b (free base forms) have \(^1\)H NMR (and IR) properties indicative of a tetrahydroisoquinoline half-chair conformation, a chair piperidine, and a trans ring fusion, with an equatorial or axial 7-phenyl group (Table II).\(^{14}\) \(^1\)H NMR data for the HBr salt of 6a show that it adopts the trans conformation to the extent of 98% on initial examination in CDCl\(_3\), but changes to an 80:20 trans-cis A mixture on standing for 22 h (end point). This behavior is related, but not quantitatively correspondent, to the observations with 3a-HBr. By contrast, 6b-HBr adopts a cis B form to the extent of at least 90%, in close analogy to the results for 3b-HBr. Both salts appear to contain half-chair tetrahydroisoquinoline and chair piperidine rings, with an equatorial 7-phenyl substituent. The bias for the cis B form, as with 3b-HBr, can again be attributed to alleviation of 1,3 steric interaction between an axial 7-phenyl substituent and an axial proton on nitrogen.

For the benzoquinolizidine series we also evaluated the parent compound, 7-HBr, by 360-MHz \(^1\)H NMR. One major species, present to the extent of ca. 95%,\(^{15}\) was detected at first. The minor constituent gradually increased over 2–4 h, at the expense of the major species, to give ultimately an ca. 65:35 mixture enriched in the first species. The two forms were assigned cis and cis A structures, respectively, on the basis of \( J(CH-NH) \) and J-\( (1,11b) \) values. Given this data, the protonated benzo[a]-quinolizidine system has, surprisingly, only a modest intrinsic preference for the trans form.

The azepino[2,1-a]quinolizines, 8a-HBr and 8b-HBr, behaved somewhat more like the corresponding pyrroloisoquinolines, 3a-HBr and 3b-HBr. Salt 8a-HBr initially gave a mixture of trans and cis A forms, with an equatorial 8-phenyl substituent, in a ratio

(13) (a) Kost, D.; Carlson, E. H.; Raban, M. J. Chem. Soc. D 1971, 656. Sandstrom, J. Endeavour 1974, 33, 111. Sandstrom, J. Dynamic NMR Spectroscopy; Academic Press: London, 1982. Greenberg, A. J. Chem. Educ. 1972, 49, 575. (b) This equation for two-site exchange of nuclei applies to equal populations of species and to uncoupled nuclei. Thus, we are necessarily making an approximation here (\( k_1 \) kcal/mol). (c) Given a \( T_c \) for the NH signals of 16b-HBr of ca. 30 °C and a \( \Delta G^\ddagger \) of ca. 15 °C, we estimate a \( \Delta G^\ddagger \) in the vicinity of 14–15 kcal/mol. However, this parameter may be limited because the NH chemical shift is fairly sensitive to temperature.

(14) For background information on benzo[a]quinolizidines cis and trans conformations, see: Reference 13a and 7 and 7.4a–c.

(15) Some variability was experienced with different samples of 7-HBr. The NMR spectrum of a sample of 7-HBr, recrystallized from 2-propanol and dried in air at \( 23 \) °C (mp 247–249 °C), exhibited the major trans-fused species to the extent of 95%. Enhancement of the minor component to 30% occurred on drying this sample for 24 h at 80 °C in vacuo (mp 248–249 °C).
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of ca. 90:10. However, the original mixture slowly converted to a 45:55 final ratio on standing for several hours at 23 °C. Again, a special selection is achieved by sequestration of the trans form in the solid phase. Still, the 7-membered ring system does not conformations, respectively. It is intriguing that 8b does not favor equatorial 8-phenyl and axial B-C ring at C12b is stabilized, relative to the other ring systems, is unclear at this time.

The free bases, 9a and 9b, largely adopted the trans and cis B structures in the solid state rather than in solution and comes from examples in this subsection for the purposes of background and chemical literature. We have collected several relevant analogues to the salts discussed herein are scattered about the literature. Some representative structures in the solid state are: (a) capaurine (24a) and 24b exhibit a cis A structure, (b) salts of the dibenzoquinolizidine (tetrahydroprotoberbine) alkaloids caparurine (24a) and 24b exhibit a cis A structure, as does the HBr salt of indolizidine alkaloid 25, in which there are diaxial malonyl and ethyl substituents (the form favored by the free base in solution). X-ray analyses for several salts of saturated systems have been reported. The salts (HCI, HCl, HBr, and HCl, respectively) of indolizidine derivatives 26 (McN-5195), 27, 28 (gephyrotoxin), and 29 show a trans ring fusion. The hydrobromide salt of the ansa compound vertaline (30), which contains a quinolizidine nucleus, prefers a cis A structure, but quinolizidine salts of 31a and 31b (with biphenyl phosphoric acid) possess a trans ring fusion.

A 360-MHz 1H NMR study of the HBr salt of indolizidine 32 revealed a trans ring geometry in CDCl3 solution; indolizidine free base also adopts the trans conformation nearly exclusively. A high preference for a trans form was also observed for 26-HBr by 360-MHz 1H NMR in our laboratories.

A 360-MHz 1H NMR study of the HBr salt of indolizidine 32 revealed a trans ring geometry in CDCl3 solution; indolizidine free base also adopts the trans conformation nearly exclusively. A high preference for a trans form was also observed for 26-HBr by 360-MHz 1H NMR in our laboratories.

Source of the Preference for Cis-Fused Protonated Bridgehead Amines. The adoption of cis-fused structures by amine salts in the solid state is not particularly bothersome since that behavior could be attributed to crystal-packing forces. Such forces, which operate in the range of 1-2 kcal/mol, are sufficient to favor a cis form even when it is not intrinsically more stable. However, we may ask ourselves the reason for the preference of cis forms in solution in the absence of any driving force, such as the adverse placement of substituents.

It is possible that some understanding here might be achieved by reference to empirical force field (EFF) calculations. Such conformational energy calculations with MM2 have already been proposed, 30


(19) Mutter, M. S.; Carson, J. R., unpublished results.
conducted on protonated forms of butaclamol and isobutaclamol (20 and 21) by Froimowitz and Matthysses. Cis B forms, in which the tetrahydroisoquinoline network bears axial phenyl and NH groups and an equatorial H11b, were found to be preferred by 1.4–1.9 kcal/mol; yet the trans arrangements were suggested to be important for neuroleptic activity. On the basis of our body of NMR results, we believe that the cis B form would not be favored under real conditions in solution. If any cis form were to be adopted, it would more likely be the cis A form.

To follow up on this point, we sought to study butaclamol hydrochloride (20-HCl) by 'H NMR. Unfortunately, 20-HCl is very insoluble in CDCl₃, so we could not collect adequate data in our preferred solvent. However, 20-HCl did dissolve, albeit sparingly, in Me₂SO-d₆. The 360-MHz 'H NMR spectrum (NH couplings italicized) of the dilute solution revealed two species in a ratio of 1:19, as determined by the NH resonances at 9.72 (minor) and 10.92 (major) ppm, as well as the "H11b" (actually H4a for this pentacyclic ring system) resonance of the minor form at 5.11 ppm (J = 5.3, 0, 0 Hz) vs the "H7" (actually H13b) resonance of the major form at 5.42 ppm (J = 5.7, 12.8 Hz). This is virtually the same end point (presumably equilibrium) that we registered for 6a-HBr in CDCl₃. Other readily assigned resonances for the major species were as follows: δ 4.80 (dd, "H11b", J = 10.7, 9.5, ca. 1 Hz), 4.19 (dd, "H6a", J = 12.4, 12.4, 12.7 Hz), 3.72 (dd, "H6e", J = 12.1, 6.0, ca. 1 Hz). For the minor species they were as follows: δ 4.65 (dd, "H7", J = 11.9, 3.6 Hz). This evidence readily permits the assignment of the trans form to the major species. Moreover, given the close analogy that exists between these results and those found for 5, we suggest that the minor species of 20-HCl in Me₂SO-d₆ solution is the cis A form. Consequently, the cis B form of protonated butaclamol has little relevance under these conditions.

Since the MM2 calculations on protonated butaclamol and isobutaclamol indicate that the cis B form is preferred by a considerable margin, there seems to be a problem with the application of computational methods here. Perhaps, this difficulty is associated with correlating the MM2 gas-phase results (applicable to "isolated" molecules) with solution phenomena involving polar or charged species (i.e., ammonium salts). Also, there may be an intrinsic problem with performing MM2 calculations on such chemical entities (e.g., incomplete parametrization for ammonium ions or domination by coulombic terms with same). Therefore, for additional understanding of the origin of the configurational/conformational effects, we decided to explore MM2 calculations on hydrocarbon systems that parallel the ammonium systems in this paper.

The hydrocarbon hydrindan (33), which corresponds to protonated indolizidine (32-HX), not only has been treated already (20 and 21) by Froimowitz and Matthysse. Cis B forms, in contrast to what was seen for the sulfonium congener of indolizidine, thioniabicyclo-[4.3.0]nonane salt 36, strongly prefers a cis B geometry. In this case, a cis A form was found to be most stable by ca. 1.5 kcal/mol.

We wondered if A(1,3) steric strain might be responsible for the reversal of MM2 energies between 33 and 34. As a test, we performed calculations on hydrindene 35 but recorded a similar preference for the cis A form, with the following energy values (kcal/mol): cis A (−78.4) > cis B (−78.0) > trans (−77.6). Significantly, both cis forms are favored over the trans form, in contrast to what was seen for hydrindan. Calculations with MNDO (in AMAPC), gave the same rank order (kcal/mol) with an even wider spread: cis A (−74.2), cis B (−1.6), trans (2.1). Therefore, the fusion of a benzene ring onto that particular bond of hydrindan (α to the bridgehead in the 6-membered ring) causes a dramatic change in the relative stability of cis- and trans-fused structures. This outcome deviates from the computational results for protonated butaclamol and isobutaclamol, where the cis B form was found to be most stable by ca. 1.5 kcal/mol.

For the purpose of further comparison, it is interesting to note that the sulfinium congener of indolizidine, thionia bicyclo-[4.3.0]nonane salt 36, strongly prefers a cis B geometry. In this case, a cis isomer was expected to be much more stable than the trans isomer from data on cis- and trans-1,2-dimethylthianium salts, and the cis A form was the one anticipated from data on the cis-thianium isomer. The results for thianium salts, along with those that we presented in the above discussion, point to the subtleties in steric factors that can influence the ultimate distribution of structure types in such bicyclic and tricyclic molecules. It is difficult to assemble any clearer picture of the intimate structural features responsible for particular configurational/
conformational properties at this time.

Conclusion

It should be evident at this point that the configurational/conformational properties of amines and their acid-addition salts can be quite different. Indeed, Eliel and co-workers have discussed, in considerable depth, the subject of free amine vs salt structure for piperidine molecules in solution; moreover, they emphasized that this issue is frequently overlooked. Other studies have appeared on derivatives containing a substituted N-methylpiperidine unit, some of which have disclosed examples of configurational/conformational differences between amines and their salts.

New species was assigned the cis A structure. At 7.5 h, an ca. 25:75 mixture was recorded. A final ratio of 1:10:90, which held constant with time, was recorded at 48 h.

Synthesis and Isolation of Three Isomers

1,2,3,4-tetrahydro-5-methyl-6-phenylpyrrolo[2,1-a]pyridine was crystallized from ethyl acetate to a suspension of succinic anhydride (14.0 g, 0.14 mol) in 75 mL of ethyl acetate, with rapid stirring. The product showed three peaks in a 4:1:2 ratio (order of increasing retention) for X-ray analysis. The enriched mixtures were subjected to reduction with borane-THF (50% in THF) and the crude material was chromatographed to get additional material.) A small sample (0.30 g) of 12b were collected and dried in vacuo to give 3 1.3 g (82%) of imide, as bright white needles, mp 122-125 °C. The imide (25.0 g, 0.085 mol) in 400 mL of methyl alcohol and then 30 mL of water. The white solid that crystallized was collected and dried in vacuo to give the corresponding amine.

NMN spectra were obtained on a Perkin-Elmer R-32 spectrometer and 60-MHz spectra were obtained on a Varian EM-360 spectrometer, in CDCl₃ (δ = singlet, δ = doublet, dd = doublet of doublets). ¹⁴C NMR spectra were recorded on a Varian FX-400 spectrometer at 15.1 MHz in CDCl₃. ¹³C peak multiplicities were determined by using INEPT or off-resonance decoupling. Certain ¹³C peak assignments were facilitated by reference to Shamma and Hindenlang. Proton and carbon chemical shifts are reported in ppm downfield from MeSi.

Staring structures for the MM2 calculations were generated by using the SYBYL molecular modeling program (Tripos Associates, Inc., St. Louis, Missouri, Version 3.3).

The X-ray diffraction analyses of 2a-HBr, 2b-HBr, and 4c-HBr were conducted by Prof. Olofson's group at the Pennsylvania State University; the X-ray analysis of 12a was conducted by Molecular Structure Corp., Colma, Station, TX.

H NMR Methods. H NMR spectra were recorded on a Bruker AM-360WB instrument in the specified solvent (generally CDCl₃). Chemical shifts are reported in ppm downfield from MeSi. Typical conditions used for 1D spectra were the following: spectral width of 6024 Hz; quadrature detection; 32K data points acquired, zero filled to 64K; pulse width of 2.0 s (25°). For 2D COSY spectra, the data matrix consisted of 512w (x) 1K (y) points. The time domain matrix was zero filled to 1K points in y with a sine-bell window function applied in both dimensions.

Example of Interconversion of Trans- and Cis-Fused Forms. Monitoring the NMR Spectrum of 4c-HBr with Time. A sample of 4c-HBr was dissolved in CDCl₃ and immediately examined by 360-MHz H NMR. One major substance was evident to the extent of 95%; this was assigned the trans structure. Over time, minor peaks in the original spectrum grew and, after 3.5 h, an ca. 50:50 ratio of two substances was apparent. The new species assigned the cis structure. At 7.5 h, an ca. 25:75 mixture was recorded. A final ratio of 1:10:90, which held constant with time, was recorded at 48 h.

Experimental Section

General Methods. Melting points are corrected. IR spectra were recorded on a Perkin Elmer 457 spectrometer at 4 cm⁻¹. TLC was performed with Kieselgel 60 F₂₅₄ (E. Merck) using UV light detection. Column chromatography was performed on silica gel (200-400 mesh) from Merck. NMR experiments were performed on a JEOL FX-60Q spectrometer at 15.1 MHz with 32K data points, with a quadrature detection, pulse width of 2.0 s (25°) and a recycle time of 4.72 s. For 2D experiments, spectral width was 6024 Hz, data points (0.184 Hz/point) before transform; recycle time of 4.72 s; pulse width of 2.0 s (25°). For 2D COSY spectra, the data matrix consisted of 512w (x) 1K (y) points. The time domain matrix was zero filled to 1K points in y with a sine-bell window function applied in both dimensions.

The enriched mixtures were subjected to reduction with borane-THF to give the corresponding amine.
slowly to obtain small colorless prisms for X-ray analysis; mp 272-277 °C. The 12c mixture (1.9 g) afforded 0.69 of 4a.HCl, 0.07 of 4b, and 0.065 of 4c by GLC (OV-17). Anal. C, H, Br, N. The 12c mixture (1.9 g) was prepared according to previously reported procedure.33 Glutaric acid (11.4 g, 0.10 mol) and phenethylamine (12.1 g, 0.10 mol) were heated in ethyl acetate with 25 mL of acetyl chloride to give the crude glutarimide, which was recrystallized from water/methanol to afford white crystals (16.5 g, 76%). This solid was reduced with sodium borohydride in acidic ethanol (11.4 g, 0.30 mol), and the result 6-ethoxyperipederin-2-one was cyclized with PPA (100 g) at 100 °C to give the crude lactam (11.5 g, 76%). The lactam was purified by preparative HPLC to give 5.8 g [60-MHz IH NMR (data not included in Table I) δ 1.6-2.1/2.1-3.2 (m, 9) 4.5-5.0] of 12a.HBr, 118474-75-2. Supplementary Material Available: Tables of bond distances, bond angles, torsional angles, and positional and thermal parameters for 2a.HBr, 2b.HBr, 4c.HBr, and 12a are presented in the supplementary material.

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Registry No. (±)-4a, 118474-84-3; (±)-1b, 118474-85-4; (±)-2a, 118474-82-1; (±)-2a.HBr, 118474-70-7; (±)-2b, 118474-83-2; (±)-2b.HBr, 118474-71-8; (±)-3a, 90390-51-5; (±)-3a.HBr, 118474-72-9; (±)-3b, 90390-52-6; (±)-3b.HBr, 118474-73-0; (±)-4a, 118474-85-9; (±)-4a.HCl, 118474-67-2; (±)-4b, 118474-89-8; (±)-4b.HBr, 118474-87-7; (±)-4c, 118474-91-2; (±)-4c.HBr, 118474-77-4; (±)-4d, 90390-65-1; (±)-4d.HBr, 118474-75-2; (±)-6b, 90390-64-4; (±)-6b.HBr, 118474-78-5; (±)-7b, 118474-79-6; (±)-8a, 90390-66-2; (±)-8a.HBr, 118474-80-7; (±)-8b, 90390-85-9; (±)-8b.HBr, 118474-87-7; (±)-9a, 118474-88-7; (±)-9a.HBr, 118474-89-9; (±)-9b, 118474-89-9; (±)-9b.HBr, 118474-91-2; (±)-11 (imid), 118474-69-4; (±)-12a, 118573-90-9; (±)-12b, 118573-87-8; (±)-12c, 118573-88-9; (±)-17a.HBr, 118474-75-2; (±)-17b.HCl, 118474-76-3; (±)-18a, 118474-86-5; (±)-18b, 118474-87-6; (±)-20-HCl, 36304-94-6; (±)-cis-34, 118474-91-2; (±)-trans-34, 118474-90-1; (±)-cis-35, 96308-32-2; (±)-trans-35, 118474-92-3; (±)-metal. 118474-92-5; sucinic anhydride, 108-30-5.

Supplementary Material Available: Tables of bond distances, bond angles, torsional angles, least-squares planes, general temperature factors, and positional and thermal parameters, ORTEP drawings featuring atom numbering schemes, and views of the unit cells for 2a.HBr, 2b.HBr, 4c.HBr, and 12a (27 pages). Ordering information is given on any current masthead page.

(33) Cromer, D. T. International Tables for X-Ray Crystallography; Kynoch Press: Birmingham, England, 1974; Vol. IV, Table 2.3.1. (34) See paragraph regarding supplementary material at the end of this paper.