The Solution Conformations of Lidocaine Analogues

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Received November 8, 1990; accepted March 15, 1991

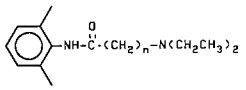
IR and ^{1}H NMR studies in $CDCl_3$ and CCl_4 of a series of tertiary aminoxylidides with the amino group in the 2 to 6 position of the acyl chain are described. Lidocaine, diethylaminoaceto-2′,6′-xylidide, forms an intramolecular five-membered ring hydrogen-bonded monomer at all concentrations in both solvents. β-Diethylamino-propiono-2′,6′-xylidide forms an intramolecular six-membered ring hydrogen-bonded monomer in $CDCl_3$ and CCl_4 but a *trans* intermolecularly associated species is the major form present at high concentrations in CCl_4. The longer-chain homologues are mixtures of nonassociated *trans* and *cis* monomers at low concentrations but associated *trans* forms predominate at high concentrations. Evidence for the presence of a hydrogen-bonded seven-membered ring intramolecular monomer in $CDCl_3$ for γ-diethylaminobutyro-2′,6′-xylidide is presented. The relationship between the molecular conformation and the partition coefficient is discussed.

KEY WORDS: lidocaine; conformations; infrared (IR); nuclear magnetic resonance (NMR); hydrogen bonding; partition coefficients.

INTRODUCTION

In a previous publication (1) the syntheses of a series of analogues of lidocaine (**1a**; Scheme I) with increasing length of the intermediate chain between the amide and the amine functions were reported and a quantitative–structure activity relationship was described. The octanol/water partition coefficients (*P*) were measured. A plot of log *P* vs molecular weight suggested that the total number of methylene groups in the chain was the major factor influencing the partition coefficient. However, lidocaine and its homologue, α-diethylaminopropiono-2′,6′-xylidide (**2a**; Scheme II), were more lipophilic than expected on the basis of their molecular weights. Several previous studies (2–4) have shown that lidocaine base exists as a *trans* intramolecularly hydrogen bonded conformation (**3a**; Scheme III) in carbon tetrachloride and chloroform at concentrations around 0.01 *M*. Since the hydrophobic groups would thus be turned toward the outside of the molecule, increased lipophilicity, as compared to the nonbonded conformations, might be expected.

Adams *et al.* (4) studied β-diethylaminopropiono-2′,6′-xylidide, **1b**, and γ-diethylaminobutyro-2′,6′-xylidide, **1c**, and proposed, on the basis of IR and ^{1}H NMR data, that **1b** exists in $CDCl_3$ as an associated *cis* dimer, **7b**, while **1c** exists as an unassociated *trans* amide, **5c**. Compound **1b** and its homologue β-diethylaminobutyro-2′,6′-xylidide, **2b**, were also more lipophilic than anticipated in our study (1), suggesting that the α and β amines were conformationally different from the longer-chain analogues **1c–e**.



1a n = 1
b n = 2
c n = 3
d n = 4
e n = 5

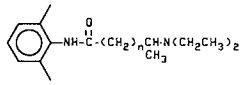
Scheme I

Recent studies (5,6) have correlated physiological properties of some of these compounds with partition coefficients and pK_a's. Strichartz *et al.* (5) used calculated partition coefficients in their first study. Later (6) Strichartz's group measured the partition coefficients of **1a** and its conjugate acid at several temperatures. They found, as we did, that the partition coefficient for the base was higher than that calculated according to the tabulations of Hansch and Leo (7). Since the conformation of the base as well as its lipophilicity could have an important effect at the site of physiological activity, a study was initiated to determine if the differences in the observed partition coefficients of the α and β aminoxylidides from the calculated values could be attributed to the conformations of the bases.

MATERIALS AND METHODS

The syntheses of the aminoxylidides have been reported previously (1). The IR spectra of the xylidides were recorded on a Perkin–Elmer 1750 FT IR at concentrations of 1, 0.5, 0.1, 0.01, and 0.001 *M* in both CCl_4 and $CDCl_3$. IR spectra were analyzed on a Perkin–Elmer Model 7300 Professional Computer using the CDS-3 software package provided. Spectra were enhanced to improve resolution using this program. IR spectra of the compounds in which the amide hydrogen has been replaced by deuterium were recorded to ensure proper assignment of the amide II bands.

^{1}H NMR spectra were recorded at 1, 0.1, and 0.01 *M* in the same solvents on a Bruker Instrument, Inc., ACE 200 or 300 FT NMR spectrometer. Spectra were evaluated using the Aspect 3000 computer with related software. The *cis–trans* ratios were determined by integration of ^{1}H NMR amide, *ortho* methyl, and aromatic hydrogen resonances in those cases when no interfering signals were present. Ratios



2a n = 0
2b n = 1

Scheme II

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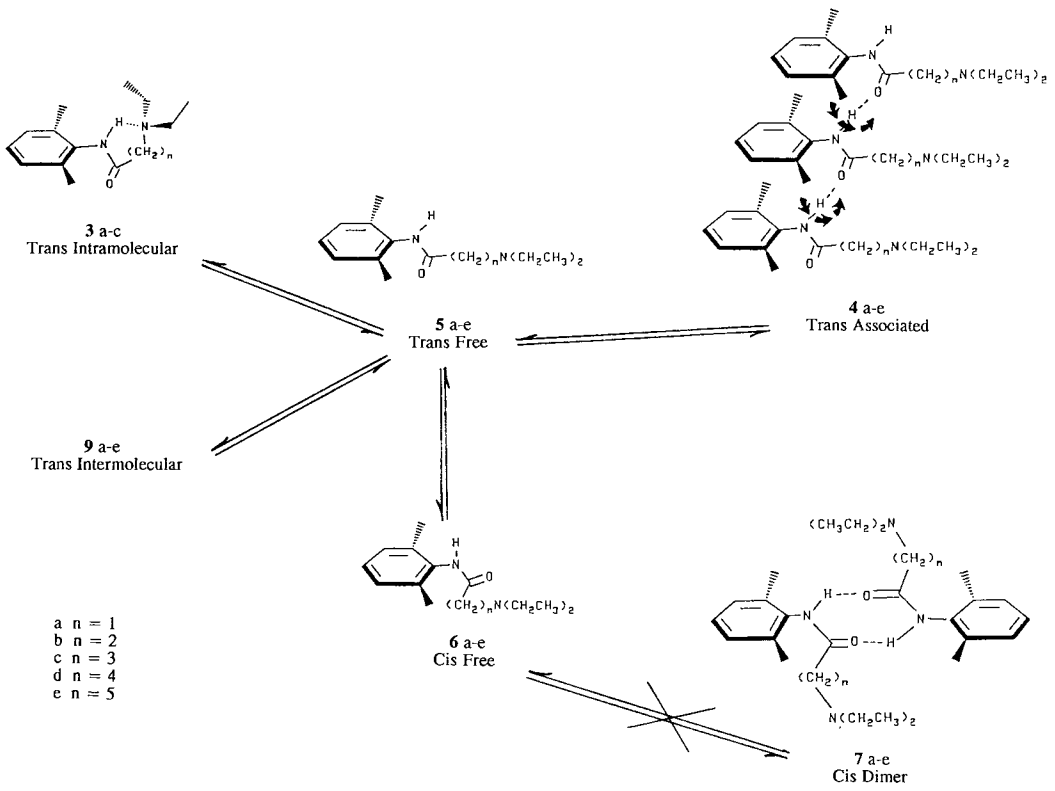


Scheme III

obtained from each region agreed within 2% for each species. These ratios also agreed within 2–3% of those obtained by measuring the relative areas of 5 and 6 in the IR spectra. The aromatic resonances split into *meta* and *para* resonances in some cases. When both resonances were present, the chemical shift of the more intense *meta* resonance is reported.

The IR and ^{1}H NMR spectra of butyro-2′,6′-xylidide, 8, a model for systems without the diethylamino function, were also recorded.

RESULTS AND DISCUSSION

The IR band assignments for the various species are summarized in Table I for CCl_4 and in Table II for $CDCl_3$. In $CDCl_3$ both the carbonyl group and the diethylamino function interact with the solvent, producing a solvent ν_{CD} band at 2245 cm^{-1} ($\Delta\nu$ = 13 cm^{-1}) for hydrogen bonding to the carbonyl group. Takahasi and Li (8) reported $\Delta\nu$ for the hydrogen bond of $CHCl_3$ with *N,N*-dimethylacetamide in CCl_4 to be 8 cm^{-1}. A solvent ν_{CD} band at 2178 cm^{-1} ($\Delta\nu$ = 80 cm^{-1}) due to hydrogen bonding to the diethylamino group is also present. The $\Delta\nu$ for this band is in excellent agreement with that found by Barrow (9), 80 cm^{-1}, for the $CDCl_3$–triethylamine system.

The chemical shifts of the amide, *o*-methyl, aromatic, and α-hydrogens at the highest and lowest concentrations in each solvent are given in Tables III and IV. The chemical shifts of the amide, *o*-methyl, and aromatic hydrogens are most useful in making conformational assignments since (i) they are present in all compounds studied and (ii) they are little influenced, within each different type of conformation, by the length of the intermediate chain.

The observed IR and ^{1}H NMR spectral changes which occur in these systems can be adequately explained by the equilibria shown in Scheme III.

CCl_4

The concentration-related changes occurring in CCl_4 for each of the individual compounds are discussed below.

1a. The first study of the structure of **1a** was conducted by Neville and Cook (10), who concluded, on the basis of an

Table I. IR Spectral Data in CCl_4

	ν_{NH} (cm^{-1})		Amide I (cm^{-1})		Amide II (cm^{-1})	
Species	NH[a]	ND[b]	NH[a]	ND[b]	NH[a]	ND[b]
3a	3321	2471	1690	1690	1493	1394
3b	3170	2315	1672	1667	1523	1413
4[c]	3317[d]	2391	1650	1647	1524	1405
5[c]	3432	2536	1699	1692	1484	1387
6[c]	3387	2511	1682[e]	—[f]	—	—
9[c]	3166[d]	—	1660	—	—	—

[a] Amide hydrogen.
[b] Amide deuterium.
[c] IR band frequencies for **4**, **5**, **6**, and **9**, when present, were almost identical in each of the compounds studied. Only one frequency is reported.
[d] Broad, varies with the concentration, frequency at 0.001 *M*.
[e] Enhanced.
[f] Not observed.

Table II. IR Spectral Data in $CDCl_3$

Species	ν_{NH} (cm^{-1})		Amide I (cm^{-1})		Amide II (cm^{-1})	
	NH[a]	ND[b]	NH[a]	ND[b]	NH[a]	ND[b]
3a	3294	2453	1676	1672	1500	1406
3b	3142[c]	2290	1662	1659	1529	1410
3c	2850[d]	2100[c]	1660	—[e]	1569	—
4[f]	3300[g]	2410	1660	1654	1519	1400
5[f]	3424	2539	1678	1670	1490	1384
6[f]	3378	—	1690	—	—	—
9[f]	3184[g]	—	—	—	—	—

[a] Amide hydrogen.
[b] Amide deuterium.
[c] Broad.
[d] Broad under CH_2 peaks (see text).
[e] Not observed.
[f] IR band frequencies for 4, 5, 6, and 9, when present, were almost identical in each of the compounds studied. Only one frequency is reported.
[g] Broad, varies with the concentration, frequency at 0.01 *M* given.

amide II frequency at 1490 cm^{-1} and an NH stretching frequency at 3312 cm^{-1} which were concentration independent, that in dilute solutions in CCl_4 **1a** existed as the dimeric *cis* amide **7a**. Chupp (2) reached an entirely different conclusion based on ^1H NMR and IR comparisons with α-amino anilides with restricted rotation around the amide bond. He concluded that lidocaine existed as the intramolecularly hydrogen bonded *trans* amide **3a** at concentrations around 0.04 *M* in CCl_4. Chupp showed that, in those anilides in which the *cis* and *trans* amide rotomers could be prepared independently, the α-methylene singlet and both the methylene quartet and the methyl triplet of the ethyl group of the *trans* rotomer were deshielded with respect to those of the *cis* rotomer. He concluded that the chemical shifts of lidocaine and the NH stretching band at 3328 cm^{-1} resembled those of the *trans* rotomers. Lumley-Jones (3) examined the IR spectra of 8, methoxyaceto-2′,6′-xylidide, and lidocaine at 0.001 *M* in CCl_4 and concluded that lidocaine had structure **3a**.

Our results support the last two studies. At all concentrations **1a** is predominantly the intramolecularly hydrogen bonded species **3a**. There appears to be a slight frequency shift of ν_{NH} (3311 to 3321 cm^{-1}) upon dilution, suggesting that a small amount of **4a** is in equilibrium at higher concentrations. The small shifts in the ^1H NMR spectra are consistent with this interpretation. The chemical shift of the amide hydrogen of **4a** appears to be at 8.9–9.0 ppm (see discussions of **1c–e** below), while that of **3a** approaches 8.4 ppm at the lowest concentrations studied. The slight upfield shift of the amide hydrogen (8.56–8.47 ppm) coupled with the downfield shifts of the *o*-methyl (2.11–2.18 ppm) and aromatic hydrogens (6.93–6.97 ppm) indicates a change from **4a** to **3a** upon dilution. No observable changes occur in the amide I (1690 cm^{-1}) or amide II (1493 cm^{-1}) bands upon dilution. No free N–H (**5a** or **6a**) was present even at the lowest concentration studied.

1b. No previous studies of **1b** have been reported in CCl_4. In our studies the spectrum of **1b** shows dramatic changes upon dilution. At 1.0 *M* the broad ν_{NH} band due to **4b** dominates the spectrum (Fig. 1), while the signal due to **3b** appears as a shoulder. Small peaks due to the presence of **5b** and **6b** are also present. On dilution the peak due to **4b** diminishes and **3b** becomes the predominant species in the equilibrium. Similar changes are evident in the amide I region; the band at 1650 cm^{-1} disappears on dilution as the 1680 cm^{-1} band grows in relative size. Little change occurs in the amide II region since both **3b** and **4b** have a moderate-strength band at 1523 cm^{-1}. The relative amounts of **5b** and **6b** also increase upon dilution. The chemical shift of the amide hydrogen of the *trans* forms moves downfield (9.25–9.52 ppm), while those of the *ortho* methyl (1.97–2.17 ppm) and aromatic hydrogens (6.79–6.96 ppm) shift to lower fields. Signals for **6b** (aromatic at 7.03 ppm and *o*-methyl at 2.30) are also present.

1c–1e. The spectra of these compounds are similar. No studies of these compounds have been previously reported in CCl_4. The spectra of these compounds (see the spectra of **1d**, Fig. 2) are dominated at high concentrations by the broad ν_{NH} band due to **4** at 3250 cm^{-1}, with a band due to another *trans* bonded species **9** (possibly that of the amide hydrogen bonded to the diethylamino group) as a shoulder at 3180 cm^{-1}. At 0.001 *M* the major bands are due to **5** (ν_{NH} 3432 cm^{-1}) and **6** (ν_{NH} 3387 cm^{-1}), with some **4** and **9** present. The frequencies of these bands are now shifted to 3315 and 3160 cm^{-1}. Changes are also evident in the amide I and II regions. At high concentrations the sharp strong amide I band at 1650 cm^{-1} and the medium-strength amide II band at 1524 cm^{-1} due to **4** are present. At lower concentrations the amide I band at 1695 cm^{-1} [splitting on enhancement into two bands, 1699 cm^{-1} (major, **5**) and 1682 cm^{-1} (minor, **6**)] appears, as does a broad amide II band at 1478 cm^{-1}. In the ^1H NMR spectra the amide hydrogen of the *trans* rotomer shifts upfield upon dilution (8.89–7.88 ppm) for **1c** and even farther upfield for **1d** and **1e**. The *o*-methyls and aromatic hydrogens of the *trans* rotomer shift downfield. Signals for **6c** (NH at 6.78, aromatic at 7.06 ppm, and *o*-methyl at 2.30 ppm) representing ~15% of the mixture by NMR integration are present at low concentrations. Similar results are found for **6d** and **6e** (see Table III).

8. Since the solubility of **8** was limited in CCl_4, only low-concentration spectra could be obtained. The NH stretching band due to **4** is still present at 0.01 *M* but is gone at 0.001 *M*, while the band due to **9** is absent at both concentrations. Butyroxylidide is thus a good model for the mixture of **5** (ν_{NH} at 3432 cm^{-1}, amide I at 1699 cm^{-1}) and **6** (ν_{NH} at 3387 cm^{-1}, amide I at 1682 cm^{-1}). The broad amide II band is centered at 1484 cm^{-1}, δ_{NH} (**5** at 6.60, **6** at 6.88 ppm), $\delta_{aromatic}$ (**5** at 6.99, **6** at 7.07 ppm), and $\delta_{o\text{-methyl}}$ (**5** at 2.17, **6** at 2.30 ppm).

$CDCl_3$

The changes in the IR and ^1H NMR spectra which occur on changes in concentration are summarized below.

1a. Adams *et al.* (4) concluded, on the evidence of an IR ν_{NH} band (broad) at 3280 cm^{-1}, an amide II band at 1495 cm^{-1}, and an NMR signal for the amide proton at 8.5 ppm, that **1a** also had structure **3a** in $CHCl_3$ at concentrations around 0.02 *M*. The α-methyl analogue of lidocaine **2a** showed absorptions similar to lidocaine and thus had a similar structure. In our studies we found the ν_{NH} at 3294 cm^{-1},

Table III. ^{1}H NMR Spectral Data in CCl_4

Compound	Con[a]	ν_{NH}		δ_0[b]		δ_a[c]		δ_α[d]	
		trans	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*	*cis*
1a	1.0	8.56	—[e]	2.11	—	6.93	—	2.93	—
	0.01	8.47	—	2.18	—	6.97	—	3.07	—
1b	1.0	9.25	—	1.97	—	6.79	—	2.20	—
	0.01	9.41	—	2.17	2.30	6.96	7.03	2.45	—
1c	1.0	8.89	—	1.85	—	6.71	—	2.00	—
	0.01	7.88	6.78	2.17	2.30	6.97	7.06	2.37	1.87[f]
1d	1.0	8.91	—	1.81	—	6.68	—	1.95	—
	0.01	6.94	6.87	2.17	2.29	6.97	7.06	2.31	1.81[g]
1e	1.0	8.91	—	1.82	—	6.69	—	1.94	—
	0.01	6.72	6.91	2.17	2.29	6.98	7.06	2.29	1.81[h]
8[i]	0.01	6.60	6.88	2.17	2.30	6.99	7.07	2.28	1.8[hj]

[a] Molar concentration.
[b] Chemical shifts of the *ortho* methyl protons.
[c] Chemical shifts of the aromatic protons.
[d] Chemical shifts of the α-methylene protons.
[e] Not observed.
[f] 15% *cis* by NMR integration.
[g] No isolated NMR signals available for integration.
[h] 18% *cis* by NMR integration.
[i] Not measured at 1.0 *M* due to limited solubility.
[j] Partially hidden by adjacent resonances.

amide I at 1678 cm^{-1}, and amide II at 1490 cm^{-1} all invariant with changes in concentration from 1.0 to 0.001 *M*. The amide NH (8.91–8.93 ppm), *o*-methyls (2.22–2.23 ppm), and aromatic hydrogens (7.03–7.09 ppm) show little change upon dilution. Again, no **5a** or **6a** is evident, even at the lowest concentration. We therefore concur with the findings of Adams *et al.* and extend the concentration range, that **1a** exists at all concentrations as the intramolecularly hydrogen bonded **3a**. This conclusion is reinforced by the presence of only one ν_{CD} band (2243 cm^{-1}), which is due to hydrogen

Table IV. ^{1}H NMR Spectral Data in $CDCl_3$

Compound	Con[a]	ν_{NH}		δ_0[b]		δ_a[c]		δ_α[d]	
		trans	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*	*cis*
1a	1.0	8.91	—[e]	2.22	—	7.03	—	3.19	—
	0.01	8.93	—	2.23	—	7.09	—	3.22	—
1b	1.0	10.22	—	2.20	2.22	7.03	7.07	2.52	2.37
	0.01	10.34	—	2.23	2.27	7.08	7.13	2.57	2.37[f]
1c	1.0	9.00	—	2.13	2.22	6.98	7.10	2.36	1.92[g]
	0.01	8.91	6.57	2.23	2.27	7.07	7.13	2.54	1.93[h]
1d	1.0	7.93	—[e]	2.07	2.20	6.94	7.10	2.25	1.88[g]
	0.01	7.1[i]	6.57	2.23	2.26	7.08	7.13	2.45	1.94[k]
1e	1.0	7.70	—	2.07	2.21	6.95	7.10	2.23	1.86[j]
	0.01	6.75	6.58	2.23	2.26	7.08	7.13	2.43	1.92[k]
8	1.0	7.68	—	2.05	2.20	6.92	7.10	2.19	1.84[g]
	0.01	6.69	6.58	2.23	2.27	7.08	7.14	2.40	1.90[k]

[a] Molar concentration.
[b] Chemical shifts of the *ortho* methyl protons.
[c] Chemical shifts of the aromatic protons.
[d] Chemical shifts of the α-methylene protons.
[e] Not observed.
[f] 1% *cis* by NMR integration.
[g] 5% *cis* by NMR integration.
[h] 7% *cis* by NMR integration.
[i] Under the aromatic resonance.
[j] 10% *cis* by NMR integration.
[k] 15% *cis* by NMR integration.

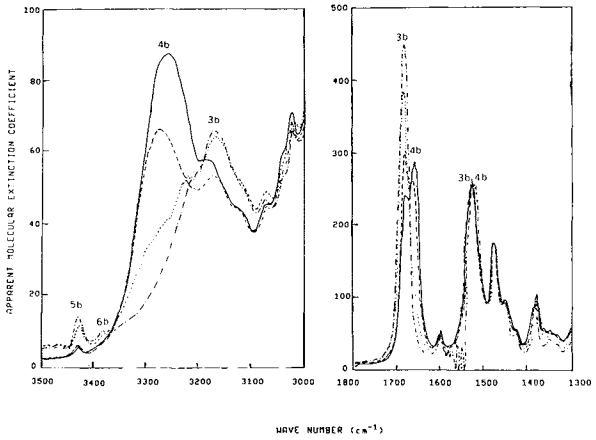


Fig. 1. IR spectral changes which occur upon dilution of β-diethylaminopropiono-2′,6′-xylidide (**1b**) in CCl_4. (——) 1.0 *M*; (– – – –) 0.5 *M*; (·····) 0.1 *M*; (·–·–·–·) 0.01 *M*.

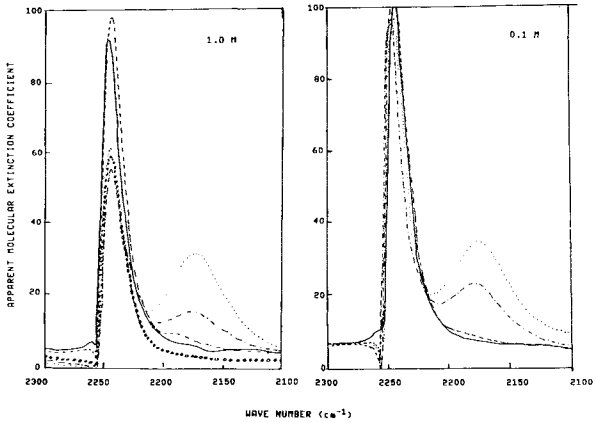


Fig. 3. Spectral differences of the various species at 1.0 and 0.1 *M* in $CDCl_3$; ν_{CD} spectral region. Major spectral changes are complete by 0.1 *M*. (——) **1a**; (– – – –) **1b**; (·–·–·–·) **1c**; (·····) **1d**; (OOOOO) **8**. Compound **1e** resembles **1d** and is not plotted for clarity.

bonding of the solvent with the carbonyl group. No ν_{CD} (2178 cm^{-1}) band due to hydrogen bonding of the diethylamino function is present (Fig. 3).

1b. Adams *et al.* (4) argued that **1b** existed, at 0.02 *M* in $CHCl_3$, as an associated *cis* dimer **7b** primarily because the chemical shift of the amide hydrogen was far downfield at 10.3 ppm. Rao *et al.* (11) had shown that the amide NH of cyclic *cis* amides was 1.3 ppm downfield from that of the cyclic *trans* amides in larger ring systems. They attributed this deshielding to the presence of the amide hydrogen inside the anisotropic deshielding region of the carbonyl group in the *cis* amide.

In our study, the ν_{NH} was broad and centered at 3142 cm^{-1}. This band was invariant with concentration changes, as were amide I (1662 cm^{-1}) and amide II (1529 cm^{-1}). The amide hydrogen (10.22–10.34 ppm), *o*-methyls (2.20–2.23 ppm), and aromatic hydrogens (7.03–7.08 ppm) of **3b** changed very little on dilution. This result is in marked contrast with our finding for **1b** in CCl_4. We conclude, therefore, that **1b** exists at all concentrations mainly as the intramolecularly hydrogen-bonded six-membered ring species **3b**. Small signals for **6b** (see Table IV) representing about 1% of the total were present at all concentrations. Again, only one ν_{CD} band at 2243 cm^{-1} with the same relative intensity as the band in **1a** is observed at each concentration (Fig. 3). If **7b** was the species present, the carbonyl function would be involved in the intermolecular hydrogen bond and only the diethylamino group would be free to bind with the solvent.

1c. Adams *et al.* also examined **1c** and concluded that it existed as an unassociated *trans* amide at 0.02 *M* in $CHCl_3$. In our studies (Fig. 4) at 1 *M*, strong bands for **4c** (ν_{NH} broad 3277 cm^{-1}, amide I 1660 cm^{-1}, amide II1523 cm^{-1}), **5c** (ν_{NH} 3424 cm^{-1}), **6c** (ν_{NH} 3378 cm^{-1}), **9c** (ν_{NH} broad 3184 cm^{-1}), and **3c** (ν_{NH}, a broad band under the CH peaks but evident as a general rise of CH peaks when compared to **1a, b, d,** and **e,** amide II a shoulder at 1569 cm^{-1}). The intensities of the free *trans* **5** and *cis* **6** peaks are lower at all concentrations than those of **1d, 1e,** or **8**. The rise above the baseline attributed to **3c** and the decreased intensity of **5c** and **6c** are not present in CCl_4 spectra. Kuhn *et al.* (12) have investigated the frequency shifts, $\Delta\nu_{NH}$, for a series of hydroxyalkyl

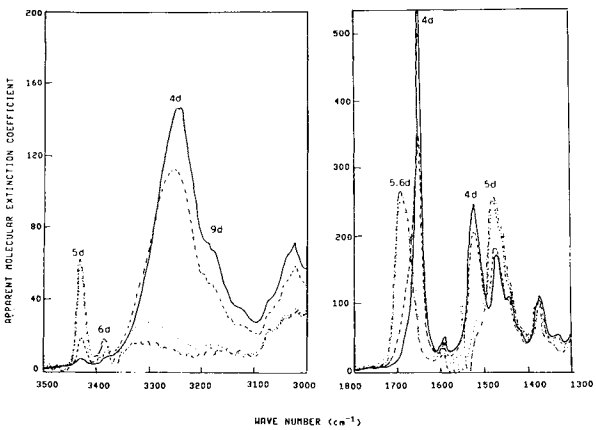


Fig. 2. IR spectral changes which occur upon dilution of δ-diethylaminovalero-2′,6′-xylidide (**1d**) in CCl_4. (——) 1.0 *M*; (– – – –) 0.1 *M*; (·····) 0.01 *M*; (·–·–·–·) 0.001 *M*.

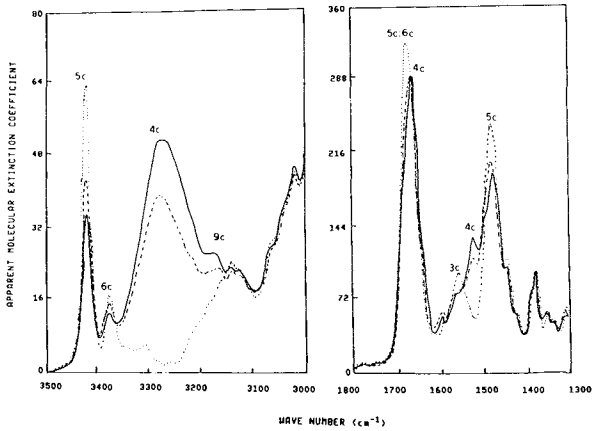


Fig. 4. IR spectral changes which occur upon dilution of γ-diethylaminobutyro-2′,6′-xylidide (**1c**) in $CDCl_3$. Little change occurs below 0.1 *M*, so spectra are not shown. (——) 1.0 *M*; (– – – –) 0.5 *M*; (·····) 0.1 *M*.

pyridines in CCl_4; $\Delta\nu$ for five-, six-, and seven-membered intramolecular hydrogen-bonded systems was 192, 203, and 357 cm^{-1}. In our series the $\Delta\nu$'s are 130, 282, and 430–580 cm^{-1}, respectively.

Below 0.1 *M*, **4c** is absent, **9c** has decreased in relative intensity, and **5c** (amide I now evident at 1678 cm^{-1} as is the amide II band at 1478 cm^{-1}), **6c** (amide I at 1690 cm^{-1} on enhancement), and **3c** (amide I at 1660 cm^{-1} on enhancement and amide II strong at 1569 cm^{-1}) are the major species present. The *o*-methyls (2.13–2.23 ppm) and aromatic hydrogens (6.98–7.07 ppm) shift downfield on dilution. Signals for **6c** representing about 5% of the total mixture at 1 *M* and 7% at 0.01 *M* were present (see Table IV). The chemical shift of the amide hydrogen of the *trans* forms changes very little upon dilution (9.00–8.91 ppm). The small change in the chemical shift of this peak upon dilution is fortuitous and offers further proof for the presence of **3c**. At high concentrations, this peak is the average of the NH proton of **4c** (δ ~8 ppm), **5c** (δ ~7 ppm), and **3c** (δ above 10.3 ppm since **3c** should form a stronger hydrogen bond than **3b**). Although **4c** disappears upon dilution, the average of **3c** and **5c** remains around δ = 8.9 ppm.

At 1 *M* the ν_{CD} band at 2245 cm^{-1} is present (Fig. 3), but at a much reduced intensity when compared to **1a** and **1b**, indicating that some fraction of the carbonyl groups is not free to form hydrogen bonds to the solvent (they are involved in hydrogen bonds in the intermolecularly associated species, **4c**). A broad CD stretching band at 2178 cm^{-1} is present, but at reduced intensity when compared to **1d** and **1e**. At 0.001 *M*, the 2245-cm^{-1} band has the same relative intensity as **1a** and **1b**, but the 2178-cm^{-1} band still fails to approach the intensity of the band in **1d** and **1e**, indicating that fewer of the diethylamino groups are free to bond with the solvent, i.e., they are tied up in the intramolecular seven-membered ring monomer, **3c**.

1d and 1e. No previous studies of the compounds have been reported. Bands due to **4**, **5**, and **6** dominate the high-concentration spectra of these compounds. The NH stretching band of **9** is also present. At low concentrations, bands due to **5** and **6** are the main bands present, although a small amount of **9** is still evident. Unlike **1c**, the amide hydrogen of the *trans* forms in these compounds shifts upfield significantly (Table IV). Again, the *o*-methyl and aromatic hydrogens shift downfield on dilution. Signals for the *cis* forms representing 5% of the mixture at 1.0 *M* and 15% at 0.01 *M* were also observed. The solvent ν_{CD} bands are similar to those of **1c** except that the band at 2178 cm^{-1} in these systems has about twice the intensity of the band in **1c**.

8. No previous studies of **8** in $CDCl_3$ have been reported. The IR spectra of **8** are very similar to those of **1d** and **1e** except that only bands due to the *trans* and *cis* nonassociated species are present at 0.001 *M*. This molecule thus is a good model for the **5** and **6** mixture in $CDCl_3$. The ν_{CD} band at 2243 cm^{-1} is identical to those in **1c–e** at all concentrations. No band at 2178 cm^{-1} is present.

The deuteration studies (Tables I and II) confirm the assignments of the bands in the amide II region. In all cases the hydrogen amide II band disappeared upon deuteration. The results of the deuteration study of **1c** in $CDCl_3$ confirm the presence of **3c**. Upon deuteration not only do the ν_{NH} bands of **4c**, **5c**, and **6c** shift to the 2600 to 2200-cm^{-1} region but the rise of the ν_{CH} peaks, caused by the presence of **3c**, is no longer present. A new, very broad peak (ν_{NH} **3c**) centered at 2100 cm^{-1} appears.

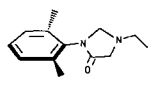
The observations of Chupp (2) concerning the chemical shifts of the *cis* and *trans* amides require some comment. Both the carbonyl group and the aromatic ring are responsible for anisotropic effects in these molecules. Due to the steric requirements of the *ortho* methyls, the planes of the aromatic ring and the amide group are orthogonal. In the *cis* form the α-hydrogens and, when *n* is 1 or 2, the protons on the diethyl amino group are within the shielding region of the aromatic ring. In the *trans* rotomer, these groups experience no anisotropic effects from the aromatic ring. These protons are therefore observed at lower fields in the *trans* form as observed by Chupp. Brown *et al.* (13) examined the chemical shifts of the aromatic protons and *o*-methyl protons of aceto-2′,6′-xylidide, which had been shown to exist as the *trans* form, and its *N*-methyl analogue, which has the aromatic ring *cis* to the acyl methyl group. They found the aromatic protons of the *cis* compound 0.07 ppm downfield and the *o*-methyls 0.03 ppm upfield from those of the *trans* compound. Previous studies in these laboratories (14) have shown that, in certain substituted tertiary amide derivatives of lidocaine in which the hydrochloride salts crystallize in the *trans* form but slowly isomerize in solution to a mixture of *cis* and *trans* isomers, the aromatic and the *o*-methyl protons appear at lower fields in the *cis* form. Although all signals show changes on dilution the *o*-methyl, aromatic, and amide hydrogen are of prime value for comparisons between the analogues since the shifts are similar in each of the compounds studied.

The presence of small amounts of the *cis* forms is evident in the appearance of second signals for all the hydrogens in some of the analogues in both solvents. With the exceptions of the aromatic and *o*-methyl hydrogens, all of the resonances of the *cis* forms are upfield from those of the *trans*, reflecting the presence of these hydrogens in the shielding region of the aromatic ring as proposed by Chupp.

In 1-ethyl-3-(2,6-dimethylphenyl)imidazolidin-4-one, **10**, a model for the nonassociated *trans* isomer **5**, the *o*-methyls appear at 2.2 ppm and the aromatic hydrogens are at 7.2 ppm in $CDCl_3$ solutions. These shifts are very similar to those observed in **3a** and **3b**, appear to be constant in the monomeric *trans* forms, and are the limits approached upon dilution by all the other compounds studied.

Although Adams *et al.* (4) attributed the large downfield shift (10.3 ppm) of the amide hydrogen of **1b** to magnetic anisotropy, the extent and strength of the hydrogen bonding involving this hydrogen have a much greater effect on its position. Any use of this hydrogen signal for conformational assignments must also consider these factors.

The normal IR spectral changes which should occur with hydrogen bonding in our system are that (i) the amide II frequency should increase, (ii) the ν_{NH} frequency should



10

Scheme IV

decrease, and (iii) the band width and the intensity of ν_{NH} should increase (15). Further, the frequency of the amide I band should decrease due to an increase in the single-bond character of the C–O bond on hydrogen bonding. The assignments made in this paper are consistent with these observations.

Suzuki *et al.* (16) have established criteria for evaluating IR spectra of the *cis* and *trans* forms of amide bonds. They assign the high-frequency association band (3280–3380 cm^{-1}) in their systems to the associated *trans* form due to the shift of this band to higher frequency upon dilution. The low-frequency band (3130–3230 cm^{-1}), which shows no frequency shift on dilution, is assigned to the *cis* dimer 7. At low concentration, "the NH association band for the *trans* form is hardly observed, while those for the *cis* forms are observed with great intensities" (16). We have assigned the *trans* associated structure, **4** to the high-intensity, high-frequency association band in our compounds, in agreement with the studies of Suzuki. The chemical shifts of the aromatic and *ortho* methyl hydrogens of the *trans* forms, which are observed on dilution, may be due to proximity effects of the neighboring molecules (see **4a–e**). In the extended *trans* polymer, each molecule is located in the shielding region of the neighboring aromatic ring. Even if free rotation about the hydrogen bond is assumed, the average effect exerted by the aromatic ring is still shielding and those protons in the adjacent molecule in the neighborhood of the aromatic ring should appear at higher fields in the associated species. No similar shielding would be evident in the *cis* dimer.

The changes which occur in going from CCl_4 to $CDCl_3$ are those anticipated on moving to a more polar, hydrogen-bonding solvent. The associated species **4** is a more prominent species in CCl_4 than in $CDCl_3$. In CCl_4, in which no hydrogen bonding interaction with the solvent is present to stabilize the nonassociated forms **5** and **6**, both the carbonyl group and the amide hydrogen are stabilized by intermolecular association, **4**, at high concentrations. In the intramolecularly hydrogen bonded monomers **3**, the amide hydrogen and diethylamino function are stabilized, while the carbonyl is not. In $CDCl_3$, **4** now has the added stabilization of the interaction of the diethylamino group with the solvent. The energies of the nonassociated forms **5** and **6** are now lowered by hydrogen-bonding interactions of the carbonyl and diethylamino groups with the solvent. This relative gain in stability makes these species more competitive with **4** at all concentrations and the equilibrium shifts toward the nonassociated forms. The intramolecular hydrogen-bonded monomers **3** gain relative to **5** and **6** since all three polar groups are now stabilized by hydrogen bonding.

The increased stabilization of **3a** and **3b** by hydrogen bonding of the carbonyl to the solvent is reflected in the lowered amide I frequencies in $CDCl_3$. The absorption frequencies of **4** show the anticipated change to higher frequencies in the more polar solvent (15), since bonding to the carbonyl group does not involve the solvent directly.

The decreasing frequency of ν_{NH} in going from five- to six- to seven-membered rings indicates increasing hydrogen-bond strengths on going to larger rings (12); at the same time the entropy becomes less favorable due to the greater loss of rotational freedom in the larger rings. Thus, although the hydrogen bond in the seven-membered ring is stronger than in the five, the free energy change for five-membered ring formation is more negative and **1a** exists exclusively as **3a**, while **1c** shows appreciable amounts of **5c** and **6c** in both solvents.

CONCLUSIONS

Compounds **1a** and **2a** have the greatest deviation of the observed partition coefficient from the calculated. Compound **1a** is exclusively in form **3a** in both CCl_4 and $CDCl_3$. Compound **1b** is largely **3b** at low concentrations in CCl_4 and at all concentrations in $CDCl_3$. Since the hydrophilic functional groups are turned inward in these conformations, greater hydrophobicity is to be expected. Failure to allow for this increased lipophilicity leads to low partition coefficient estimates by calculation. Compounds **1c–e** show much larger quantities of the more hydrophilic conformations **5** and **6**, especially at lower concentrations. Since the conformations in these molecules change upon dilution, the partition functions may be concentration dependent. This dependence is observed in the abnormal solubility properties of the **1c**, **1d**, and **1e** in CCl_4. In CCl_4, these analogues undergo solubility changes which mimic the conformational changes. Dilution of the 1 *M* solutions to 0.1 *M* (resulting in breakup of the associated species **4** and formation of the more polar monomeric species **5** and **6**) causes some of the base to oil out and eventually crystallize. Compound **1b** also oils out, but to a much lesser extent. Compound **1a** is soluble at all concentrations. At lower concentrations (0.01 *M*) the solubility of the less soluble monomeric forms is no longer exceeded and solution results.

At the low concentrations of these compounds usually existing in physiological systems, the solution conformations of **1a** and **1b** are significantly different from those of the higher homologues. The most commonly used amide-type local anesthetics, e.g., mepivicaine, bupivicaine, and etidocaine, are lidocaine like (i.e., $n = 1$) and should also exist in the intramolecularly hydrogen-bonded form. The enhanced pharmacological properties of these molecules when compared to those of the higher homologues have been attributed to their more favorable pK_a's and partition coefficients (17). Some of this increased desirability may also be due to the different solution conformations.

These studies are presently being extended to more polar solvents which better mimic the membrane. Investigations into the structures of the protonated forms [to which the activity at the site has been attributed (1)] are also being undertaken to determine the role of the conformations of the conjugate acid in influencing partition coefficients and pharmacological activity.

ACKNOWLEDGMENTS

This work was supported in part by a grant from Astra Alab AB, by the National Science Foundation through Grants CHE87-12543 and USE-8852774, and by the College of the Holy Cross. The authors wish to thank Dr. Bertil H. Takman for many helpful discussions.

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