Lidocaine: Evidence for the *trans*-Configuration

Keyphrases ☐ Lidocaine—*trans*-configuration ☐ NMR spectroscopy—structure ☐ IR spectrophotometry—structure

Sir:

A recent communication (1) gave IR data which purported to show that lidocaine was an unusual example of an acyclic secondary amide possessing the *cis*-configuration. The bases for this spatial assignment were: (*a*) the amide II band situated at a lower frequency (1494 cm.$^{-1}$) than that usually associated with *trans*-amides (>1500 cm.$^{-1}$), and (*b*) an invariance with dilution of the single N—H stretching band at 3312 cm.$^{-1}$, presumably arising from *cis*-dimeric association.

Entirely different conclusions were reached in recently published studies regarding spatial properties of some closely related acetanilides (2) and α-haloacetanilides (3, 4), including the immediate precursor of lidocaine (5), 2-chloro-2′,6′-acetoxylidide (I).

The strong dependence of both the NMR spectra and chemical reactivity of the α-halogen on the spatial configuration of these anilides was amply demonstrated. It was shown that *ortho*-substituted tertiary α-haloacetanilides could exist in two rotomeric forms, the predominant isomer, A, being spatially constituted with the α-methylene group *cis* and orthogonal to the anilide ring. In this configuration, the α-halogen was quite unreactive and its chemical properties contrasted sharply with the other rotomer, B, possessing the α-methylene group in a much less constricted environment, *i.e.*, *trans* and away from the anilide ring.

Moreover, secondary (*N*-hydrogen) α-haloacetanilides were shown to be entirely constituted with the α-methylene *trans* and away from the anilide ring; their NMR spectral properties and chemical reactivity thus closely resembled the B rotomers of the tertiary anilides. This was consistent with the usual *trans*-assignment (amidic proton *trans* to carbonyl oxygen) for most secondary amides, although contrasting slightly with findings for similar, hindered, secondary α-unsubstituted acetanilides (2), where, for instance, 2′,6′-acetoxylidide (II) is only 74% rather than all *trans* (B configuration).

Relevant to this communication was the finding, substantiated in other systems (2, 6, 7), that the *cis*- or *trans*-spatial configuration strongly and consistently influenced the NMR resonance of selected groupings in the amide. Thus, the α-methyl or α-methylene and nucleophilic groups attached thereto, which were constituted *trans* and away from the aromatic ring, were deshielded and absorbed at a lower field than rotomers that possessed the α-methylene *cis* and orthogonal to the ring. Likewise, in tertiary amides the N—CH_3 *cis* to the carbonyl oxygen was upfield from the *trans*-N—CH_3 group.

Moreover, the ability to separate tertiary α-haloacetanilide rotomers A and B into pure form given sufficient *ortho*-bulk (*i.e.*, *ortho-tert*-butyl) provides a convenient means, by simple nucleophilic displacement, for preparing new compounds of known spatial configurations. Under controlled conditions, reactive rotomer B can alkylate a nucleophile many times faster than its equilibration to A. Thus, a new compound with configuration B may be prepared, and its equilibration to an equilibrium mixture of A and B may be observed and measured.

Therefore, confirmation of the *cis*- or *trans*-configuration of lidocaine can be ascertained from a comparison of its spectra with selected materials, including rotomers of known configurations. Accordingly, Table I compiles pertinent NMR and IR absorptions for lidocaine; I; II; the tertiary anilide homolog of lidocaine, *N*-methyl-2-diethylamino-2′,6′-acetoxylidide (III); 2-chloro-2′-*tert*-butyl-6′-ethylacetanilide (IV); 2-diethylamino-2′-*tert*-butyl-6′-ethylacetanilide (V); and the A and B forms of its *N*-methyl homolog, 2-diethylamino-*N*-methyl-2′-*tert*-butyl-6′-ethylacetanilide (VI).

Table I—Spectral Data for Lidocaine and Related Materials

	Pertinent NMR Shift δ CCl_4[a]				Pertinent IR, cm.$^{-1}$ CCl_4[b]	
Material	N—CH_3 Singlet	$XCH_2C(=O)$ Singlet	N—$(CH_2CH_3)_2$ Quartet	N—$(CH_2CH_3)_2$ Triplet	νN—H	Amide II[c]
Lidocaine	—	3.01	2.62	1.10	3328	1497
I	—	4.15	—	—	3410	1507
II A[d]	—	1.71	—	—	3238[e]	1543[e]
II B[d]	—	2.05	—	—	—	—
III A[d]	3.05	2.74	2.52	0.80	—	—
III B[d]	3.30	3.30	[f]	1.10	—	—
IV	—	4.05	—	—	3424	1508
V	—	3.06	2.69	1.12	3338	1495
VI A[g]	3.05	2.73	2.53	0.81	—	—
VI B	3.29	3.29	2.69	1.10	—	—

[a] For NMR shifts of respective tertiary α-haloamides, see *Reference 3*. [b] Beckman IR 12 in dry CCl_4 at 0.033–0.046 *M*. [c] As verified by sensitivity to deuteration. [d] Spectra of both rotomers from equilibrium mixture, 74% IIB, $CDCl_3$; >90% IIIA. [e] KBr pellet. [f] Obscure. [g] VIB was prepared from IIE (*Reference 3*) with excess diethylamine, then equilibrated in CCl_4 over several days to about 90% VIA.

Examination of the tertiary anilides, III and VI, shows that the B isomer is present at equilibrium, as in the α-halo series, only in minor amounts; hence, substitution of halogen by diethylamino does not produce any unusual change in rotomer distribution. It could be reasonably questioned then why such an unusual departure from normal *trans*, as recently claimed (1), would take place with secondary α-amino-acetanilides, such as lidocaine.

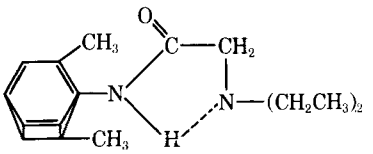
The *trans*-tertiary amides (carbonyl oxygen *cis* to anilide ring), VIB and IIIB, as predicted, have resonance absorptions for N—CH_3 downfield from those for VIA and IIIA. Moreover, the α-methylene and N—$(CH_2CH_3)_2$ groups also are downfield from these more highly shielded groups in VIA and IIIA. The resonance absorptions for these latter two moieties in lidocaine, positioned between IIIA, VIA and IIB, VIB, are of little use for structural determinations. Compelling, however, is the consistent position of the N—$(CH_2\underline{CH_3})_2$ triplet. Materials possessing the α-methylene and, hence, diethylamino *cis* and over the anilide ring have this moiety well within the aromatic shielding zone (6) and therefore at a higher field (δ 0.8 p.p.m.) than the δ 1.1 observed for materials constituted with the α-methylene *trans* to the anilide ring.

In contrast, the position of the amide II band does not appear to be a reliable criterion for spatial assignments, a conclusion previously reached (8). As was found for similar compounds (9, 10), *trans*-α-chloroacetanilides I and IV absorb very close to 1500 $cm.^{-1}$, at considerably lower frequencies than the amide II band normally found in *trans*-α-unsubstituted acetamides. (Note that II, predominately *trans*, has a prominent amide II band at about 1540 $cm.^{-1}$.)

Assignment of the *trans*-configuration to lidocaine can be reconciled with the observed single, solvent invariant N—H stretch and lower than usual amide II band by reference to the internally bonded structure shown for *trans*-lidocaine. Ample precedent for this type of hydrogen bonding has been noted in *trans*-α-halo- and α-alkoxy acetamides (9, 10). Such internal bonding could produce a single solvent invariant νN—H; the νN—H found for lidocaine at even 100 $cm.^{-1}$ lower frequency than the same function in α-halo-substituted amides is a tribute to the strong amido–amino (N—H- - -N) association in this amide (11).

As suggested for similar association in α-haloacetanilides (9), such bonding could force an equilibrium shift to a wholly *trans*-configuration (as contrasted with some minor *cis* in materials such as II). Finally, the amide II band near 1500 $cm.^{-1}$ found for lidocaine (and related *trans*-materials, I, IV, V) could arise from a lesser amount of intermolecular association. As shown earlier (10), α-substitution and steric hindrance to intermolecular association cause a frequency drop in this band. Protonation of the amino group would lessen the internal bonding, and the spectral characteristics presumably found for lidocaine hydrochloride (1) could revert more closely to those of "normal" *trans*-amides.

The assignment of the *trans*-associated structure for lidocaine is further strengthened by its behavior to vapor phase osmometric measurements in benzene. In this nonbonding solvent, as well as carbon tetrachloride, lidocaine over a 0.1–0.005 *M* concentration range shows no evidence of intermolecular association and is strictly monomeric. In contrast, certain authentic *cis* and dimerically bonded amides such as 2-pyridone have been shown to give a corresponding multiple of its molecular weight under these conditions (12).



trans-lidocaine

(1) G. A. Neville and D. Cook, *J. Pharm. Sci.*, **58**, 636(1969).
(2) H. Kessler and A. Rieker, *Ann.*, **70**, 857(1967).
(3) J. P. Chupp and J. F. Olin, *J. Org. Chem.*, **32**, 2297(1967).
(4) J. P. Chupp, J. F. Olin, and H. K. Landwehr, *ibid.*, **34**, 1192 (1969).
(5) "The Merck Index," 6th ed., Merck & Co., Inc., Rahway, N. J., 1952, p. 335.
(6) C. E. Johnson and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).
(7) L. A. LaPlanche and M. T. Rogers, *J. Amer. Chem. Soc.*, **85**, 3728(1963); *ibid.*, **86**, 337(1964).
(8) L. J. Bellamy, "Advances in Infrared Group Frequencies," Methuen and Co. Ltd., Great Britain, 1968, chap. 8.
(9) R. A. Nyguist, *Spectrochim. Acta*, **19**, 509(1963).
(10) R. D. McLachlan and R. A. Nyguist, *ibid.*, **20**, 1397(1964).
(11) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman, San Francisco, Calif., 1960, chaps. 5 and 6.
(12) M. H. Krackov, C. M. Lee, and H. G. Mautner, *J. Amer. Chem. Soc.*, **87**, 892(1965).

J. P. CHUPP
Research Department
Agricultural Division
Monsanto Company
St. Louis, MO 63166

Received January 12, 1970.
Accepted for publication May 27, 1970.
The author is indebted to Dr. J. Freeman for the IR spectra and to C. Scott for vapor phase osmometric measurements.

Extrinsic Optical Activity from a Micellar Solution

Keyphrases ☐ Micellar solutions—extrinsic optical activity ☐ Sulfaethidole—betaine-induced optical activity ☐ Polarimetry—analysis

Sir:

Extrinsic optical activities have been observed following the interaction of macromolecules with suitable small molecules (1–3) and following the interaction of optically active solvents with solutes (4, 5). We now report optical activity induced into a symmetrical molecule by an optically active surfactant in the micellar form. L- and D-*N*-decyl-*N*,*N*-dimethylalanine hydrobromides (betaines) were used as the surfactants; their