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.

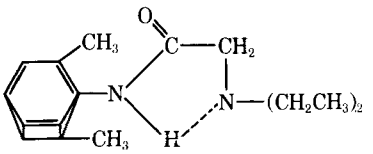
The *trans*-tertiary amides (carbonyl oxygen *cis* to anilide ring), VIB and IIIB, as predicted, have resonance absorptions for N—CH_3 downfield from those for VIA and IIIA. Moreover, the α-methylene and N—$(CH_2CH_3)_2$ groups also are downfield from these more highly shielded groups in VIA and IIIA. 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

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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

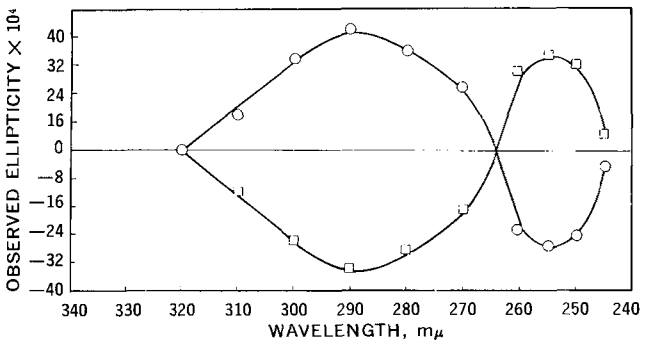

Figure 1—*Extrinsic circular dichroism curves for 7.0 × 10⁻⁴ M SETD in an 8.9 × 10⁻² M aqueous betaine solution. Key:* O, D-*betaine;* □, L-*betaine; and S/N ratio = 20:1. All measurements were made in a 0.1-cm. cell.*

CMC's, measured by optical rotatory dispersion and circular dichroism, have been found to be approximately 1×10^{-2} *M* at 25° (6, 7). Sulfaethidole (SETD) was used as the optically inactive molecule; this drug has been found to become optically active when bound to bovine serum albumin (8), giving peaks in ellipticity at 280 (negative) and 257 mμ (positive) which are consistent with the UV spectra.

All measurements were made in a 6002 attachment to a Cary 60 spectropolarimeter[1] at 25°. Under the experimental conditions, the betaine showed no optical activity above 240 mμ (7), and the SETD alone showed no activity at any wavelengths. Figure 1 shows the optical activity induced in the SETD molecules by the L- and D-betaines at concentrations considerably above their CMC. Peaks of opposite sign are seen at wavelengths of 288 and 255 mμ. We have not observed any induced optical activities at concentrations of betaine below the CMC.

Figure 2 shows the effect of betaine concentration on the ellipticity at 285 mμ with the SETD concentration constant. These ellipticities are small, as is the signal–noise (S/N) ratio, but it appears that the plot cuts the betaine concentration axis at approximately the CMC. At a concentration of 6.0×10^{-2} *M*, the ellipticity seems to have reached a plateau. This is probably the result of all the SETD being solubilized by the micellar betaine, so that subsequent additions of betaine can cause no further interaction. These extrinsic effects probably are due to the interaction of the hydrophobic core of the micelle with the hydrophobic portion of the drug molecule. It is possible that the extrinsic effects observed in aqueous macromolecular solutions are also predominantly hydrophobic in origin.

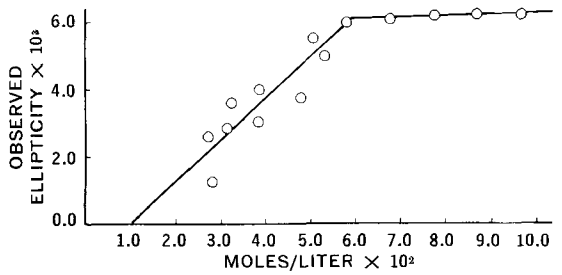

Figure 2—*Plot of observed ellipticity at 285 mμ against* D-*betaine concentration for a constant SETD concentration of 7.0 × 10⁻⁴ M. S/N ratio = 20:1 at largest ellipticities and 4:1 at the lowest. All measurements were made in a 0.2-cm. cell.*

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Macromolecular Dissolution: Temperature Effects on Polymer–Drug Preparation

Keyphrases □ Macromolecular dissolution—temperature of product formation effect □ Polyethylene maleic anhydride–phenylpropanolamine interaction temperature—effect on dissolution rate □ Temperature of preparation, polymer–drug system—physicochemical properties

Sir:

Polymer–drug interaction systems have been a source of study for application toward the design of prolonged-release dosage forms (1–3). The general method of preparing these systems has differed from investigator to investigator and between the types of polymers and drugs. However, at no time has the effect of preparation temperature on dissolution and/or drug release from the polymer been investigated.

This report concerns the effects of preparation tem-

Table I—Dissolution Rates as Effected by Preparation Temperature

Temperature	Dissolution Rate, × 10^{-1}, Δ Refractometer Scale Units/min.
27°	4.14
40°	3.36
45°	3.82
50°	3.83
55°	2.89
60°	0.24
80°	0.26
100°	0.09