Chemical Shift Nonequivalence and *syn-anti*-Isomerization in an *N*-Benzenesulphonylimine

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Summary A combination of methods employing diastereomeric transformation and n.m.r. line-shape analysis have been used to determine the activation parameters over a 100° temperature range ($\Delta H^{\ddagger} = 15{\cdot}7$ kcal./mole and $\Delta S^{\ddagger} = -2$ e.u.) for *syn–anti*-isomerization of *N*-(1,2,3-trimethyl-2-butenylidene)benzenesulphonamide.

ALTHOUGH *syn–anti*-isomerism at the C=N double bond in imines has been extensively studied,[1–5] information concerning the configurational stability of *N*-arenesulphonylimines is lacking.† Bleiholder and Shechter reported chemical shift nonequivalence in *N*-(1,2,3-trimethyl-2-butenylidene)benzenesulphonamide (I), but ascribed it to a torsional barrier about the α-methyl bond rather than *syn–anti*-isomerism at nitrogen.[6] We report here conclusive evidence that this nonequivalence results from the

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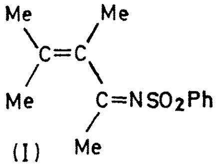
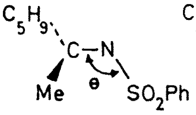
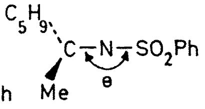
† Although the *N*-toluene-*p*-sulphonyl derivative of dimethyl iminocarbonate has been examined, the barrier was apparently too low to be measured using n.m.r. spectroscopy.[3] However, the barrier to stereomutation in an *N*-benzenesulphonylquinoneaniline has been measured.[1]

existence of diastereomers of (I) in solution.¶ The configurational stability was examined using both dynamic nuclear magnetic resonance spectroscopy[7] and diastereomeric transformation.


(I)


(II)


(III)

The room-temperature n.m.r. spectrum of imine (I) in methylene chloride (Figure, A) exhibits two singlets at δ 2·22 and 2·65 in a ratio of 1·7 : 1·0 arising from the α-methyl group. At −50° (Figure, B), the ratio changes slightly to 1·5 : 1·0. The change in the ratio of the two signals from the 2 : 1 ratio observed in carbon tetrachloride[6] provides sufficient grounds to discard an interpretation based on slow rotation about the carbon–methyl bond.

Further, it is possible to obtain spectra of a solution containing exclusively one isomer. Crystallization of (I) proceeds with second-order diastereomeric transformation‡ and the solid phase is composed of a single diastereomer.[2,9,10] When imine (I) is dissolved at room temperature, equilibrium is rapidly attained by stereomutation at the C=N double bond. However, when the imine is dissolved at temperatures below −70°, the rate of isomerization is slow enough that the initial spectrum is that of the single diastereomer present in the solid state (Figure, C). At temperatures between −50° and −60°, stereomutation occurs at a measurable rate,§ and the n.m.r. spectra reflect the changing diastereomeric ratio (Figure, D). The rate of isomerization could be measured by monitoring the growth in integrated intensity of the signal at δ 2·7 at the expense of that at δ 2·2. This method was employed to calculate the first-order rate constants for isomerization at −57·5° ($k = 1{\cdot}69 \times 10^{-4}$ sec.$^{-1}$, $\Delta G^{\ddagger} = 16{\cdot}2$ kcal./mole), −54·5° ($k = 4{\cdot}53 \times 10^{-4}$ sec.$^{-1}$, $\Delta G^{\ddagger} = 16{\cdot}0$ kcal./mole), and −52·5° ($k = 7{\cdot}11 \times 10^{-4}$ sec.$^{-1}$, $\Delta G^{\ddagger} = 16{\cdot}0$ kcal./mole).

The rate of stereomutation can also be calculated at high temperature from the coalescence of the signals due to the α-methyl groups in the two diastereomers. Using the approximate equation [$k_c = (\pi/\sqrt{2})\Delta\nu$],[11] the rate of exchange and free energy of activation were calculated at the coalescence temperature ($T_c = 51°$, $\Delta\nu = 24{\cdot}0$ c./sec., $k = 56$ sec.$^{-1}$, and $\Delta G^{\ddagger} = 16{\cdot}4$ kcal./mole). Since the application of this approximate equation furnishes only an estimate, the rate constant was also determined using a non-iterative complete line-shape analysis spectrum simulator program based on the time-dependent Bloch equations[11] ($k = 67$ sec.$^{-1}$, $\Delta G^{\ddagger} = 16{\cdot}3$ kcal./mole). Although the rate constants determined by these two methods are not identical, the resulting free energies of activation are equal within experimental error. The change in $\Delta G^{\ddagger}$ from −60° to +50° allows a reliable determination of the activation enthalpy and entropy[10,12] ($\Delta H^{\ddagger} = 15{\cdot}7$ kcal./mole, $\Delta S^{\ddagger} = -2$ e.u.). The low entropy of activation is in accord with *syn–anti*-isomerization being the process corresponding to the diastereomeric transformation.

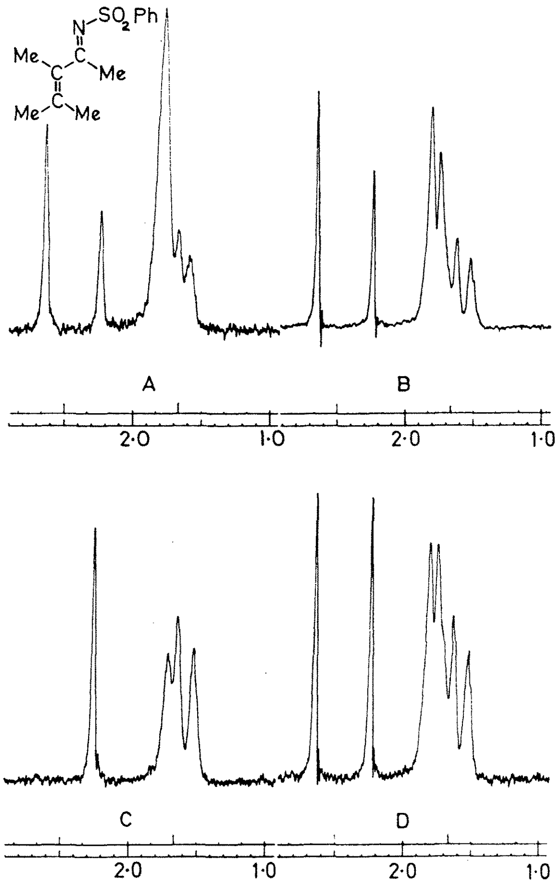


FIGURE. *N.m.r. spectra of* (I) *in methylene chloride*: (A) *room temperature*; (B) *dissolved at room temperature spectrum measured at* −50°; (C) *dissolved at* −70° *spectrum measured at* −57°; (D) *dissolved at* −70° *spectrum measured at* −57° *after partial equilibration.*

Two mechanisms have been suggested to account for stereomutation in imines: (i) inversion at nitrogen, and (ii) torsion about the C=N double bond. Curtin *et al.*,[2] Kessler,[1] and Jeffery *et al.*[2] have advanced the view that available experimental results rule out a torsional mechanism, while Marullo and Wagener[4] have argued that the

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‡ We suggest this as a general term to describe the situation wherein a mixture of diastereomers in solution crystallizes in such a manner that the solid phase is composed of a single diastereomer as the result of ready stereomutation in solution. We draw an analogy to the more limited term second-order asymmetric transformation which, as used by Eliel,[8] refers to the transformation of a mixture of diastereomers into a single diastereomer upon crystallization as the result of ready inversion of a labile asymmetric carbon atom. We believe that such diastereomeric transformations will be found to occur frequently when molecules containing configurational units which are labile on the isolation time scale but stable on the n.m.r. time scale are crystallized and that this extension of a well established stereochemical term will fill a void in presently used nomenclature.

§ By analogy to the term first-order asymmetric transformation which is used to describe the stereomutation which results in mutarotation, we might describe this relaxation toward equilibrium as a first-order diastereomeric transformation.

¶ Professor Shechter has indicated to us that he and Dr. R. J. Stedman have independently come to the same conclusion. The existence of *syn-anti*-isomers of an *N*-toluene-*p*-sulphonylimine was inferred from the n.m.r. spectrum of a birdcage imine, but the barrier was not reported. (R. J. Stedman, A. C. Swift, and J. R. E. Hoover, *Tetrahedron Letters*, 1965, 2525.)

dramatic lowering of the activation free energy in compounds with hetero-atoms bound to the imino-carbon atom provides compelling evidence for the torsion model.

Further evidence on this point may be obtained by comparing the barrier and coalescence temperature in (I) ($T_c = 51^\circ$, $\Delta G_c^{\ddagger} = 16{\cdot}3$ kcal./mole) with that in the *N*-phenylimine, *N*-isopropylideneaniline, ($T_c = 126^\circ$, $\Delta G_c^{\ddagger} = 20{\cdot}3$ kcal./mole).[3] Apparently the benzenesulphonyl group is considerably more effective than phenyl at lowering the barrier by delocalization of electrons on nitrogen. By contrast, in the corresponding *N*-substituted aziridines, the free energies of activation, which must correspond to barriers to inversion of the nitrogen pyramid, exhibit a different order in their relative magnitudes. Thus, the coalescence temperature for *N*-phenylaziridine (T_c -40°)[13] is actually somewhat lower than that for *N*-benzenesulphonylaziridine (T_c -30°).[14]

Discussions of the relative merits of the two mechanisms have implied that they are distinguishable and mutually exclusive. However, the two corresponding transition states (II) and (III) differ only in the magnitude of θ, the C–N–R angle, and associated differences in the hybridization of the nitrogen atom and its formal charge. This angle is *ca.* 109° in the torsion model[4] (II) and 180° in the linear inversion model (III). However, θ need not be restricted to one of these two values, but might well adopt values between these two extremes. Thus, we might well imagine that a continuum of mechanisms with intermediate values of θ is possible. Substituents such as methoxy, methanethio, and dimethylamino which can stabilize a positive charge on carbon would effect a diminution of θ while substituents which lower barriers to nitrogen inversion would result in transition states with larger values of θ.

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