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# THERMODYNAMIC ASYMMETRIC INDUCTION: A NEW APPROACH TO THE DEVELOPMENT OF RULES FOR THE DETERMINATION OF ABSOLUTE CONFIGURATIONS[1a]

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Summary: The absolute configurations of chiral primary amines can be determined using the optical rotations of the corresponding N-p-toluenesulfonyl-N-2,4-dinitrobenzensulfenyl derivatives.

Kinetic asymmetric induction has been used as the basis for numerous methods for the determination of absolute and relative configurations.[2] Successfully and commonly used methods based upon asymmetric synthesis and kinetic resolution have been embodied in such rules as Prelog's Rule,[3] Cram's Rule,[4] Horeau's Rule,[5] and others.[6] This paper outlines a strategy for development of similar rules based on thermodynamic asymmetric induction[7] at stereolabile chiral units and describes one such rule employing the sulfenamide chiral axis. Our approach gives rise to rules that are operationally similar to the well known rule of shift elaborated by Freudenberg[8] but differ in that the mechanism of operation of that rule is specified and optimization of such rules can be accomplished on rational rather than simply empirical grounds.

Stereolabile chiral units such as the sulfenamide chiral axis suffer rapid stereomutation and a system containing a stereolabile chiral unit X and a stereostable chiral unit of a given configuration $I_R$ exists as an equilibrium mixture of stereoisomers which differ in configuration at the stereolabile chiral unit ($X_RI_R \rightleftarrows X_SI_R$). The equilibrium constant, $K_{eq}$, must differ from unity on symmetry grounds and is an expression of thermodynamic asymmetric induction on the stereolabile unit X by the stereostable inducing unit $I_R$. This true equilibrium between diastereomers is analogous to the pseudoequilibrium between diastereomeric transition states in asymmetric synthesis and kinetic resolution. Just as the sense of kinetic asymmetric induction is usually determined by the order of arrangement of small, medium, and large groups in the inducing unit, we may expect that the configuration of the stereolabile chiral unit in the predominant diastereomer will be similarly determined. If the configuration of the predominant diastereomer could be independently determined, we could, using an empirical rule similar to those used in kinetic induction, deduce the configuration of the inducing chiral unit.

The key to our approach is a convenient means for assessing the configuration of X in the predominant diastereomer. This can be done if the moiety contains an optically active chromophore which gives rise to a Cotton effect in the ORD (or CD) spectrum whose sign reflects the configuration and whose intensity is essentially unaffected by perturbations with other portions of the molecule. We require that the spectra of the two diastereomers be quasi-enantiomeric in the region of this Cotton effect, a phenomenon which is commonly observed. In this case, the Cotton effects of the two diastereomers will partially cancel; and the minor diastereomer will only attenuate the effect of the major diastereomer. In principle, the resultant Cotton effect will not only provide information about the configuration of X in the major diastereomer but about the magnitude of the induction (as expressed by $K_{eq}$) as well.

The sensitivity of the method will be enhanced if the amplitude of the Cotton effect is large. It is for this reason that we suggest that the chromophore in X be an inherently dissymmetric chromophore. Then even small inductions will be readily apparent in ORD (or CD) spectra.

The optical rotation at the sodium D-line is the sum of the tails of all of the Cotton effects in the ORD spectrum. Thus, if all of the chiral units in a molecule give rise to independent Cotton effects, the D-line rotation will be a summation of independent contributions from each of the chiral units in the molecule. This is the origin of the Principle of Optical Superposition. In the present instance, the contribution to the D-line rotation of the stereolabile unit will be maximized when: a) the induction is large, b) the amplitude of the Cotton effect is large, and c) the Cotton effect occurs at long wave length (leading to a more substantial tail at the D-line). Indeed, if these conditions are met, the contribution from the chromophore in X should dominate the summation at the D-line and will constitute the sole determinant of the sign of rotation.

These elements comprise our general method. A molecule containing a chiral unit I whose configuration is to be determined is converted into a derivative X-I bearing a labile chiral unit whose configuration (in the predominant diastereomer) is determined by thermodynamic asymmetric induction and is reflected in a long wavelength Cotton effect due to an inherently dissymmetric chromophore which dominates the D-line rotation.

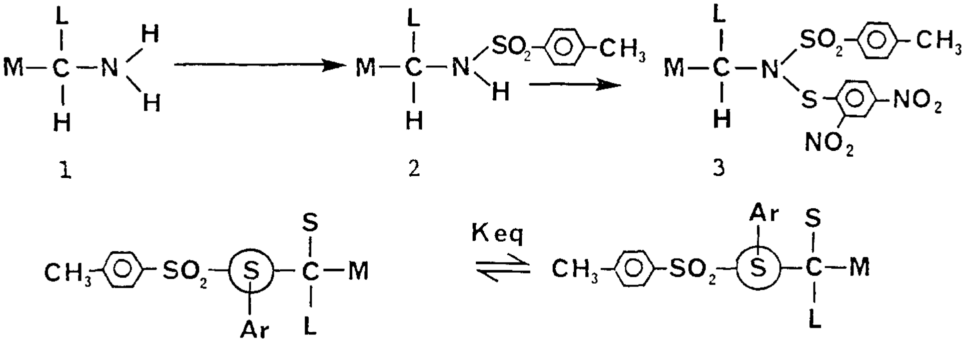
This scheme has been realized experimentally by conversion of optically active amines, 1, via their Hinsberg derivatives, 2, into the corresponding sulfenylsulfoamides, 3, as indicated in Scheme 1. The chiral center in the amine moiety induces asymmetry at the sulfenamide chiral axis by shifting the equilibrium between diastereomers. The magnitude of the induction (but not the sign) can be conveniently determined by measuring $K_{eq}$ using low temperature NMR spectroscopy. Previous studies[7] demonstrated that the magnitude of the induction was related to the relative sizes of the ligands at the asymmetric carbon atoms. The ORD/CD spectra of nitrobenzenesulfenamides are characterized by a long wave length Cotton effect (near 350 nm) which is associated with the nitrobenzene sulfenyl ring.[9]

Previous studies have indicated that the sign of this Cotton effect correlates with the absolute configuration at the sulfenamide chiral unit.[9] The magnitude of this Cotton effect is great enough that we may suppose that its tail will dominate the D-line rotation if the magnitude of the induction is reasonably large. Thus, we may expect that the D-line rotations of these compounds can furnish a reliable rule for deduction of the absolute configurations of the starting amines.

Table 1. Rotations of Sulfenyl Sulfonamides 3 at the Sodium D-Line.

| Compound | L= | M= | $[\alpha]_D$ (amine) EtOH | $[\alpha]_D$ (sulfonamide) EtOH | $[\alpha]_D$ (sulfenamide) $CHCl_3$ | Configuration Lit.(Ref) | Configuration Rule |
|---|---|---|---|---|---|---|---|
| 3a | $CH_3CH_2$ | $CH_3$ | +3.20 | +1.28 | +15.3 | S (10) | S |
| 3b | $(CH_2)_4CH_3$ | $CH_3$ | -7.28 | +7.90 | -6.6 | R (11) | R |
| 3c | $C(CH_3)_3$ | $CH_3$ | +1.49 | -12.85 | +16.7 | S (12) | S |
| 3d | $C_6H_5$ | $CH_3$ | +31.8 | +72.50 | -141.6 | R (17) | R |
| 3e | P-$C_6H_4Br$ | $CH_3$ | +25.89 | +70.51 | -109.7 | R (11) | R |
| 3f | $C_6H_5$ | $CH_2CH_3$ | +5.65 | +49.89 | -120.4 | R (13) | R |
| 3g | $CH_2C_6H_5$ | $CH_3$ | -32.83 | -18.96 | -29.6 | R (15) | R |
| 3h | α-Napthyl | $CH_3$ | +51.9 | -8.35 | -572.9 | R (15) | R |
| 3i | α-Napthyl | $CH_3$ | -47.9 | +7.6 | +575.4 | S (16) | S |

Scheme 1



1 2 3

4a 4b

Table 1 gives data on the D-line rotations for eight different amines of structure 1 and their derivatives 2 and 3. The rotations of the sulfenylsulfonamides were used to predict the absolute configuration according to the rule: amines of configuration 1 (this corresponds to the S configuration for all of the compounds used) yield dextrorotatory sulfenylsulfonamides, amines whose configurations are enantiomeric with 1 yield levarotatory derivatives.

While this method for determination of absolute configurations has the same limitations as those utilizing asymmetric synthesis and kinetic resolution, it is far simpler to employ. The derivative used can be prepared in one day using small amounts of the target amine and commercially available reagents. We stress that many other derivatives which incorporate stereolabile chiral units with characteristic long wave length Cotton effects can be employed and that the method is capable of generalization to virtually all functional groups.

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