Tetrahedron Letters No. 37, pp. 3441 - 3444, 1971. Pergamon Press. Printed in Great Britain.

PYRAMIDAL INVERSION BARRIERS AND LINEAR FREE ENERGY RELATIONSHIPS

Joseph Stackhouse, Raymond D. Baechler, and Kurt Mislow

Department of Chemistry, Princeton University, Princeton, New Jersey 08540

Received in USA 1 July 1971, 1971; received in UK for publication 8 August 1971)

It has been recognized that Hammett type free energy relationships may be usefully applied to the process of pyramidal inversion. The first such application dealt with the racemization of sulfoxides (1), and similar treatments have appeared for phosphine (2) and aziridine (3) systems. Linear log k/log k' plots have been obtained (2,3) for p-phenyl substituted compounds which serve to correlate inversion rates among these systems. The recently reported (4) empirical correlation of nitrogen inversion barriers proves to be an approximate formulation of the standard Hammett type treatment. The purpose of this communication is to indicate an important limitation inherent in such an approximation.

For the treatment of pyramidal inversion barriers, it is most convenient, in view of the paucity of reliable values for $\Delta H^\ddagger$ and $\Delta S^\ddagger$, to correlate different systems by the direct comparison of their free energy barriers ($\Delta G^\ddagger$), although these frequently are determined at different temperatures. This unavoidable assumption of a temperature independent $\Delta G^\ddagger$ does not present a serious difficulty when dealing with simple inversion barriers where $\Delta S^\ddagger$ is typically near zero. It has been suggested elsewhere (5) that the magnitude of substituent effects upon nitrogen inversion barriers may be roughly proportional to barrier height. In the approximate formulation (4), the effect which various groups (X = Cl, OR, NR_2, C_6H_5, Tosyl) adjacent to nitrogen have upon the inversion barrier of amines is expressed by a z value, which, as indicated in equation 1, is defined as the ratio of the energy barrier for a specific amine bearing the appropriate

$$\underline{z}_X = \Delta G^\ddagger_X / \Delta G^\ddagger_{CH_3} \qquad \text{eq. 1}$$

group (i.e., N-X) to that of the analogous $N\text{-}CH_3$ compound. It may be shown that this z value is rigorously related to the Hammett parameters as follows. A linear relation of substituent effects upon energy barriers between two reaction series can be described by equation 2, where m and n

$$\Delta G^n_b - \Delta G^n_a = (\rho^n/\rho^m)(\Delta G^m_b - \Delta G^m_a) = \rho^n \sigma_b \qquad \text{eq. 2}$$

*refer to different reactions, *a* and *b* refer to different substituents, and* ρ *is the equivalent of* the Hammett reaction constant; *a* and *m* refer to an arbitrarily chosen standard substituent and reaction, with $\rho^m = 1$. The term $(\Delta G_b^m - \Delta G_a^m)$ is the equivalent of the Hammett substituent constant, σ_b. Nitrogen inversions in systems containing the groups (*i.e.*, X) which have been characterized by *z* values in the approximate formulation may be formally regarded as distinct reaction series in which the standard reaction is the inversion of the N-CH_3 system. That portion of any particular amine system (*e.g.*, the 2,2-dimethylaziridines) which excludes the N-X or N-CH_3 moiety may be selected arbitrarily as the standard substituent, *a*. The general substituent, *b*, refers to the corresponding portion of any other amine system. The *z* values are thus redefined as in equation 3, which may be derived from equation 2 by rearrangement of terms into the familiar

$$\underline{z}^n = \Delta G_b^n/\Delta G_b^m = (\rho^n/\rho^m) + (\Delta G_a^n - (\rho^n/\rho^m)\Delta G_a^m)/\Delta G_b^m \qquad \underline{\text{eq. 3}}$$

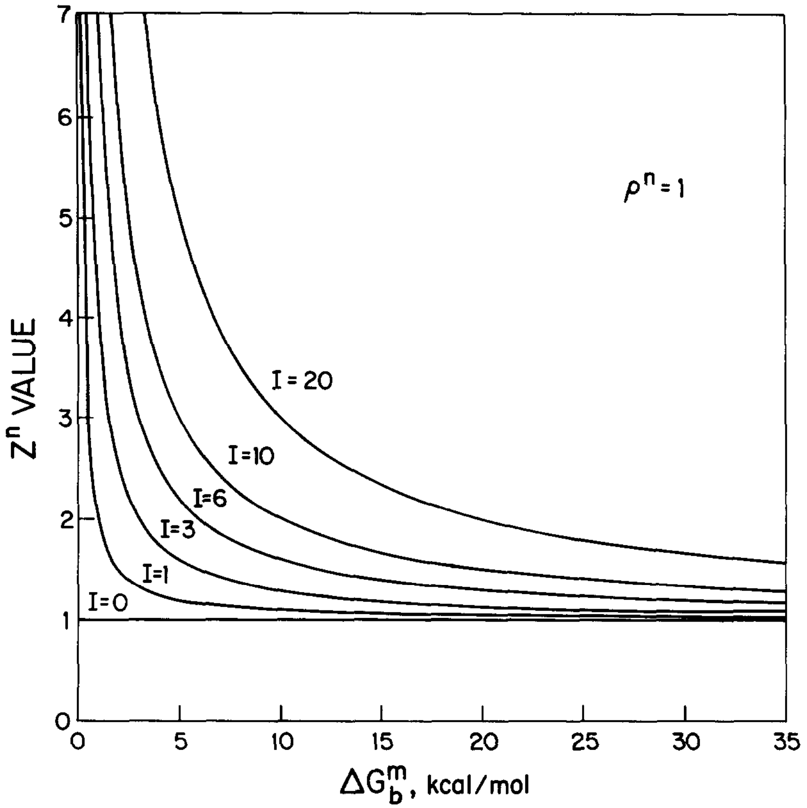
slope-intercept form, followed by division of the resulting equation by ΔG_b^m. Since $\rho^m = 1$ for the standard reaction, this expression may be simplified as in equation 4, where *I* is a constant

$$\underline{z}^n = \rho^n + \underline{I}/\Delta G_b^m \qquad \underline{\text{eq. 4}}$$

corresponding to the intercept of the linear free energy plot of ΔG_b^n *vs.* ΔG_b^m. Equation 4 is a restatement of equation 1 in terms of Hammett parameters. Clearly, when $\underline{I}/\Delta G_b^m$ is small relative to ρ^n, $\underline{z}^n$ will approach ρ^n and will be independent of the identity of the substituent *b*; in this limiting case, *z* is thus the equivalent of a Hammett reaction constant. By the same token, since the predictive utility of the empirical correlation of inversion barriers is dependent on *the approximate constancy of *z*, it is of interest to examine the sensitivity of *z* to changes in *b*.*

The dependence of *z* on ΔG_b^m, for various values of *I*, follows from equation 4 and can be graphically depicted as in Figure 1. Evidently, *z* will be approximately constant only when *I* is small in comparison to ΔG_b^m, which is not always the case. For example, in a correlation between nitrogen (ΔG_b^m) and phosphorus (ΔG_b^n) inversion barriers (6), or between sulfoxide (ΔG_b^m) and sulfonium ion (ΔG_b^n) barriers (6), *I* differs substantially from zero. The barrier range over which *z* is approximately constant decreases in direct proportion to the extent that *I*, the intercept, deviates from zero. To maintain a barrier range which is constant for a specific allowable variation in *z*, increases in *I* require a corresponding increase in the magnitude of the barriers under consideration. In the nitrogen systems which have been considered (4), these intercept values happen to be sufficiently small so that the $\underline{I}/\Delta G_b^m$ term is indeed negligible. This will generally be the case when ΔG_b^m is *ca.* 10 kcal/mol or greater (*i.e.*, for barriers conveniently measured by DNMR or direct kinetics) and accounts for the empirical observation that *z* values appear to be nearly constant throughout a variety of systems (4). On the other hand, as seen by inspection of Figure 1, such constancy in z is not to be expected for barriers of less than 5-10 kcal/mol.

Figure 1



It must be emphasized that the approximate formulation is additionally prone to all the sources of error which affect the standard Hammett treatment. For example, non-linear behavior may create a serious difficulty in certain cases, as when correlations are attempted between reaction series which include both saturated and aromatic ring systems, or between systems with large, but varying, steric requirements.

In summary, the present analysis reveals that the empirical correlation (4) corresponds to an approximation of the Hammett treatment; that the deviation of z from the Hammett ρ depends upon the magnitude of the intercept of the linear free energy plot of the appropriate reaction series; that in plots with nonzero intercept, z will be approximately constant within a limited range of barriers, the magnitude of this range depending upon the magnitude of the barriers and the magnitude of the intercept; and that deviations in the constancy of *z* may additionally be caused by any factors which would cause deviations in the corresponding Hammett ρ value. It is therefore inadvisable to ascribe conformational changes other than pyramidal inversion (*e.g.*, rotation, ring inversion) to compounds where *z* values deviate significantly from the defined average *z*.

Acknowledgement. We thank the National Science Foundation (GP-22542) for support of this work.

References.

1. D. R. Rayner, A. J. Gordon, and K. Mislow, *J. Amer. Chem. Soc.*, *90*, 4854 (1968).
2. R. D. Baechler and K. Mislow, *ibid.*, *92*, 3090 (1970).
3. J. D. Andose, J. M. Lehn, K. Mislow, and J. Wagner, *ibid.*, *92*, 4050 (1970).
4. H. Kessler and D. Leibfritz, *Tetrahedron Letters*, 4289, 4293, 4297 (1970).
5. J. M. Lehn and J. Wagner, *Tetrahedron*, *26*, 4227 (1970).
6. J. Stackhouse, R. D. Baechler, and K. Mislow, work to be published elsewhere.