Equilibration Studies: The Relative Chemical Binding Energies of 2-Methoxypyridine–*N*-Methylpyrid-2-one and 4-Methoxypyridine–*N*-Methylpyrid-4-one

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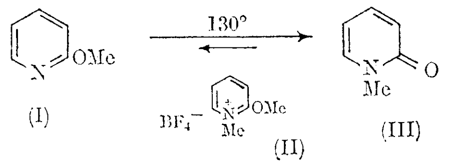
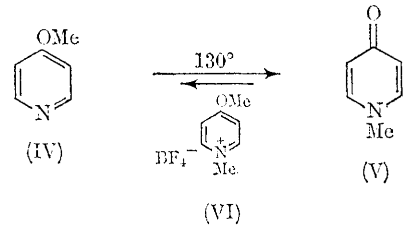
THE equilibration of heteroatom-alkylated isomers by use of the common alkylated derivative as a catalyst was recently recognized as a general reaction and applied to a study of relative molecular stabilities in the pyrone series.[1] This method, in conjunction with calorimetric techniques, can be used for the determination of the differences in chemical binding energy between each of the isomer pairs 2-methoxypyridine–*N*-methylpyrid-2-one and 4-methoxypyridine–*N*-methylpyrid-4-one.



Heating a mixture of 2-methoxypyridine (I) and a catalytic amount of 2-methoxy-*N*-methylpyridinium fluoroborate (II) in a sealed tube at 130° for 3·5 hr. gave *N*-methylpyrid-2-one (III) and the catalyst in 96% and 86% isolated yields, respectively.[2] Competing reactions could not be detected by n.m.r. or ultraviolet spectra, or g.l.c. monitoring of the reaction. G.l.c. analysis established that the ratio [III]/[I] was $>10^5$ and the corresponding standard free energy difference, $\Delta G^0_{(l)}$, was >9 kcal./mole. The calorimeter designed for room-temperature studies by Arnett, Bentrude, Burke, and Duggleby[3] was modified for use at higher temperatures and the heat of reaction for the conversion of (I) into (III) at 130° was determined to be $12{\cdot}4 \pm 0{\cdot}8$ kcal./mole. This corresponds to the standard enthalpy difference between the liquid isomers, $\Delta H^0_{(l)}$. A similar equilibration of 4-methoxypyridine (IV) and *N*-methylpyrid-4-one (V) by the catalytic action of 4-methoxy-*N*-methylpyridinium fluoroborate (VI) established the ratio [V]/[IV] was $>10^4$. The corresponding $\Delta G^0_{(l)}$ is >7 kcal./mole. The standard enthalpy difference, $\Delta H^0_{(l)}$, was determined by calorimetry to be $8{\cdot}8 \pm 0{\cdot}5$ kcal./mole in favour of the pyridone.



Conversion of these liquid-phase values to the gas phase at one atmosphere in an isothermal energy cycle with the use of empirically calculated heats of vaporization,[4] vapour-pressure–temperature relationships,[5] and the ideal-gas approximation results in the standard free energies and enthalpies shown in the Table. This correction eliminates contributions from intermolecular interaction differences between the isomers in their liquid-phase standard states. The differences between the standard enthalpies for the liquid and gas phases of 4 kcal./mole for the two isomers and 6 kcal./mole for the four isomers provides a clear example of the importance of evaluating such factors in studies of relative thermodynamic stabilities.

TABLE

Standard free energies and standard enthalpies of isomerization

Reaction	ΔG^0 (g, 760 mm.) kcal./mole	ΔH^0 (g, 760 mm.) kcal./mole
(I) → (III)	<-6	$-7{\cdot}9$
(IV) → (V)	<-2	$-1{\cdot}4$

The kinetic energy contributions to the gas-phase energy differences are probably not important. This assumption may be partially justified by calculations[6] which show small contributions to the entropy difference between the isomers from molecular and internal rotations. The difference in zero-point energies between the isomers is also estimated to be small.[7] If these assignments are valid the gas-phase standard enthalpy differences approximate to the differences in chemical binding energies for the isomer pairs. Accordingly *N*-methylpyrid-2-one (III) is about 8 kcal./mole more stable than 2-methoxypyridine (I). On the other hand *N*-methylpyrid-4-one (V) appears to be only about 1 kcal./mole more stable than 4-methoxypyridine. This difference is sufficiently small, relative to the uncertainties in the data and the approximations, that (IV) and (V) may be considered to have about the same chemical binding energy. These results and current investigations of related isomer pairs should provide further understanding of amide–imidate equilibria, a basis for the discussion of resonance energy in these systems[8] and some insight into the tautomeric ratios for the corresponding hydroxypyridine–pyridone systems.[9]

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[1] P. Beak, *Tetrahedron Letters*, 1963, 863; *Tetrahedron*, 1964, **20**, 831; D. J. Fry and J. D. Kendall, *J. Chem. Soc.*, 1951, 1716, appear to be the first to have employed a common alkylated salt as a catalytic agent in the conversion of 2-methylthiobenzthiazole into 2,3-dihydro-3-methylbenzthiazole-2-thione on heating with 2-methylthiobenzthiazole methiodide.

[2] J. W. Schulenberg and S. Archer, *Org. Reactions*, 1965, **14**, 24.

[3] E. M. Arnett, W. G. Bentrude, J. J. Burke, and P. M. Duggleby, *J. Amer. Chem. Soc.*, 1965, **87**, 1541.

[4] S. H. Fishtine, *Ind. Eng. Chem.*, 1963, **55**, 47.

[5] S. B. Lippencott and M. M. Lyman, *Ind. Eng. Chem.*, 1946, **38**, 320.

[6] K. S. Pitzer, "Quantum Chemistry," Prentice-Hall, Inc., Englewood Cliffs, New Jersey, 1958, pp. 443, 492.

[7] This is the difference in the sum of $1/2\ h\nu$ for the fundamental vibrational frequencies. Although a complete analysis has not been carried out for these molecules, partial assignments which corroborate this assumption are available: A. R. Katritzky, *Quart. Rev.*, 1959, **13**, 353; A. R. Katritzky and N. A. Coats, *J. Chem. Soc.*, 1959, 2062; A. R. Katritzky and R. A. Jones, *ibid.*, 1960, 2947; A. R. Katritzky and A. R. Hands, *ibid.*, 1958, 2202; D. Cook, *Canad. J. Chem.*, 1965, **43**, 741.

[8] J. A. Elvidge and L. M. Jackman, *J. Chem. Soc.*, 1961, 859; see however J. Musher, *J. Chem. Phys.*, 1965, **43**, 4081, and R. J. Abraham and W. A. Thomas, *J. Chem. Soc.* (*B*), 1966, 127.

[9] A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1956, 1294; S. F. Mason, *ibid.*, 1958, 674; E. S. Levin and G. N. Rodionova, *Doklady Akad. Nauk S.S.S.R.*, 1965, **164**, 584.