Equilibration Studies. Determination of the Enthalpy Difference between Methyltropic Isomers from Heats of Methylation

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Abstract: Enthalpy differences between methyltropic isomers are obtained by measurement of the heat evolved on methylation of each isomer to a common product or measurement of the heat evolved on equilibration of the isomers. The enthalpy difference between the liquid isomers is obtained directly for cases involving liquid samples or, for solid materials, in conjunction with measured heats of solution and heats of fusion. Heats of vaporization are determined for the isomers from vapor pressure–temperature measurements and are used to calculate gas phase enthalpy differences. The liquid and gas phase enthalpy differences obtained for the isomer pairs are: ($\Delta H°_l$ kcal/mol, $\Delta H°_g$ kcal/mol, isomer pair) −4.6 ± 2.2, −2.1 ± 3.2, 2-methylthio-3,4,5,6-tetrahydropiperidine-1-methyl-2-thiopiperidone; −0.5 ± 1.2, −27.9 ± 3.9, 1-methyl-4-thiopyridone-4-methylthiopyridine; −7.6 ± 1.6, −19.0 ± 3.6, 4-methoxy-6-methyl-2-thiopyrone-6-methyl-2-methylthio-4-pyrone; −5.7 ± 0.6, −8.8 ± 2.1, 2-methoxy-6-methyl-4-pyrone-4-methoxy-6-methyl-2-pyrone. These values are considered to be useful estimates of the free energy differences between the isomers, and the results are discussed in terms of localized and delocalized bonding in these systems. This study provides the first quantitative information about the binding energy difference between a 2-pyrone and a 4-pyrone and between a nonconjugated methyltropic thioamide and a thioimidate. Comparison of analogous isomer pairs shows that replacement of a carbonyl group by a thiocarbonyl group leads to large destabilization of the thiocarbonyl isomer relative to its methyltropic isomer in amide–imidate and pyrone systems.

Determination of the enthalpy difference between isomers by direct measurement of the heat of equilibration has been used to establish the differences in stabilities between seven methyltropic amides and imidates.[1,2] Those results have been useful in evaluations of chemical binding energies[3] and have established the important role which can be played by solvation in methyltropic[1] and related prototropic[4,5] equilibria. Extensions of enthalpy measurements to other systems should give useful information about the relative stabilities of isomeric functional groups. We wish to report a study which provides quantitative information about the enthalpic effect of the position of oxygen in pyrone isomers and the substitution of sulfur for oxygen in carbonyl groups of isomer pairs by measurement of the heats of methylation of methyltropic isomers, a method which appears to be more general than the direct equilibration procedure previously used.

Results

The difference in the heats of methylation of the methyltropic isomers **1** and **2** to give the common product **3** provides a measure of the enthalpy difference between the isomers. Measurement of the vapor pressures of the isomers as a function of temperature allows determination of the heats of vaporization and, consequently, a gas phase enthalpy difference. In the present study the isomer pairs 2-methoxypyridine (**4**)–

$$X=YZCH_3 \qquad CH_3XY=Z$$
$$1 \qquad\qquad 2$$
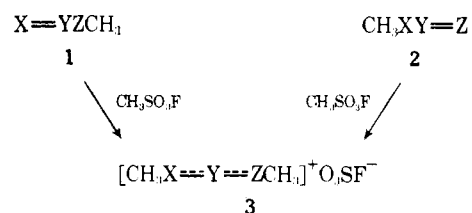
1-methyl-2-pyridone (**5**), 2-methylthio-3,4,5,6-tetrahydropiperidine (**6**)–1-methyl-2-thiopiperidone (**7**), 4-methylthiopyridine (**8**)–1-methyl-4-thiopyridone (**9**), and 4-methoxy-6-methyl-2-thiopyrone (**10**)–6-methyl-2-methylthio-4-pyrone (**11**) have been investigated by this technique. The enthalpy difference between 2-methoxy-6-methyl-4-pyrone (**12**) and 4-methoxy-6-methyl-2-pyrone (**13**) has been determined by the heat of equilibration procedure.

Heats of Methylation. The reaction of each isomer of the compounds **4–11** with methyl fluorosulfonate in 1,2-dichloroethane at ambient temperature was found to give the expected common methylated salt in quantitative yield. The heats of methylation were readily determined, as detailed in the Experimental Section, and the values obtained are shown in the first column of Table I. The liquid phase enthalpy difference between **4** and **5** was previously determined by measurement of the heat of equilibration[1,2] to be 12.1 ± 0.8 kcal/mol, a value within experimental error of 13.7 ± 1.5 kcal/mol, which is obtained by subtracting the heats of methylation for **4** and **5** (Table I).

In addition to the data available from heats of combustion, determinations of enthalpy differences between isomers from heats of conversion to a common product have been reported for the isomerization of substituted Dewar benzenes and prismanes to benzenes,[6] for hy-

(1) P. Beak, J. Bonham, and J. T. Lee, Jr., *J. Amer. Chem. Soc.*, **90**, 1569 (1968).

(2) P. Beak, T. S. Woods, and D. S. Mueller, *Tetrahedron*, **28**, 5507 (1972).

(3) For an interesting extension to protomeric equilibria of the thermodynamic comparison originally made to estimate the effect of delocalization on the relative energies of 2-methoxypyridine and 1-methyl-2-pyridone **1**, see M. J. Cook, A. R. Katritzky, P. Linda, and R. D. Tack, *J. Chem. Soc., Perkin Trans. 2*, 1080 (1973), and references cited therein.

(4) For an analysis of solvation effects on protomeric equilibria, see P. Beak and T. S. Woods, *Tetrahedron Lett.*, 775 (1972).

(5) P. Beak and F. S. Fry, Jr., *J. Amer. Chem. Soc.*, **95**, 1700 (1973).

(6) J. F. M. Oth, *Recl. Trav. Chim. Pays-Bas*, **87**, 1195 (1968); W. Adam and J. C. Chang, *Int. J. Chem. Kinet.*, **1**, 487 (1969); D. M. Lemal and L. H. Dunlap, Jr., *J. Amer. Chem. Soc.*, **94**, 6563 (1972).

Table I. Enthalpies of Methylation, Solution, Fusion, and/or Vaporization (kcal/mol) for Methyltropic Isomer Pairs 4–5, 6–7, 8–9, 10–11, 12–13, and 14–15

Compd$_{(state)}$	$\Delta H^\circ_{methylation}$	$\Delta \bar{H}^\circ_{solution}$	$\Delta H^\circ_{melting}$	$\Delta H^\circ_{vaporization}$
2-Methoxypyridine$_{(l)}$ (4)	−25.9 ± 1.0			9.8 ± 0.5 (9.7 ± 0.75)[a]
1-Methyl-2-pyridone$_{(l)}$ (5)	−12.2 ± 0.5			14.1 ± 0.7 (14.7 ± 6.75)[a]
2-Methylthio-3,4,5,6-tetrahydropiperidine$_{(l)}$ (6)	−35.3 ± 0.9			13.0 ± 0.5
1-Methyl-2-thiopiperidone$_{(s)}$ (7)	−29.9 ± 0.9	3.1 ± 0.2	3.9 ± 0.2	15.5 ± 0.5
4-Methylthiopyridine$_{(s)}$ (8)	−36.5 ± 0.3	4.6 ± 0.2	4.2 ± 0.2	13.8 ± 0.7
1-Methyl-4-thiopyridone$_{(s)}$ (9)	−36.0 ± 0.2	3.2 ± 0.1	3.8 ± 0.2	41.2 ± 2.0
4-Methoxy-6-methyl-2-thiopyrone$_{(s)}$ (10)	−24.8 ± 0.4	2.3 ± 0.1	5.1 ± 0.1	26.1 ± 1.3
6-Methyl-2-methylthio-4-pyrone$_{(s)}$ (11)	−17.9 ± 0.7	3.9 ± 0.1	6.0 ± 0.2	14.9 ± 0.7
2-Methoxy-6-methyl-4-pyrone (12)				17.0 ± 0.8
4-Methoxy-6-methyl-2-pyrone (13)				13.9 ± 0.7
2-Methoxy-3,4,5,6-tetrahydropyridine (14)				9.7 ± 0.5 (9.7 ± 0.75)[a]
1-Methyl-2-piperidone (15)				13.5 ± 0.7 (13.0 ± 0.75)[a]

[a] Previous estimates, ref 1.

drogenations of isomeric olefins,[7] and for the reactions of o-, m-, and p-di-tert-butylbenzenes to an identical mixture of products.[8] Those studies and the present work require less precision than do measurements of heats of combustion to give data of comparable accuracy. Advantage is thereby gained in speed and simplicity of operation relative to heat of combustion determinations.

The use of methyl fluorosulfonate as a highly reactive methylating agent is well precedented.[9] Calorimetrically determined heats of methylation for compounds related to sulfonium salts of biological interest have been reported,[10] as have measurements of the heats of alkylation of ethyl mercaptan and ficin by chloroacetamide.[11] Heats of alkylation[12] and dealkylation[13] of aromatics also have been directly determined.

Heats of Solution and Heats of Melting. The compounds 7–11 are solids at ambient temperature and were dissolved in 1,2-dichloroethane prior to addition of methyl fluorosulfonate in the calorimetric experiments. Enthalpy values for these compounds in the liquid state are obtained from the heats of methylation by corrections for heats of solution and heats of melting.

The directly measured partial molal heats of solution for 7–11 in 1,2-dichloroethane at ambient temperature are summarized in Table I. Heats of melting at the melting point for these compounds were determined by conventional differential scanning calorimetry and are also presented in Table I.

Heat of Equilibration. The position of equilibrium between 2-methoxy-6-methyl-4-pyrone (12) and 4-methoxy-6-methyl-2-pyrone (13) has been established through the function of 2,4-dimethoxy-6-methylpyrilium fluoroborate as an equilibration catalyst, to lie on the side of 13.[14] In the present study the enthalpy of the conversion of 12 to 13 at 115° has been established calorimetrically to be −5.7 ± 0.6 kcal/mol, after correction for a small heat of solution of the catalyst in 13.

Heats of Vaporization. The important influence which phase can have in equilibration studies has been noted in previous work.[1,2,4,5] If the potentially dominant influence of solvation is to be eliminated, conversions of the liquid phase enthalpy differences to gas phase differences must be carried out. In many cases this is achieved implicitly without formal consideration because comparisons of series of equilibria involving similar functional types in the same solvent can result in the cancellation of solvation energies.[4] Before comparison of energies is made, enthalpy differences for the neat liquids must be converted to the corresponding gas phase values by consideration of heats of vaporization in a conventional thermodynamic cycle. Our prior studies of related systems have involved estimated heats of vaporization.[1,2] In the present work the heats of vaporization have been more directly determined by measurements of vapor pressure as a function of temperature and application of the Clasium–Clapeyron equation. The resulting heats of vaporization for compounds 4–13 are summarized in Table I. Although the accuracy of heats of vaporization as determined by this method may be lower than for direct

(7) M. A. Dolliver, T. L. Gresham, G. B. Kistiakowsky, and W. E. Vaughan, J. Amer. Chem. Soc., 59, 831 (1937); R. B. Turner, D. E. Nettleton, Jr., and M. Perelman, ibid., 80, 1430 (1958).

(8) E. M. Arnett, J. C. Sanda, J. M. Bollinger, and M. Barber, J. Amer. Chem. Soc., 89, 5389 (1967).

(9) M. G. Ahmed, R. W. Alder, G. H. James, M. L. Sinnott, and M. C. Whiting, Chem. Commun., 1533 (1968), and subsequent references, e.g., J. Org. Chem., 38, 18, 12A (1973).

(10) J. Durell, M. Rawitscher, and J. M. Sturtevant, Biochim. Biophys. Acta, 56, 552 (1962); S. H. Mudd, W. A. Klee, and P. S. Ross, Biochemistry, 5, 1653 (1966).

(11) J. R. Whitaker and L. S. Lee, Arch. Biochem. Biophys., 148, 208 (1972).

(12) E. P. Babin, Z. S. Borodina, I. M. Kolesnikov, and N. Z. Rudenko, Izv. Vyssh. Ucheb. Zaved., Khim. Khim. Teknol., 9, 250 (1966); E. P. Babin, Z. S. Borodina, and V. A. Kornpanets, Zh. Fiz. Khim., 36, 2768 (1962); R. G. Ismailov, I. M. Kolesnikov, N. I. Guseinov, G. M. Mamedaliev, S. M. Aliev, R. I. Guseinov, and V. A. Salaschenko, Dokl. Akad. Nauk Azerb. SSR, 27, 29 (1971); J. Skrzpek and A. Szmyd, Zesz. Nauk. Politech. Slask., Chem., 53, 21 (1970).

(13) I. G. Petrenko and V. I. Filippova, Khim. Tverd. Topl., 1, 113 (1969); G. Z. Anistratenko and E. V. Lebedev, Neft. Gazov. Prom., 4, 46 (1968).
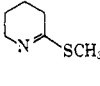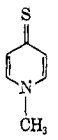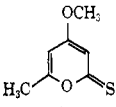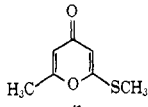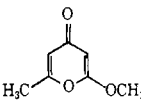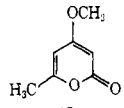
(14) P. Beak, Tetrahedron, 20, 831 (1964).

Table II. Enthalpy Differences for the Isomer Pairs 6–7, 8–9, 10–11, and 12–13 (kcal/mol)

Isomer pair				
A[a]	B[a]	$\Delta H°_l$	$\Delta H°_g$	$\Delta E_{chemical\ binding}$
6	**7**	-4.6 ± 2.2	-2.1 ± 3.2	-2.1 ± 4.7
9	**8**	-0.5 ± 1.2	-27.9 ± 3.9	-27.9 ± 5.4
10	**11**	-7.6 ± 1.6	-19.0 ± 3.6	-19.0 ± 5.1
12	**13**	-5.7 ± 0.6	-8.8 ± 2.1	-8.8 ± 3.6

[a] The compound in column B is of lower enthalpy.

measurement, the errors assigned appear to encompass the range of values obtained for most cases by different methods.[15] Also included in Table I are the previous estimates[1] of the heats of vaporization for **4, 5**, 2-methoxy-3,4,5,6-tetrahydropyridine (**14**), and 1-methyl-2-piperidone (**15**) which can now be seen to be satisfactorily close to the measured values. The changes in relative enthalpies which occur when heats of vaporization are considered vary from 2.5 to 26.4 kcal/mol and again illustrate the importance of phase effects.[1,2,4]

Discussion

Summarized in Table II are the differences in liquid and gas phase enthalpies between the isomer pairs **6–7, 8–9**, and **10–11**. These values are based on the enthalpy measurements made on the individual isomers, as illustrated in Figure 1 for the case of **6** and **7**. The enthalpy difference between **12–13**, also presented in Table II, is based on a direct measurement. An essential assumption in this analysis is that differences in heat capacities between two isomers of a pair are negligible. Accordingly, differences in the temperatures at which enthalpies of phase transitions are measured for the isomer pairs are not considered critical and the reference state is the pure liquid at a convenient temperature. An alternative way of reaching a similar result is to note that the previous analysis, which suggested that kinetic energy differences between **4** and **5** are small,[1] is applicable to isomers **6–13**. If these assumptions are valid, the entropy difference between any pair of the isomers will be small[16] such that the gas phase enthalpy differences closely approximate differences in free energies and the difference in chemical binding energies between the isomers can be obtained

(15) E. Morawetz, *J. Chem. Thermodyn.*, **4**, 455 (1972).

(16) The entropy difference between **8** and **9** will be affected by an R ln 2 symmetry based entropy difference in favor of **8**. This amounts to an energy difference of 1.4 gibbs or ca. 0.4 kcal/mol at ambient temperature, a value which is small with respect to the errors in Table II.
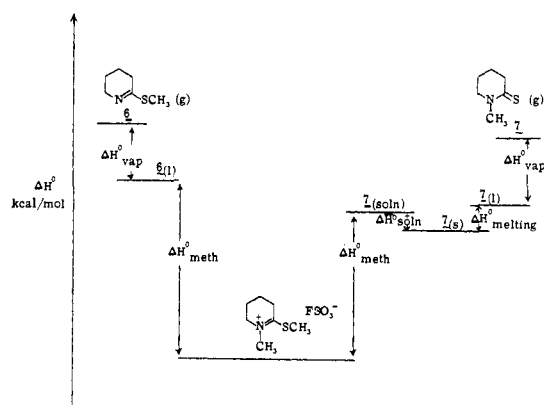

Figure 1. Enthalpy differences between 2-methylthio-3,4,5,6-tetrahydropyridine (**6**) and 1-methyl-2-thiopiperidone (**7**).

by adding an estimated maximum difference in zero point vibrational energy of ±1.5 kcal/mol to the gas phase enthalpies.[1] This provides the fourth column of Table II, which would be of interest primarily for evaluation of quantum mechanical calculations. Column three in the table, which lists the gas phase enthalpy differences between the isomers, provides values which are suitable for discussion of the energy differences ($\Delta E°_g$) between isolated molecules.[2,17]

The energy difference between 2-methoxy-6-methyl-4-pyrone (**12**) and 4-methoxy-6-methyl-2-pyrone (**13**) of -8.8 kcal/mol is the first quantitative value for such an energy difference between a 2-pyrone and a 4-pyrone. This value shows not only the usual greater stability for the 2-one system[2] but, in its similarity to the corresponding energy difference of -10.6 kcal/mol between 2-methoxy-1,6-dimethyl-4-pyridone (**20**) and

(17) T. C. Cottrel, *J. Chem. Soc.*, 1448 (1948); H. A. Skinner and G. Pilcher, *Quart. Rev., Chem. Soc.*, **17**, 264 (1963); J. D. Cox and G. Pilcher, "Thermochemistry of Organic and Organometallic Compounds," Academic Press, New York, N. Y., 1970, pp 527–529.

12. 13. X = O $\Delta E^\circ_g = -8.8 \pm 2.1$ kcal/mol

20. 21. X = NCH₃ $\Delta E^\circ_g = -10.6 \pm 1.9$ kcal/mol
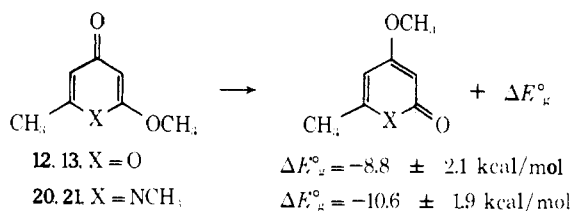
4-methoxy-1,6-dimethyl-2-pyridone (21), also suggests that this energy difference might not be especially sensitive to the heteroatom in the ring.[18]

The energy difference between 12 and 13 can be analyzed in terms of localized and delocalized bonding. If the same localized model[19] is assumed for both isomers, the difference in energy of 12 and 13 is due to delocalization and the 2-pyrone 13 would have 8.8 kcal/mol greater stabilization energy than 12. However, if more refined localized models, based on the values of Benson,[20] are used, an energy difference in favor of hypothetical localized 13 of 8.0 kcal/mol is predicted[21] and the isomers 12 and 13 are then considered to possess essentially the same stabilization energies.

If that assignment can be extended to the parent heterocycles, it follows that 2-pyrone and 4-pyrone do not differ significantly in aromatic character. In fact, the conclusion has recently been reached that the pyrones are nonaromatic, at least on the basis of magnetic susceptibility anisotropies.[22] The historically important role which the assignment of aromatic character to the 4-pyrones[23,24] played in the recognition of π-electron delocalization and in development of the resonance theory should not be minimized but neither magnetic nor thermodynamic criteria indicate significant delocalization in 4-pyrones.[25] Moreover, the high basicity and dipole moments which have been cited in support of the aromaticity of 4-pyrones have been noted as equivocal.[14,26] It seems clear that 2- and 4-pyrones should not be assigned differing aromatic character and, in the absence of compelling evidence, should be considered nonaromatic.

The difference of −2.1 kcal/mol between 2-methyl-thio-3,4,5,6-tetrahydropyridine (6) and 1-methyl-2-thio-piperidone (7) appears to be the first gas phase quantitative measure of an energy difference between methyl-

tropic nonconjugated thioamide and thioimidate functional groups.[27] Comparison of this value with the corresponding energy difference of −14.6 kcal/mol[28] between corresponding oxygen-containing isomers 14 and 15

6. 7. X = S $\Delta E^\circ_g = -2.1 \pm 3.2$ kcal/mol

14. 15. X = O $\Delta E^\circ_g = -14.6 \pm 1.7$ kcal/mol

shows that substitution of sulfur for oxygen reduces the stability of the amide relative to the imidate by 12.5 kcal/mol. While such a result might be expected for structures involving localized bonding,[29] the often assigned greater delocalization of thioamides relative to amides[30] raises the possibility that delocalization energies could overcome local bond energies. For example, the difference in localized bond energies for 6–7 compared to 14–15 with one set of bond energy values is 6 kcal/mol in favor of more amide for the latter pair.[31] Thus, if the delocalization energy of the thioamide were 6 kcal/mol greater than that of the amide, the energy differences for 6–7 and 14–15 would be expected to be the same. On the other hand, the local bond values are not sufficiently reliable to establish from the above experimental results that the thermodynamic stabilization energy of the thioamide is 6.5 kcal/mol (12.5 − 6.0) less than that of the amide. As previously noted[1] such assignments of delocalization energies are highly model dependent and of doubtful value.

Consideration of the effects of similar substitution of sulfur for oxygen in functionally related compounds shows that extension of the energy difference based on the comparison of 6–7 and 14–15 is not useful unless a very close structural relationship exists. For example, comparison of the gas phase energy differences of +7.6 kcal/mol[32] for the isomer pair 2-methyl-thiopyridine (16)–1-methyl-2-thiopyridone (17) with

16. 17. X = S $\Delta E^\circ_g = 7.6 \pm 2.8$ kcal/mol

4. 5. X = O $\Delta E^\circ_g = -8.0 \pm 2.3$ kcal/mol
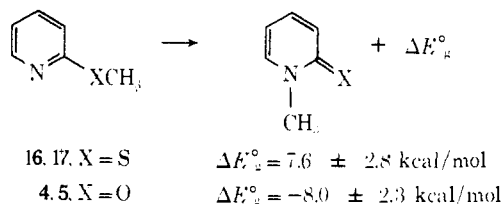
the value of −8.0 kcal/mol[1] for the isomer pair 2-methoxypyridine (4)–1-methyl-2-pyridone (5) shows a difference of 15.6 kcal/mol, comparable to the value of 12.5 kcal/mol for the saturated analogs. However,

(18) For a 2-one-4-one system in which liquid phase isomerization only slightly favors a 2-one for sulfur in the ring, see H. J. Teague and W. P. Tucker, J. Org. Chem., 32, 3140 (1967). Presumably transformation to the gas phase would show increased stability for the 2-one.

(19) In this case the localized model is a ring consisting of two C–O, two C–C, two >C=C<, and a >C=O appropriately arranged and bearing two hydrogens, a methyl, and a methoxyl as substituents.

(20) S. W. Benson, "Thermochemical Kinetics," Wiley, New York, N. Y., 1968, Chapter 2 and Appendix.

(21) The energy difference results from a cumulative difference in the bonds CO(Cd)(O), Cd(Cd)(O), Cd(H)(Cd), and O(Cd)(CO) for localized 13 relative to CO(Cd)₂ (considered equivalent to CO(Cb)₂), Cd(O)₂ (considered equivalent to Cd(C)₂), Cd(H)(CO) and O(Cd)₂) for localized 12.

(22) C. L. Norris, R. C. Benson, P. Beak, and W. H. Flygare, J. Amer. Chem. Soc., 95, 2766 (1973), and references cited therein.
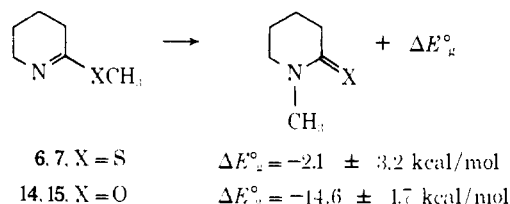
(23) F. Arndt, E. Scholz, and P. Nachtweg, Ber., 57, 1903 (1924).

(24) G. M. Badger, "Aromatic Character and Aromaticity," Cambridge University Press, Cambridge, England, 1969, pp 28–29; A. Albert, "Heterocyclic Chemistry," Althone Press, London, England, 1968, pp 336–342.

(25) The relationship of these criteria is a matter of continuing interest: ref 1; A. J. Jones, Rev. Pure Appl. Chem., 18, 253 (1968); W. H. Flygare, T. G. Schmalz, and C. L. Norris, J. Amer. Chem. Soc., 95, 7961 (1973); S. W. Staley and W. G. Kingsley, ibid., 95, 5804 (1973).

(26) D. J. Bertelli and T. J. Andrews (J. Amer. Chem. Soc., 91, 5280 (1969)) have shown that apparently high dipole moments in tropones do not indicate extensive delocalization.

(27) W. Water and J. Krohn, Ber., 102, 3786 (1969), have reported two heats of combustion in which a thioamide is favored over an isomeric thioimidate by 4–6 kcal/mol and in the solid and liquid states.

(28) This value is the gas phase enthalpy difference between 14 and 15 obtained from the liquid phase enthalpy difference of −17.4 ± 0.5¹ kcal/mol and the heats of vaporization in Table I.

(29) C. C. Price and S. Oae, "Sulfur Bonding," Ronald Press, New York, N. Y., 1962, pp 5–8.

(30) T. Nishiguchi and Y. Iwakwa, J. Org. Chem., 35, 1591 (1970), and references cited therein.

(31) Essentially this is the local bond energy difference between 6–7 and 14–15 is the difference of [(C=S) − 2(C—S)] − [(C=O) − 2(C—O)] from the following bond energies: C=S, 138 kcal/mol; C–S, 69 kcal/mol; C=O, 176 kcal/mol; C–O, 85 kcal/mol; D. A. Johnson, "Sulfur in Organic and Inorganic Chemistry," Vol. 2, A. Senning, Ed., Marcel Dekker, New York, N. Y., 1972, pp 44, 59.

(32) P. Beak and J. T. Lee, Jr., J. Org. Chem., 34, 2125 (1969).

comparison of the energy difference of −27.9 kcal/mol for the pair 4-methylthiopyridine (**8**) and 1-methyl-thiopyridone (**9**) with the value of +0.2 kcal/mol[1] for the energy difference between 4-methoxypyridine (**18**)

8, 9, X = S $\Delta E^{\circ}_{\mu} = -27.9 \pm 3.9$ kcal/mol
18, 19, X = O $\Delta E^{\circ}_{\mu} = 0.2 \pm 2.0$ kcal/mol
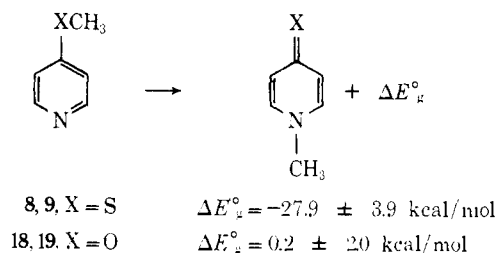
and 1-methyl-4-pyridone (**19**) results in an energy difference of 28 kcal/mol, almost twice that for the 2-pyridone comparison even though the bonds involved are formally the same and the delocaliza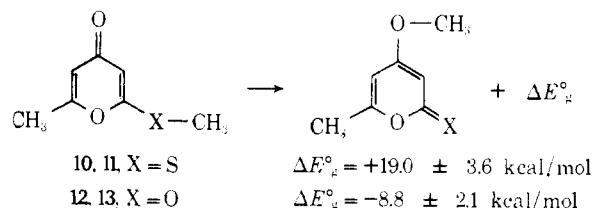tion energies of the rings could be presumed to be similar.[33] If, alternatively, the difference in the 2- and 4-substituted systems is presumed to lie in different stabilization energies of the pyridones, it might be expected that the 4-pyridone would show less effective conjugation than the 2-pyridone, in contrast to the assignment necessary to rationalize the observed energy differences. Nonetheless, the above differences could be rationalized if the 2-thiosubstituted pyridine were considered to have significantly greater stabilization energy than the 4-thiosubstituted pyridine. Such assignments should primarily be taken to indicate the uncertainties associated with the dissection of molecular stabilities into localized and delocalized energies in these systems. Clearly, related systems need to be investigated in their own right if information about fundamental stabilities is desired.

The effect of substitution of sulfur for oxygen in the carbonyl group of the pyrones may be seen in the contrast between the energy difference of −8.8 kcal/mol for **12** and **13** and that for **10** and **11** of 19.0 kcal/mol.

10, 11, X = S $\Delta E^{\circ}_{\mu} = +19.0 \pm 3.6$ kcal/mol
12, 13, X = O $\Delta E^{\circ}_{\mu} = -8.8 \pm 2.1$ kcal/mol

Essentially the effect of the thiocarbonyl is sufficiently destabilizing relative to its isomeric 4-pyrone that the energy difference which usually favors the 2-pyrone is overcome, thus providing the first case of the greater stability of 4-one in methyltropic equilibria. Like the above comparisons, this isomerization also involves formally the energy difference between a thiocarbonyl and two carbon–sulfur single bonds and two carbon–oxygen single bonds and a carbonyl group, a change in localized bond energies which should amount to ca. 6 kcal/mol.[31] Again the difference between expectation and observation could reflect an inappropriate choice of local bond values or differences in delocalization energies. Despite those uncertainties, the above comparisons consistently show that substitution of a thiocarbonyl for a carbonyl group destabilizes

(33) A similar delocalization energy for 2- and 4-pyridones relative to the isomeric pyridines has been reported by M. J. Cook, A. R. Katritzky, P. Linda, and R. D. Tack, *J. Chem. Soc., Perkin Trans. 2*, 1080 (1973).
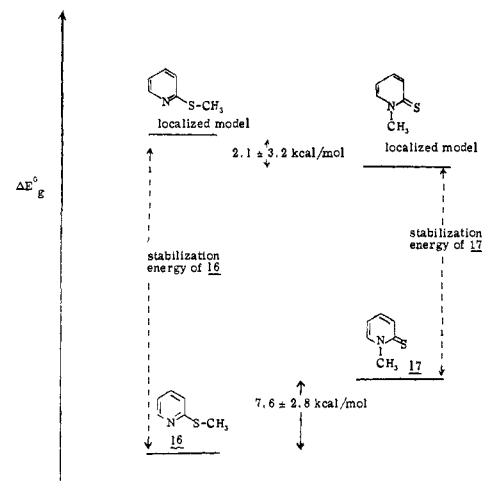
Figure 2. Estimate of the differences in stabilization energy for 2-methylthiopyridine (**16**) and 1-methyl-2-thiopyridone (**17**).

the thiocarbonyl compound relative to its carbonyl isomer.

Quantitative comparisons should clearly be limited to structurally very similar systems. Within this restriction and with the models and assumptions previously discussed,[1] an assessment of the relative thermodynamic stabilization energies of pyridine and pyridone isomers can be made for the 2-thiosubstituted systems. Thus the value for the energy difference of **6** and **7** used for the localized model and combined with the energy difference of +7.6 kcal/mol[32] for 2-methylthiopyridine (**16**)–1-methyl-2-thiopyridone (**17**), as shown in Figure 2, gives a difference in stabilization energy of 9.7 ± 6.0 in favor of the pyridine ring. This value compares reasonably well with a value of 6.1 ± 4.0,[34] which may be calculated for the difference in stabilization energy of 2-methoxypyridine (**4**) and 1-methyl-2-pyridone (**5**) using earlier gas phase values.[1] Both compare well with recent comparisons for protomeric systems, suggesting that in those cases solvent effects do cancel.[3,4] It also should be noted that π-energy differences in the amide and imidate functionalities are canceled by these comparisons and do not affect the result.

Despite the quantitative limitations noted, and to the degree that differences in ground-state energy are important, the present results provide some insight into the chemistry of the functions studied. A generally higher ground-state energy for imidates relative to amides, which is implied in the 17 and 14 kcal/mol liquid and gas phase enthalpies of **14** relative to **15**, is consistent with the synthetically useful conversion of amides to imidates as an important method for the activation of amides toward nucleophilic substitution.[35,36] A limitation on such rationalizations is noted, however, in the fact that differences in ground-state energies are not of dominant importance in the hydrolysis of some amides and imidates, but rather the

(34) The error is based on gas phase enthalpy differences.[2,17]
(35) R. G. Glushkov and V. B. Granik, *Advan. Heterocycl. Chem.*, 12, 185 (1970); E. Bertele, H. Boos, J. D. Dunitz, F. Elsinger, A. Eschenmoser, I. Felner, H. P. Gribi, H. Gschwend, E. F. Meyer, M. Pesaro, and R. Schefold, *Angew. Chem., Int. Ed. Engl.*, 3, 490 (1964).
(36) R. F. Borch, *Tetrahedron Lett.*, 61 (1968); J. Oishi, M. Ochiai, M. Nogai, and Y. Ban, *ibid.* 492, 497 (1968); A. Pilotti, A. Reuterhäll, K. Jorgell, and C. G. Cindblad, *Acta Chem. Scand.*, 23, 818 (1969).

partitioning of reactive intermediates plays a more critical role.[37] The fact that dimethylformamidium salts apparently preferentially transfer an alkyl group from oxygen[38] to a carboxylate nucleophile may also be understood in terms of imidate and amide stabilities, as the leaving group with loss of an oxygen bound group is the more stable amide rather than the imidate which would result from loss of a nitrogen bound group. The similar stabilities of thioamides and thioimidates implied by the similar enthalpies of 6 and 7 suggest that insofar as ground-state energy differences are important these isomers may not differ in reactivity as much as the oxygen isomers. Although the relative reactivity of thioamides and amides has not been quantitatively investigated, and will undoubtedly prove to be due to a variety of effects, a greater chemical reactivity of thioamides[39] would be consistent with the apparent destabilization of the carbon heteroatom double bond introduced on substitution of oxygen for sulfur. However, the present data really do not provide direct comment on that issue. It is interesting to note that in protomeric equilibria in solution the thioamide is favored[39b,40] by *ca.* 10^8 kcal/mol,[34] although conversion to the gas phase and differences in local bond energies cloud the significance of comparison with present data.

The use of heats of methylation to obtain enthalpic information appears to be a viable approach for investigation of a number of isomeric functions. The conditions are considerably milder than for the heat of equilibration procedure[1] and the results are obtained more rapidly and conveniently than by determination of heats of combustion.

Experimental Section[41]

Materials. All reagents and solvents used were commercially available and were not further purified unless otherwise specified. Methyl fluorosulfonate was obtained from the Aldrich Chemical Co., distilled (bp 91–93°), and stored over calcium hydride in a dry argon atmosphere at −15°. All fluoroborate and fluorosulfonate salts were stored in amber bottles in a nitrogen dry bag.

2-Methoxypyridine (4) (Aldrich Chemical Co.) was purified by vacuum distillation. 1-Methyl-2-pyridone[2] (5), 2-methylthio-3,4,5,6-tetrahydropyridine[32,42] (6), 1-methyl-2-thiopiperidone[32,43] (7), 4-methylthiopyridine[44] (8), 1-methyl-4-thiopyridone[45] (9),

(37) See, for example, C. R. Smith and K. Yates, *J. Amer. Chem. Soc.*, **94**, 8811 (1972); R. DeWolfe and R. L. Newcomb, *J. Org. Chem.*, **36**, 3870 (1971); T. C. Pletcher, S. Koehler, and E. H. Cordes, *J. Amer. Chem. Soc.*, **90**, 7072 (1968); R. K. Chaturvedi and G. L. Schmir, *ibid.*, **90**, 4413 (1968), and references cited therein.

(38) W. Kantlehner and B. Funke, *Ber.*, **104**, 3711 (1971).

(39) For reviews of thioamides see (a) K. A. Petrov and L. N. Andreev, *Russ. Chem. Rev.*, **40**, 505 (1971); (b) W. Walter and J. Voss, "Chemistry of the Amides," S. Patai, Ed., Interscience, New York, N. Y., 1970, p 383; (c) for some recent examples of the synthetic utility of thioamides see Y. Yamada, D. Miljkovic, P. Wehrli, B. Golding, D. Löliger, R. Keese, K. Müller, and A. Eschenmoser, *Angew. Chem., Int. Ed. Engl.*, **8**, 343 (1969); and M. Roth, P. Bubs, E. Götschi, and A. Eschenmoser, *Helv. Chim. Acta*, **54**, 710 (1971).

(40) W. Walter, *Z. Chem.*, **10**, 371 (1970).

(41) Melting points were determined on a Büchi capillary melting point apparatus and are corrected; boiling points are uncorrected. Infrared spectra were obtained on Perkin-Elmer Model 137 or 521 infrared spectrophotometers. The nmr spectra were recorded on Varian Associates T-60, A-60A, A-56/60 and HA-100 spectrometers by the authors or by R. Thrift and associates. Chemical shifts are reported in δ (ppm) relative to the internal standard tetramethylsilane. The mass spectra were determined by C. Cook and associates on Atlas CH4 and Varian MAT CH5 mass spectrometers. Elemental analyses were performed by J. Nemeth and associates. The errors indicated for the measured enthalpy differences are calculated standard deviations unless otherwise stated.

(42) J. V. Kostir and Z. Padr, *Chem. Listy*, **40**, 276 (1946).

(43) J. Renault, *Bull. Soc. Chim. Fr.*, 1001 (1953).

(44) H. King and L. L. Ware, *J. Chem. Soc.*, 873 (1939).

4-methoxy-6-methyl-2-pyrone[14,46] (13), 2-methoxy-3,4,5,6-tetrahydropyridine[1] (14), and 1-methyl-2-piperidone[1] (15) were prepared by established procedures. The ir and nmr spectra and elemental analyses of these compounds were consistent with those of the established structures.

2-Methoxy-6-methyl-4-pyrone (12). The trimethylsilyl blocking group was used according to the procedure of Beak, Woods, and Mueller.[2] To a solution of 4-hydroxy-6-methyl-2-pyrone (12.6 g, 0.1 mol) in 100 ml of dry pyridine was added excess trimethylchlorosilane (32.5 g, 0.3 mol), which caused immediate precipitation of pyridine hydrochloride. After the resulting mixture had been heated to reflux for 1 hr and the solvent had evaporated, the residue was cooled to 0° and excess methyl fluorosulfonate (21.0 g, 0.18 mol) was added slowly under a nitrogen atmosphere. Following complete addition, and after the vigorous reaction had subsided, the resulting viscous liquid was warmed to ambient temperature, dissolved in methanol–water (1:1), neutralized with aqueous sodium hydroxide, and extracted with dichloromethane. The product was separated from the isomeric 2-pyrone by column chromatography on silica gel. Recrystallization from hexane gave 2.7 g (19%) of **12**: mp 93.5–94.5° (lit.[46] mp 92.5–94°). The ir, nmr, mass spectra, and elemental analysis were consistent with those of the established structure.[14]

4-Methoxy-6-methyl-2-thiopyrone (10) was prepared in 45% overall yield from the reaction of 4-methoxy-6-methyl-2-pyrone (5.0 g, 35.7 mmol) and phosphorus pentasulfide (5.0 g, 22.5 mmol) in 125 ml of benzene heated at reflux for 90 min.[47] The resulting red solution was decanted, the residue was washed repeatedly with chloroform, all decantants were combined, and the solvent was evaporated. The crude solid isolated was purified by column chromatography and recrystallization from hexane to yield 2.5 g (45%) of red-orange needles: mp 125–126°; nmr (CDCl₃) δ 6.60 (d of d, 1, H-3), 6.07 (d of d, 1, H-5), 3.81 (s, 3, OCH₃), and 2.32 (d of d, 3, CCH₃); J_{35} = 2.30 Hz, J_{37} = 0.85 Hz, and J_{57} = 0.40 Hz; ir (CHCl₃) 2950 (C–H), 1640 (C=C), 1530, 1410, 1155 (C=S), 1090 (C–O–C), and 945 cm⁻¹; mass spectrum (10 eV) *m/e* (rel intensity) 158 (7), 157 (10), 156 (100), 149 (53), 141 (12), and 112 (29).

Anal. Calcd for C₇H₈O₂S: C, 53.82; H, 5.16; S, 20.53. Found: C, 53.51; H, 5.26; S, 20.71.

6-Methyl-2-methylthio-4-pyrone (11) was prepared in 61% overall yield by the rearrangement of 4-methoxy-6-methyl-2-thiopyrone (3.63 g, 23.2 mmol) and catalyzed by methyl fluorosulfonate (265 mg, 2.32 mmol) in 50 ml of refluxing 1,2-dichloroethane, under a dry nitrogen atmosphere, for 20 hr. The resulting black liquid was purified by column chromatography, and the desired product was recrystallized from hexane to yield 1.98 g (61%) of **11** as a white solid: mp 71–72°; nmr (CDCl₃) δ 6.07 (d of d, 1, H-5), 5.98 (d of d, 1, H-3), 2.42 (s, 3, SCH₃), and 2.23 (d of d, 3, CCH₃); J_{35} = 2.14 Hz, J_{57} = 0.86 Hz, and J_{37} = 0.10 Hz; ir (CHCl₃) 3100 (C–H), 1700 (C=O), 1645 (C=C), 1600, 1420, 1390, 1215, 1100 (C–O–C), 900, and 845 cm⁻¹; mass spectrum (10 eV) *m/e* (rel intensity) 158 (6), 157 (9), 156 (100), 128 (27), 113 (9), and 72 (23).

Anal. Calcd for C₇H₈O₂S: C, 53.82; H, 5.16; S, 20.53. Found: C, 53.61; H, 5.14; S, 20.74.

2-Methoxy-1-methylpyridinium Fluorosulfonate. Reaction of 2-methoxypyridine (218 mg, 2.00 mmol) and methyl fluorosulfonate (228 mg, 163 μl, 2.00 mmol) in 150 ml of 1,2-dichloroethane at ambient temperature for 2 hr gave a pure white powder after the solvent had been removed. The yield was 443 mg: mp 82–83°; nmr (CD₃CN) δ 8.28–8.53 (m, 2 H-3,6), 7.33–7.63 (m, 2, H-4,5), 4.27 (s, 3, OCH₃), and 4.00 (s, 3, NCH₃); ir (Nujol) 3100 (C–H), 1635 (C=N), 1580 (Ar ring), 1510 (Ar ring), 1280 (S=O), 1160 (C–O), 1060, 1030, 1000, 815, 770, and 685 cm⁻¹.

Anal. Calcd for C₇H₁₀NO₄SF: C, 37.66; H, 4.52; N, 6.27; S, 14.36. Found: C, 37.39; H, 4.38; N, 6.45; S, 14.20.

The salt was also prepared quantitatively from 1-methyl-2-pyridone by an identical procedure and identified by nmr spectroscopy and mixture melting point criterion.

1-Methyl-2-methylthio-3,4,5,6-tetrahydropyridinium Fluorosulfonate. A quantitative yield of white crystals of the salt (mp 47°) was produced from 1-methyl-2-thiopiperidone and 2-methylthio-3,4,5,6-tetrahydropyridine upon reaction with methyl fluorosulfonate in 1,2-dichloroethane at ambient temperature followed by evaporation of the solvent. The nmr spectrum is identical with that reported for the corresponding fluorosulfonate salt;[21] ir

(45) R. A. Jones and A. R. Katritzky, *J. Chem. Soc.*, 3610 (1958).

(46) J. D. Bu'Lock and H. G. Smith, *J. Chem. Soc.*, 592 (1960).

(47) F. Arndt and S. Avan, *Chem. Ber.*, **84**, 343 (1951).

(Nujol) 2350, 1630, 1410, 1370, 1270 (broad), 1170 (broad), 1130, 1090, 1070, and 960 cm^{-1}.

Anal. Calcd for C$_7$H$_{14}$NO$_3$SF: C, 34.57; H, 5.76; N, 5.76; S, 26.34. Found: C, 34.46; H, 5.70; N, 5.69; S, 26.60.

4-Methylthio-1-methylpyridinium Fluorosulfonate. A quantitative yield of white crystals was produced on reaction of 1-methyl-4-thiopyridone (196 mg, 1.57 mmol) and methyl fluorosulfonate (0.2 ml, 2.4 mmol) in 150 ml of dichloroethane at ambient temperature followed by evaporation of the solvent. The material has mp 102–104°; nmr (DMSO-d_6) δ 1.96 (3 H, SCH$_3$), 3.48 (3 H, =N$^+$CH$_3$), 7.90 (2 H, d), 8.62 (2 H, d) and J_{23} = 6.8 Hz; ir (Nujol) 3010, 3030, 1630, 1550, 1500, 1380, 1350, 1280 (broad), 1238, 1200, 1110, 1070, 1050 cm^{-1}.

The same salt was formed by reaction with 4-methylthiopyridine (194.9 mg, 1.56 mmol) and methyl fluorosulfonate (0.2 ml, 2.4 mmol) under the same conditions and has identical nmr, ir, and melting point with the above material.

Anal. Calcd for C$_7$H$_{10}$NO$_3$SF: C, 35.15; H, 4.18; N, 5.86; S, 26.78. Found: C, 35.32; H, 4.23; N, 5.86; S, 26.90.

2,4-Dimethoxy-6-methylpyryllium fluoroborate was obtained in 68% overall yield from the reaction of 4-methoxy-6-methyl-2-pyrone and trimethyloxonium fluoroborate in 50 ml of nitromethane at ambient temperature and in 62% overall yield from 2-methoxy-6-methyl-4-pyrone. The material has mp 149–150° (lit.[14] mp 152–154°); nmr (CD$_3$CN) δ 6.96 (d of d, 1, H-5), 6.62 (d of d, 1, H-3) 4.32 (s, 3, OCH$_3$), 4.17 (s, 3, OCH$_3$) and 2.57 (d of d, 3, CCH$_3$): J_{35} = 2.20 Hz, J_{57} = 0.77 Hz, and J_{37} = 0.32 Hz; ir[2] (Nujol) 3080 (C–H), 2850 (C–H), 1670 (C=O), 1545 (Ar ring), 1485, 1250 (C–O–C), 1160, 1040 (BF$_4$), 940, and 905 cm^{-1}.

4-Methoxy-6-methyl-2-methylthiopyryllium fluorosulfonate was obtained quantitatively by the reaction of 4-methoxy-6-methyl-2-thiopyrone or 6-methyl-2-methylthio-4-pyrone and excess methyl fluorosulfonate in 1,2-dichloroethane at ambient temperature for 1 hr. The product obtained by evaporation of the solvent has mp 141–144°; nmr (CD$_3$CN) δ 7.27 (d of d, 1 H-3), 7.10 (d of d, 1, H-5), 4.17 (s, 3, OCH$_3$), 2.73 (s, 3, SCH$_3$), and 2.63 (d of d, 3, CCH$_3$): J_{35} = 2.40 Hz, J_{57} = 0.80 Hz, and J_{37} = 0.35 Hz; ir (Nujol) 3050 (C–H), 1640 (C=O), 1520, 1340, 1270 (C–O–C), 1170, 1130, 1060 (S=O), 1030, and 940 cm^{-1}.

Anal. Calcd for C$_8$H$_{11}$FO$_5$S$_2$: C, 35.55; H, 4.10; S, 23.73. Found: C, 35.64; H, 4.18; S, 23.86.

Calorimetric Determination of the Liquid Phase Heat of Equilibration of 2-Methoxy-6-methyl-4-pyrone (12) and 4-Methoxy-6-methyl-2-pyrone (13). The calorimeter and the procedure have been described.[1,2] The measured heat of equilibration at 115° with **12** as a melt and the catalyst as a solid is presented in Table III. The

Table III. Calorimetrically Determined $\Delta H°_1$ between 2-Methoxy-6-methyl-4-pyrone (**13**) and 4-Methoxy-6-methyl-2-pyrone (**12**) at 115°

Initial mmol 13	Initial mmol catalyst	Heat evolved, cal	$\Delta H°_1$, kcal/mol
5.00	0.29	24.3	−4.9
5.00	0.29	30.5	−6.1
5.00	0.29	26.2	−5.2
		Av	−5.4 ± 0.6
			(−5.7 ± 0.6)[a]

[a] With ΔH_{soln} value of +0.3 kcal/mol subtracted.

heat of solution of the solid catalyst in the major isomer is 0.3 kcal/mol. Analysis of the product by tlc and ir and nmr spectroscopy shows only the major isomer and catalyst to the limits of detection, estimated as >97%. The 2-pyrone **13** was obtained in 91% isolated yield and the catalyst in 69% isolated yield from one run. Each isomer and the catalyst were shown to be separately stable, at 115° for 3 hr, the maximum duration of a run.

Calorimetric Determination of the Heats of Methylation of Methyltropic Isomer Pairs 4–5, 6–7, 8–9, and 10–11 in 1,2-Dichloroethane at Ambient Temperature. The calorimeter and the general procedure used were identical with those described for the liquid phase enthalpy of isomerization experiment, except for the following modifications. All experiments were conducted at ambient temperature with 150 ml of 1,2-dichloroethane as the bath solvent in the calorimeter. The neat liquid isomers were placed in a glass reaction vial which had a weakened bottom and methyl fluoro-

sulfonate was dissolved in the bath solvent for the methylation of **4, 5,** and **6.** Conversely, neat methyl fluorosulfonate was placed in the vial, and the solid isomers were dissolved in the solvent for the methylations of 7, 8, 9, 10, and 11. After electrical calibration the reaction was initiated by breaking the bottom of the vial with a ball-tipped, 3-mm solid glass rod and the evolved heat was measured. Calibration after the experiment showed negligible changes in heat capacity due to the reaction. All isomer pairs and the fluorosulfonate product salts remained in solution during the measurements and are stable in 1,2-dichloroethane at ambient temperature. The fluorosulfonate salts could be recovered quantitatively from the respective reactions, and no side products were detected by nmr or ir spectroscopy or melting point analysis. The experimental heats of methylation are presented in Table IV.

Table IV. Calorimetrically Determined $\Delta H°_{meth}$ for the Reaction of Methyltropic Isomers with Methyl Fluorosulfonate in 1,2-Dichloroethane at Ambient Temperature

Compd, mmol	CH$_3$OSO$_2$F, mmol	Heat evolved, cal		$\Delta H°_{meth}$, kcal/mol
4 2.00	2.00	52.9		−26.4
2.00	2.00	49.3		−24.7
2.00	2.00	53.3		−26.6
			Av	−25.9 ± 1.0
5 3.00	3.00	38.3		−12.8
4.00	4.00	49.2		−12.3
3.00	3.00	33.8		−11.3
			Av	−12.2 ± 0.5
6 1.97	12.35	66.74		−33.9
2.08	7.41	73.63		−35.4
2.16	4.94	78.39		−36.3
2.06	4.94	73.27		−35.5
			Av	−35.3 ± 0.9
7 2.14	12.35	63.18		−29.4
2.05	7.41	63.77		−31.0
2.09	4.94	59.67		−28.6
2.06	4.94	62.60		−30.4
			Av	−29.9 ± 0.9
8 1.56	2.47	56.36		−36.1
1.24	2.47	45.36		−36.6
1.26	2.47	46.31		−36.8
			Av	−36.0 ± 0.2
9 1.57	2.47	56.29		−35.9
1.59	2.47	57.51		−36.2
1.59	2.47	56.92		−35.8
			Av	−36.5 ± 0.3
10 2.00	10.00	49.0		−24.5
2.00	10.00	50.6		−25.3
2.00	10.00	49.0		−24.5
			Av	−24.8 ± 0.4
11 2.00	10.00	36.6		−18.3
2.00	10.00	35.8		−17.9
2.00	10.00	37.2		−17.6
			Av	−17.9 ± 0.4

Calorimetric Determination of Heats of Solution in 1,2-Dichloroethane. The calorimeter, temperature employed, and general procedure were identical with those described for the heat of methylation experiment except that the neat isomer being studied was placed in the reaction vial and no methyl fluorosulfonate was present. Reaction was initiated by breaking the blistered vial, allowing the isomer to be dissolved in the solvent, 1,2-dichloroethane. Heats of solution are summarized in Table V.

Measurement of the heats of fusion of 7, 8, 9, 10, and **11** at their respective melting points was accomplished by use of a Du Pont 900 thermal analyzer equipped with a differential scanning calorimeter cell. The following formula was used to calculate the heats of

$$\Delta H_{fus}(cal/mmol) = E(AT_s)(\Delta T_s)/Ma$$

fusion where E = calibration coefficient (mcal/(°min)), A = peak

Table V. Calorimetrically Determined Heats of Solution in 1.2-Dichloroethane at Ambient Temperature and Heats of Melting at the Melting Points

Compd	$\Delta H°_{soln}$, kcal/mol	$\Delta H°_{melting}$, kcal/mol
1-Methyl-2-thiopiperidone	3.1 ± 0.2	3.9 ± 0.2
1-Methyl-4-thiopyridone	3.2 ± 0.1	3.8 ± 0.2
4-Methylthiopyridine	4.6 ± 0.2	4.2 ± 0.2
4-Methoxy-6-methyl-2-thiopyrone	2.3 ± 0.1	5.1 ± 0.1
6-Methyl-2-methylthio-4-pyrone	3.9 ± 0.1	6.0 ± 0.2

The exact temperature of the manometer block is determined by means of a thermocouple fastened to the manometer block, a potentiometer, and a 0° reference bath.

The sample is degassed repeatedly before and after melting, prior to taking any vapor pressure measurements. Readings are then made at each temperature until the vapor is equilibrated throughout the system and gives a constant value for three consecutive readings. All vapor pressure measurements are taken with compounds in the liquid state. Temperature changes are regulated by a voltage control on the oven and each new temperature reading is made after the oven and manometer block have been allowed to thermally equilibrate for *ca.* 30 min.

Table VI. Determination of the Heat of Vaporization of 4–15

Compound	Range $T(P_{vap})$ [°K(Torr)]	$\Delta H°_{vap}$, kcal/mol	5% error, kcal/mol	σ^a	CL^b	r^c
4	304.7 (10.3)–337.6 (49.0)	9.8	0.5	0.2	0.2	0.994
5	353.6 (1.3)–400.0 (14.0)	14.1	0.7	0.1	0.1	0.999
6	313.1 (1.1)–350.7 (9.6)	13.0^d	0.7			
7	363.5 (0.42)–369.8 (0.60)	15.5	0.8			
8	346.7 (1.75)–383.1 (11.00)	13.8	0.7	0.4		0.999
9	440.3 (1.90)–465.1 (23.00)	41.2	2.0	2.0		0.995
10	401.6 (0.33)–415.2 (0.96)	26.1	1.3	1.6	3.5	0.985
11	387.7 (0.9)–432.7 (6.8)	14.9	0.7	0.1	0.1	0.999
12	370.4 (0.42)–384.0 (0.97)	17.0	0.8	0.2	0.3	0.998
13	385.7 (2.3)–434.2 (17.0)	13.9	0.7	0.2	0.2	0.998
14	292.3 (4.0)–337.3 (42.0)	9.7	0.5	0.2	0.2	0.994
15	341.0 (2.4)–385.1 (22.5)	13.5	0.7	0.2	0.2	0.996

^{a} Standard deviation in kcal/mol. ^{b} 95% confidence limit in kcal/mol. ^{c} Linear correlation coefficient. ^{d} Four runs gave errors of ±0.2 for both compounds.

area (in.^{2}). T_x = X axis sensitivity (°/in.), ΔT_s = Y axis sensitivity (°/in.), M = mass of sample (mg). and a = rate of heating (°/min). For all of the measurements, T_s = 10.0°/in., ΔT_s = 1.0°/in., and a = 10.0°/min. The value for the calibration coefficient, E, determined by Byrn[48a] and Woods[48b] from calibrations with indium and several organic compounds with known ΔH_{fus} of 154 mcal (min) was used in all calculations. All peaks areas were measured with a Gelman Instruments Co. planimeter. Control experiments, conducted by reobtaining ΔH_{fus} values from melted material in an earlier determination of heats of fusion gave identical, reproducible results. The calculated values are collected in Table V.

Determination of the Heats of Vaporization. A capacitance manometer purchased from the Granville-Phillips Co., modified as described in detail by Fry,[49] was used for all vapor pressure measurements. The manometer is operated inside an insulated oven with one side of its diaphragm (chamber A) connected by glass tubing to a glass sample cell, also inside the oven, which holds the compound being vaporized. A universal glass joint and stopcock, joining all the glass tubing, is constructed so that a pump vacuum of approximately 5 × 10⁻³ Torr can be maintained continuously on the opposite side of the manometer's diaphragm (chamber B), and also established independently or jointly on chamber A and/or the sample cell. Vapor pressure measurements are made by allowing vapor from the sample to expand and equilibrate in chamber A of the manometer at a known temperature. The deflection of the diaphragm, calibrated in differential pressures of the vapor pressure of the sample and the pump vacuum, on opposite sides of the diaphragm, may be read directly on the manometer's control unit.

(48) (a) S. R. Byrn, Ph.D. Thesis, University of Illinois, 1971, pp 126–127; (b) T. S. Woods, Ph.D. Thesis, University of Illinois, 1972, p 165. Available from University Microfilms, Ann Arbor, Mich. 48106.

(49) F. S. Fry, Jr., Ph.D. Thesis, University of Illinois, 1973. Available from University Microfilms, Ann Arbor, Mich. 48106.

Vapor pressure measurements for the compounds of interest, except 4-methoxy-6-methyl-2-thiopyrone, were made continuously increasing the temperature in 5–10° increments so that from six to eight separate vapor pressure readings could be made. The thio-2-pyrone **10** rapidly isomerized to the thio-4-pyrone **11** in the melt, thus necessitating a modified procedure for obtaining accurate vapor pressure data. In that case, a vapor pressure reading was made within 15 min after **10** had melted in the sample cell. This was the shortest time interval in which an equilibrium could be established throughout the system. After three consecutive, identical vapor pressure readings had been obtained at the established temperature, the sample cell was cooled rapidly and removed from the system, and an nmr spectrum of the condensed material on the walls of the cell was taken to ascertain the ratio of **10**:**11**. This procedure was repeated at four different temperatures, with a fresh sample of **10** placed in the cell prior to each new set of vapor pressure readings. The vapor pressure of **10** at each of the four temperatures was calculated by applying Raoult's law.

The heats of vaporization (ΔH_{vap}) were calculated from the slopes of the linear Clausius-Clapeyron plots of ln P_{vap} *vs.* 1/T for each of the compounds. The data are summarized in Table VI.

The accuracy of this technique was established by Fry, who obtained the accepted literature vapor pressure values for naphthalene.[49] A maximum error of ±5% deviation of the measured values from one another and from the literature value is obtained for the ΔH_{vap} of naphthalene in repetitive experiments. This error was used as the estimated error associated with each ΔH_{vap} calculated in the present study, with the exception of 4-methoxy-6-methyl-2-thiopyrone (**10**). In that case alone, the standard deviation and 95% confidence limit exceed the estimated 5% error; therefore, the calculated 95% confidence limit was used as the associated error. The estimated errors and linear correlation coefficient are also presented in Table VI.