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# Equilibration Studies: Amide–Imidate and Thioamide–Thioimidate Functions

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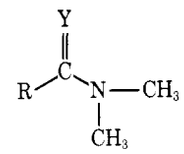
Heats of methylation and vaporization have been determined for the following isomer pairs: *N,N*-dimethylbenzamide (**1**)–*N*-methyl-*O*-methylbenzimidate (**2**); *N,N*-dimethylacetamide (**3**)–*N*-methyl-*O*-methylacetimidate (**4**); and *N,N*-dimethylthiobenzamide (**5**)–*N*-methyl-*S*-methylthiobenzimidate (**6**). These enthalpies are used to calculate liquid- and gas-phase enthalpy differences for the isomer pairs: [$\Delta H°_l$, $\Delta H°_g$ (kcal/mol)] $-17.8 \pm 1.8$, $-16.6 \pm 3.2$, **1–2**; $-17.0 \pm 1.5$, $-16.3 \pm 2.5$, **3–4**; $-4.5 \pm 0.7$, $-2.7 \pm 2.4$, **5–6**. These values are used, in conjunction with earlier studies, to suggest that the gas-phase enthalpy difference between an unstrained dialkylamide and the corresponding dialkylimidate will be $15 \pm 3$ kcal/mol, and the enthalpy difference between a dialkylthioamide and the corresponding dialkylthioimidate will be $2 \pm 3$ kcal/mol in favor of the amides. The enthalpy difference between an unstrained amide and its corresponding imidic acid isomer is estimated as $8 \pm 3$ kcal/mol in the vapor.

Gas-phase energy differences provide readily available fundamental data about chemical binding energies. This information can be useful in establishing relative chemical bond strengths and in testing energy predictions of current theory. Corresponding condensed-phase energy differences are important in understanding the effects of association and/or environment on molecular energies and in providing information about the prospective driving forces for chemical reactions.[1–4]

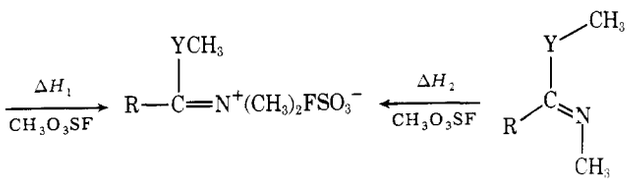
Our continuing studies of energy differences between alkylmeric and protomeric isomers have been most extensive for amide–imidic acid derivatives. We now report that the gas- and liquid-phase enthalpy differences between the *N,N*-dimethylamide–*N*-methyl-*O*-methylimidate and *N,N*-dimethylthioamide–*N*-methyl-*O*-methylthioimidate functions are unaffected by alkyl or aromatic substitution. This relative insensitivity to intramolecular environment, in conjunction with earlier data, suggests that parent systems provide useful guides to energy differences of alkylmeric isomers. This data also may be used to provide an estimate of the energy difference between parent amide–imidic acid systems.

## Results

Heats of methylation and heats of vaporization were determined for the isomer pairs *N,N*-dimethylbenzamide (**1**)–*N*-methyl-*O*-methylbenzimidate (**2**), *N,N*-dimethylacetamide (**3**)–*N*-methyl-*O*-methylacetimidate (**4**), and *N,N*-dimethylthiobenzamide (**5**)–*N*-methyl-*S*-methylthiobenzimidate (**6**) (Table I). The differences in the heats of methylation give the differences in liquid-phase enthalpies for the isomer pairs ($\Delta H°_l$, Table II).[5] Inclusion of the differences in the heats of vaporization in a standard thermodynamic cycle gives the differences in the gas-phase enthalpies ($\Delta H°_g$, Table II). In these cases, the differences in the heats of vaporization of each isomer and the resulting correction for the differential molecular environment in the condensed and vapor phases are not large. Apparently the intermolecular forces in these liquids, unlike those in previous cases, are comparable for each isomer of the pair.[2,6]



**1**, R = $C_6H_5$; Y = O
**3**, R = $CH_3$; Y = O
**5**, R = $C_6H_5$; Y = S



**2**, R = $C_6H_5$; Y = O
**4**, R = $CH_3$; Y = O
**6**, R = $C_6H_5$; Y = S

$\Delta H°_l = \Delta H_1 - \Delta H_2$

**Table I. Enthalpies of Methylation and/or Vaporization for Methyltropic Isomers 1–6 (kcal/mol)**

| Compd | $\Delta H°_{meth}$[a] | $\Delta H°_{vap}$[b] |
|---|---|---|
| 1 | $16.6 \pm 1.2$ | $14.8 \pm 0.7$ |
| 2 | $34.4 \pm 0.6$ | $13.6 \pm 0.7$[d] |
| 3 | $16.1 \pm 0.7$ | $10.9 \pm 0.5$[a] |
| 4 | $33.1 \pm 0.8$ | $10.2 \pm 0.5$ |
| 5 | $26.1 \pm 0.2$ | $17.6 \pm 0.9$ |
| | | $6.0 \pm 0.2$[c] |
| 6 | $36.6 \pm 0.3$ | $15.8 \pm 0.8$ |

[a] The estimated error is 5% (see ref 1 for discussion) for 3 runs in each case. [b] The error is the standard deviation. [c] The heat of fusion. [d] In kcal/mL.

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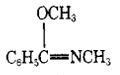
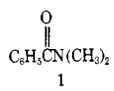
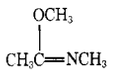
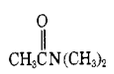
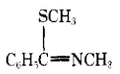
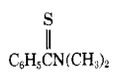
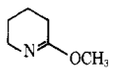
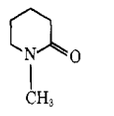
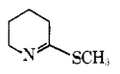
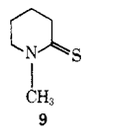
**Table II. Enthalpy Differences for the Isomer Pairs (kcal/mol)**

| Registry no. | Isomer pair[a] | Registry no. | $\Delta H°_l$ | $\Delta H°_g$[b] |
|---|---|---|---|---|
| 1775-61-7 |  2  1 | 611-74-5 | −17.8 ± 1.8 | −16.6 ± 3.2 |
| 3619-34-9 |  4  3 | 127-19-5 | −17.0 ± 1.5 | −16.3 ± 2.5 |
| 40780-82-3 |  6  5 | 15482-60-7 | −4.5 ± 0.7 | −2.7 ± 2.4 |
| 5693-62-9 |  8  7 | 931-20-4 | −17.4 ± 0.5[c] | −14.1 ± 2.0[c] |
| 19766-29-1 |  10  9 | 13070-07-0 | −4.6 ± 2.2[d] | −2.1 ± 3.2[d] |

[a] The amides and thioamides **1, 3, 5, 7,** and **9** are of lower enthalpy. [b] With the addition of 1.5 kcal/mol due to possible differences in kinetic and zero point energies, this value can be considered $\Delta E°_{\text{chem binding}}$. [c] Reference 6. [d] Reference 2.

**Table III. Combustion Analyses**

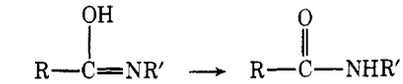
| Compound | Registry no. | % C | | % H | | % N | | % S | |
|---|---|---|---|---|---|---|---|---|---|
| | | Calcd | Obsd | Calcd | Obsd | Calcd | Obsd | Calcd | Obsd |
| *N,N*-Dimethyl-*O*-methylbenzimidatium fluorosulfonate | 60045-86-5 | 45.62 | 45.48 | 5.36 | 5.45 | 5.32 | 5.13 | 12.18 | 12.24 |
| *N,N*-Dimethyl-*O*-methylacetimidatium fluorosulfonate | 63985-90-0 | 29.84 | 29.74 | 6.01 | 5.86 | 6.96 | 6.97 | 15.94 | 16.00 |
| *N,N*-Dimethyl-*S*-methylthiobenzimidatium fluorosulfonate | 60011-05-4 | 42.98 | 42.69 | 4.96 | 4.96 | 5.01 | 5.01 | 22.96 | 22.77 |

The imidates **2** and **4** show a single NMR resonance for the *N*-methyl protons and are assigned the *E* configuration as shown.[7] The thioimidate **6** shows two *N*-methyl resonances, consistent with the 45:55 *E/Z* ratio previously assigned.[8]

## Discussion

The gas-phase enthalpy differences of 16.6 ± 3.2 for the acyclic aromatic amide–imidate isomer pair **1–2** and of 16.3 ± 2.5 for the acyclic alkyl amide–imidate isomer pair **3–4** are quite close to the value of 14.1 ± 2.0 for the cyclic alkyl amide–imidate isomer pair *N*-methylvalerolactam–*O*-methylvalerolactim (**7–8**), as shown in Table II. This comparison suggests that the enthalpy difference for unstrained dialkylamide–dialkylimidate pairs is relatively independent of the nature of the group bonded to carbon. A value of 15 ± 3 kcal/mol seems a reasonable estimate for this gas-phase energy difference.[9] The large energy difference in favor of the amide, which persists or is amplified in the liquid phase, provides a rationale for the driving force of a number of synthetically useful conversions.[2,10] The independence of the energy difference towards the intramolecular environment suggests that measurements of enthalpy differences of alkyltropic functional groups will serve as a useful guide for general enthalpy differences in a number of systems.[11,12]

Previous comparisons of the gas-phase enthalpy differences of 1-methyl-2-pyridone–2-methoxypyridine and 2-pyridone–2-hydroxypyridine[1] show that the net conversion of $NCH_3$, $OCH_3$ to NH, OH $\sigma$ bonds provides approximately 7.4 kcal/mol in favor of the OH isomer. Accordingly, it can be estimated that benzamide, *N*-alkylbenzamides, acetamide, and *N*-alkylacetamides will be 9 kcal/mol more stable enthalpically in the gas phase than the corresponding imidic acids. If these enthalpy estimates are generally applicable, a general gas-phase energy difference in favor of an unstrained amide over its imidic acid may be estimated as 8 ± 3 kcal/mol.



$\Delta H°_g = -8 \pm 3$ kcal/mol

A value of 26 kcal/mol has been calculated for the energy difference between formamide and its isomeric imidic acid.[13]

A comparison of the gas-phase enthalpy difference for **5–6** of 2.7 ± 2.4 kcal/mol with the previously determined value of 2.1 ± 3.2 kcal/mol for 1-methyl-2-thiopiperidone–2-methylthio-3,4,5,6-tetrahydropyridine (**9–10**) is given in Table II. It seems reasonable that this enthalpy difference will also be relatively insensitive to intramolecular environment and that a general enthalpy difference of 2 ± 3 kcal/mol may be assigned between unstrained dialkylthioamides–dialkylthioimidates. The previously noted destabilization of a thiocarbonyl isomer relative to the corresponding oxygen system clearly persists in this case.[2]

## Experimental Section

Melting points and boiling points are uncorrected. Elemental analyses were performed by Mr. J. Nemeth and associates.

The reactants **1**, **2**, **3**, **4**, **5**, and **6** were analytically pure materials which had physical properties, infrared spectra, and nuclear magnetic resonance spectra consistent with the assigned structures.[14] All materials are liquids except **5**. *Methyl fluorosulfonate is reported to be very toxic and should be handled with appropriate caution;*[15] it (Aldrich) was distilled and stored in a dry argon atmosphere at −15 °C.

***N,N*-Dimethyl-*O*-methylbenzimidatium fluorosulfate** was prepared from separate reactions of **1** and **2** with excess methyl fluorosulfonate in ethylene dichloride. Removal of the solvent and excess methylating agent in vacuo gave quantitative yields: mp 95–98 °C; NMR (acetonitrile-$d_3$) $\delta$ 7.70 (ArH), 3.90 ($OCH_3$), 3.42, 3.13 [$N(CH_3)_2$]; IR (Nujol) 1610, 1600, 1510 $cm^{-1}$;[16] combustion analysis, Table III.

***N,N*-Dimethyl-*O*-methylacetimidatium fluorosulfonate** was prepared by a procedure similar to that used above from **3** and from **4**: mp 117–120 °C; NMR (acetonitrile-$d_3$) $\delta$ 4.00 ($OCH_3$), 3.18, 3.07 [$N(CH_3)_2$], 2.35 ($CCH_3$); IR (Nujol) 1680 $cm^{-1}$;[16] combustion analysis, Table III.

***N,N*-Dimethyl-*S*-methylthiobenzimidatium fluorosulfonate** was prepared by a procedure similar to that used above from **5** and from **6**: mp 103–106 °C; NMR ($Me_2SO$-$d_6$) $\delta$ 7.33 (ArH), 3.55, 3.20 [$N(CH_3)_2$], 2.17 ($SCH_3$); IR (Nujol) 1616, 1269, 1068, 774 $cm^{-1}$;[16] combustion analysis, Table III.

**Heats of methylation and vaporization for 1–6 and the heat of fusion of 5** were determined by the techniques previously described.[2] The only detectable products from the calorimetric runs were the fluorosulfonate salts. The salts were isolated and shown to be virtually identical with authentic material by IR and NMR criteria.

**Acknowledgment.** We are grateful to the National Science Foundation for support of this work.

**Registry No.**—Methyl fluorosulfonate, 421-20-5.

## References and Notes

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(4) P. Beak, J. Covington, and S. G. Smith, *J. Am. Chem. Soc.*, **98**, 8284 (1976).
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(8) W. Walter and C. O. Meese, *Chem. Ber.*, **109**, 922 (1976).
(9) Justification for the assumption that differences in kinetic energies of the isomers will lead to enthalpy differences which are negligible with respect to the enthalpy differences is given in ref 2 and 6.
(10) For examples, see L. E. Overman and L. A. Clizbe, *J. Am. Chem. Soc.*, **98**, 2353 (1976); L. E. Overman, *ibid.*, **98**, 2901 (1976); R. G. Glushkov and V. B. Granik, *Adv. Heterocycl. Chem.*, **12**, 185 (1970); and ref 2, footnotes 35 and 36.
(11) For another example, note that the enthalpy differences of a 2- and 4-pyrone system and a 2- and 4-pyridone system are 9.7 ± 2.3 kcal/mol: P. Beak, T. S. Woods, and D. S. Mueller, *Tetrahedron*, **28**, 5507 (1972), and ref 2.
(12) It is possible to perturb the amide–imidate enthalpy difference by intramolecular effects. For example, as earlier noted,[6] the enthalpy difference is reduced by 6 kcal/mol when the functions are part of an aromatic ring, a result which allows a thermodynamic estimate of the relative aromaticity of the pyridine and pyridone rings. For discussion, see A. K. Burnham, J. Lee, T. G. Schmalz, P. Beak, and W. H. Flygare, *J. Am. Chem. Soc.*, **99**, 1836 (1977).
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(15) D. M. W. Van den Ham and D. Van der Meer, *Chem. Eng. News*, **54**, 5 (1976).
(16) Satisfactory analytical data were obtained.

# Modified Cephalosporins: Synthesis of Benzo[3,4]cephams[1]

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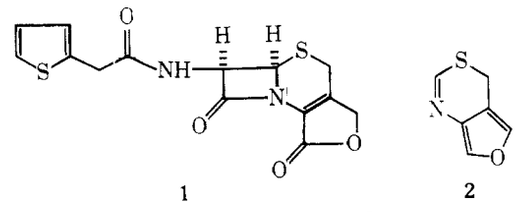
*Received August 4, 1977*

A synthetic route to a benzo[3,4]cepham system is described. The key step of the synthesis involved treatment of the novel 7-*tert*-butoxycarbonyl-4*H*-benzo-3,1-thiazine (**4**) with azidoacetyl chloride and triethylamine to furnish the *trans*-$\beta$-lactam **13a**. Conversion of **13a** to the cephalosporin analogue **17** followed established synthetic methodology.

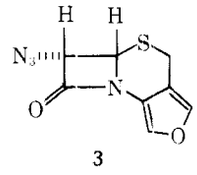
A novel totally synthetic route to (±)-desacetylcephalothin lactone (**1**) was recently reported from our laboratories, the key step being the reaction of azidoacetyl chloride/triethylamine with the novel 4*H*-furo[3,4-*d*]-1,3-thiazine (**2**) to give the furo[3,4]cephams **3**.[3] This paper describes the synthesis of benzo[3,4]cephams via the new thiazine **4**.



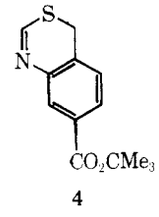
**1**



**2**

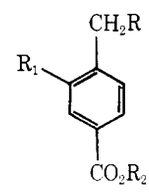


**3**



**4**

Reaction of 4-bromomethylbenzoic acid (**5**) with nitric acid gave the 3-nitro compound **6**, which was converted into the *tert*-butyl ester **7**. Silver perchlorate promoted hydrolysis of



**5**, R = Br; $R_1 = R_2 = H$
**6**, R = Br; $R_1 = NO_2$; $R_2 = H$
**7**, R = Br; $R_1 = NO_2$; $R_2$ = *tert*-butyl
**8**, R = OH; $R_1 = NO_2$; $R_2$ = *tert*-butyl
**9**, R = OH; $R_1 = NH_2$; $R_2$ = *tert*-butyl
**10**, R = OH; $R_1$ = NHCHO; $R_2$ = *tert*-butyl
**11**, R = OCHO; $R_1$ = NHCHO; $R_2$ = *tert*-butyl
**12**, R = Cl; $R_1$ = NHCHO; $R_2$ = *tert*-butyl

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