J. Am. Chem. Soc. **1994**, *116*, 2197–2198

# The Energy Components of the Anomeric Effect for 2-Methoxytetrahydropyran. An Experimental Comparison of the Gas Phase and Solutions

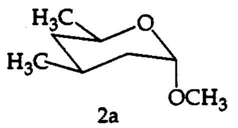
Kenneth B. Wiberg* and Manuel Marquez

*Department of Chemistry, Yale University*
*New Haven, Connecticut 06511*

*Received November 29, 1993*

The anomeric effect is probably the most studied of the "stereoelectronic effects" in organic chemistry[1] and has been examined both experimentally and theoretically. In the case of 2-methoxytetrahydropyran, the axial conformer (**1a**) is known to be preferred over the equatorial form (**1e**) by about 1 kcal/mol,[2,3] although it has been claimed that this is due to a difference in entropy rather than enthalpy.[4] It is also known that there is a difference in dipole moments between the anomeric forms of **1**,[5] and as a result there should be a significant solvent effect on the energy difference. Such effects have been noted by an examination of the solvent dependence of the NMR coupling constants, and of the optical rotation.[2,4] However, it is difficult to obtain very precise equilibrium constants using these methods, and it is even more difficult to obtain the enthalpy difference from the temperature dependence of the free energy change since the change in dielectric constant of the solvent with temperature contributes to the free energy change.[6]

In order to obtain better experimental data that might then be related to the dielectric continuum[7–9] and molecular dynamics models[10] for solvent effects, we have carried out calorimetric studies[11] of the heats of hydrolysis of the anomeric forms of 4,6-dimethyl-2-methoxytetrahydropyran (**2a** and **2e**).[12] The methyl groups act as conformational anchors and permit the two forms to be isolated. The hydrolysis reaction leads to the same products from the two anomers, and as a result the difference in heats of hydrolysis when the pure liquid compounds are added to 0.1 N HCl directly gives the difference in heats of formation as pure liquids at 25 °C. The data are shown in Table 1 and indicate an energy difference of 0.98 ± 0.07 kcal/mol.


2a


2e

**Table 1.** Enthalpies of Hydrolysis and Solution (cal/mol)

| medium | Δ*H* (**2a**) | Δ*H* (**2e**) | ΔΔ*H* |
|---|---|---|---|
| 0.1 N HCl[a] | −3321 ± 38 | −4301 ± 53 | 980 ± 65 |
| $CCl_4$ | −2493 ± 11 | −2486 ± 10 | −7 ± 15 |
| benzene | −2458 ± 11 | −2525 ± 11 | 67 ± 16 |
| *n*-$Bu_2O$ | −2802 ± 11 | −2976 ± 12 | 170 ± 16 |
| $(EtO_2)CHCH_3$ | −2988 ± 19 | −3290 ± 21 | 302 ± 28 |
| pyridine | −3209 ± 16 | −3618 ± 17 | 409 ± 23 |
| DMSO | −3642 ± 27 | −4072 ± 32 | 430 ± 42 |
| $Me_2C{=}O$ | −3140 ± 22 | −3612 ± 28 | 472 ± 36 |
| $CH_3CN$ | −3392 ± 30 | −3933 ± 30 | 541 ± 42 |
| $CH_3OH$ | −3000 ± 27 | −3782 ± 21 | 782 ± 34 |
| $H_2O$ | −2706 ± 11 | −3986 ± 25 | 1280 ± 27 |

[a] Hydrolysis reaction. The remaining entries are enthalpies of solution.

**Table 2.** Enthalpy, Free Energy, and Entropy Differences between **2a** and **2e** (cal/mol; cal/deg/mol)

| medium | $\Delta\Delta H_f$(**2e**–**2a**) | *K*(**2a**/**2e**) | Δ*G*(**2e**–**2a**) | Δ*S*(**2e**–**2a**) |
|---|---|---|---|---|
| gas phase | 1210 ± 70 | (7.0) | (1150) | 0.2[a] |
| pure liquid | 980 ± 65 | | | |
| $CCl_4$ | 987 ± 67[c] | 4.43 ± 0.10 | 882 ± 7 | 0.3 |
| benzene | 913 ± 67 | 5.37 ± 0.05 | 996 ± 6 | 0.0 |
| *n*-$Bu_2O$ | 810 ± 67 | 4.18 ± 0.06 | 848 ± 9 | −0.1 |
| $(EtO)_2CHCH_3$ | 678 ± 71 | 3.66 ± 0.13 | 769 ± 12 | −0.3 |
| pyridine | 571 ± 69 | *b* | | |
| DMSO | 550 ± 77 | 3.19 ± 0.11 | 687 ± 20 | −0.4 |
| $Me_2C{=}O$ | 508 ± 74 | 2.83 ± 0.06 | 617 ± 13 | −0.4 |
| MeCN | 439 ± 77 | 2.09 ± 0.02 | 436 ± 5 | 0.0 |
| $CH_3OH$ | 198 ± 73 | 2.12 ± 0.04 | 446 ± 7 | −0.8 |
| $H_2O$ | −300 ± 70 | *b* | | |

[a] Calculated from the vibrational frequencies and moments of inertia. [b] It was not possible to equilibrate the anomers in pyridine solution, and they underwent hydrolysis in acid aqueous solution. [c] The uncertainties include those for the pure liquid. The relative energies have considerably smaller uncertainties (cf. Table 1).

**Table 3.** Calculated Energies for **1a** and **1e**

| | **1a** | **1e**[a] | **1e′**[b] |
|---|---|---|---|
| HF/6-31G*, hartrees | −383.910 02 | −383.907 68 | −383.903 04 |
| $\mu$, D | 0.33 | 1.86 | 2.10 |
| $\Delta\Delta E$, kcal/mol | 0.00 | 1.47 | 4.38 |
| ZPE, kcal/mol[c] | 108.52 | 108.27 | 108.30 |
| $H° - H°_0$, kcal/mol | 5.66 | 5.69 | 5.68 |
| $\Delta\Delta H°$, kcal/mol ($\epsilon = 1$) | 0.00 | 1.25 | 4.18 |
| $S°$, eu | 86.41 | 86.64 | 86.55 |
| $\Delta\Delta G°$, kcal/mol ($\epsilon = 1$) | 0.00 | 1.18 | 4.14 |

[a] The lower energy 180, +sc equatorial rotamer. [b] The higher energy 180, −sc equatorial rotamer. [c] Based on HF/6-31G* frequencies scaled by 0.893.

We should like to determine the energy difference in the gas phase and in a variety of solvents. The difference in heats of vaporization is needed in order to correct the liquid-phase data to the gas phase. The heat of vaporization of **2a** was determined via ebulliometry, and the difference in heats of vaporization was obtained from these data and the experimentally determined difference in vapor pressures between **2a** and **2e** as a function of temperature. This gave $\Delta H_v$ of **2a** as 12.9 ± 0.1 kcal/mol and the $\Delta\Delta H_v$ as 0.23 ± 0.02 kcal/mol. The small difference is in accord with the very small difference in boiling point.[12] The gas-phase energy difference is then 1.21 ± 0.07 kcal/mol, in remarkably good agreement with the results of ab initio calculations for **1a** and **1e** (Table 3).[5,13] However, the effect of the extra methyl groups in **2a** and **2e** remains to be calculated.

The effect of a solvent on the relative energy could be determined from the difference in heats of solution of **2a** and **2e**. These data were obtained for a variety of solvents and are included in Table 1. It can be seen that solvents with a small dielectric constant, such as $CCl_4$ and benzene, have little effect on the energy

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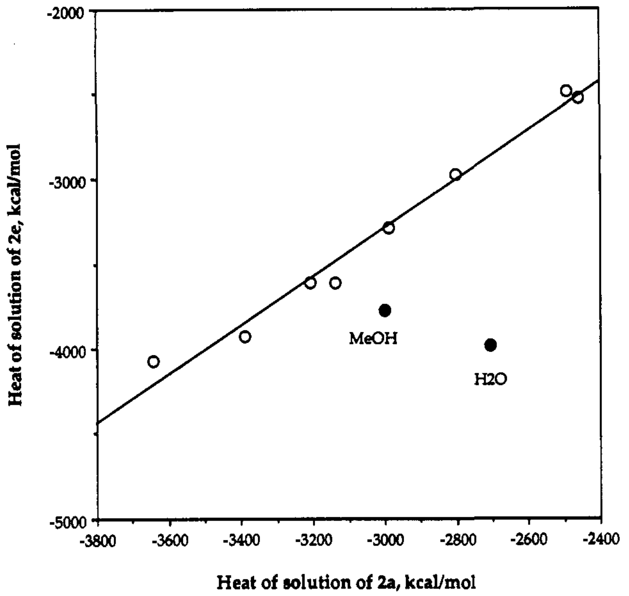

**Figure 1.** Relationship between heats of solution of the axial (**2a**) and equatorial (**2e**) forms of 4,6-dimethyl-2-methoxytetrahydropyran.

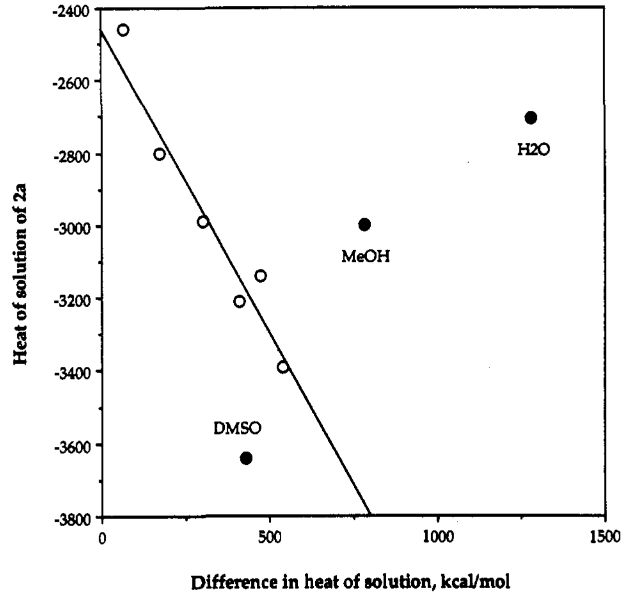

**Figure 2.** Relationship between the heat of solution of **2a** and the difference between the heats of solution of **2a** and **2e**.

difference, and that it decreases with increasing solvent dielectric constant. The hydroxylic solvents give the largest effect. Water reverses the relative energies of **2a** and **2e**.

It is clear that the energy difference between **1a** and **1e** observed by NMR is mainly an enthalpy effect and is not due to entropy. This conclusion is in accord with our calculation of the entropy difference between **1a** and **1e**.[5] It nevertheless seemed important to determine independently if solvents may cause a significant entropy difference between the anomeric forms. It was found that **2a** and **2e** could be equilibrated in a number of solvents via the use of an acid catalyst.[14] The ratio of the two forms could be determined either by gas chromatography after neutralizing the acid catalyst or via NMR spectroscopy. The two methods gave the same result. The equilibrium constants, free energy changes, and enthalpy changes are summarized in Table 2, along with the calculated entropy changes. It can be seen that the entropy changes are essentially 0 from the gas phase to solutions.

These data allow one to determine which solvents are relatively free from specific interactions with **2a** and **2e**. Such information is important, for only these solvents are appropriate for a self-consistent reaction field treatment of solvent effects. If a solvent only modifies the electrostatic energy of the compounds, then the heats of solution should be related. This may be examined in Figure 1, which shows a linear correlation for most of the solvents, but also clearly shows that methanol and water do give specific interactions, presumably via hydrogen bonding. A more stringent test is found in a comparison of the heat of solution of one anomer (**2a**) with the difference in heats of solution between **2a** and **2e** (Figure 2). Here, it can be seen that DMSO also behaves differently than the nonassociating solvents. This may be related to the self-association of this solvent.[15]

The observation of a significant solvent effect on both the $\Delta H$ and $\Delta G$ of isomerization shows that a large component of the anomeric effect is the electrostatic interaction between the C–O dipoles that is reduced, but cannot be completely eliminated, by going to a solvent with a high dielectric constant. This is in accord with recent observations of Perrin, Anderson, and Fabian on the effect of replacing the ring oxygen with nitrogen.[16] The calorimetric measurement of the heats of solution also provides a means of experimentally determining which solvents are nonassociating for a given system. The data show that the hydrogen-bonding solvents, methanol and water, give specific interactions with **2a** and **2e** beyond the effect of their dielectric constants.

We have carried out a corresponding study for the two anomeric forms of 4,6-dimethyl-2-methoxy-1,3-dioxane, and we are examining the solvation effects suggested by several SCRF models. Here, it should be noted that Jorgensen et al.[17] have calculated via statistical perturbation theory that the equatorial conformer of **1** is stabilized relative to the axial by 0.11 kcal/mol in $CCl_4$, 1.6 kcal/mol in acetonitrile, and 2.1 kcal/mol in water, and Montagnani and Tapia[8] using a SCRF model calculated a 0.6 kcal/mol change in $CCl_4$ and 1.4 kcal/mol in water. The effect of the methyl groups in **2a** and **2e** on the results of the calculations is presently being studied. The results of these studies will be presented in a subsequent report.

**Acknowledgment.** This investigation was supported by the National Institutes of Health.

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