of the arm consisted of a "thirsty glass" plug sealed in place with heat-shrinkable polyethylene. The tip was positioned as close to the working electrode as possible to minimize ohmic drop.

Tetra-*n*-butylammonium perchlorate (Eastman), the supporting electrolyte, was purified by recrystallization from ethyl acetate twice and drying in vacuo at 140 °C for 10 h. It was stored in the drybox. All cell preparations were done in the drybox and all electrochemical experiments were performed under N_2 atmosphere in quiet solutions. Typically, 70 mL of solvent and 10 g of n-Bu_4NClO_4 were used. Samples were 1 mM in concentration.

D. Attempted Addition of an Alkenyl Group to *p*-Benzoquinone Catalyzed by Ni(acac)$_2$–Dibah. Nickel bis(acetylacetonate) (0.0825 g, 0.32 mmol) was dissolved in 3 mL of THF, cooled to 0 °C, and reduced with Dibah (0.65 mL, 0.5 M). Via a dropping funnel were added sublimed *p*-benzoquinone (0.2307 g, 2.14 mmol) and **6** (1.1 g, 3.12 mmol) in 10 mL of THF. After 2 h at 0 °C the dark solution turned yellowish. At 4 h the reaction mixture was an orange homogeneous solution. It was hydrolyzed with saturated aqueous NH_4Cl, washed with $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. A yellowish solid was obtained: NMR (C_6D_6) δ 7.1 (s). Minor signals at ca. δ 1 were detected. No vinylic protons were present.

E. Reduction of *p*-Benzoquinone with Ni(acac)$_2$–Dibah. Nickel bis(acetylacetonate) (0.07 g, 0.27 mmol) was dissolved in 10 mL of ether and cooled to −78 °C. It was reduced with an equimolar amount of Dibah (0.36 mL, 0.75 M) and stirred until the solution color was dark brown. *p*-Benzoquinone (0.114 g, 1.1 mmol) in 25 mL of THF was added via cannula. The dark reaction mixture was stirred at −78 °C for 45 min, after which it was hydrolyzed by pouring into dilute aqueous H_2SO_4. It was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to give a brownish yellow solid. Analysis by GC/MS on column E gave a component with m/e 110, with a fragmentation pattern identical with that of standard *p*-hydroquinone. Other identifiable, high molecular weight components were present.

General Procedure for the Nickel-Catalyzed Cross-Coupling of an Alkenyl Group from 6 with Aryl Halides. The following general procedure illustrates the cross-coupling reaction catalyzed by nickel compounds. Ni(acac)$_2$ (0.0243 g, 0.10 mmol) was dissolved in 5 mL of THF [for studying the Negishi catalyst system, PPh_3 (4 equiv) was added at this point] and cooled to 0 °C. Dibah (0.13 mL, 0.75 M) was syringed in. Chlorobenzene (0.1163 g, 1.0 mmol), **6** (0.6 g, 1.77 mmol), and undecane, internal standard (0.0478 g), dissolved in 10 mL of THF, were added dropwise. The reaction was stirred at 0 °C for 3.5 h, then worked up in the usual manner and analyzed by VPC and GC/MS. Column F was used for iodobenzene experiments while column E was used for bromo- and chlorobenzene because of separation problems. Spectral data for **17** are as follows: ^{1}H NMR (CCl_4) δ 7.2 (m, 5), 6.28 (d, 1, J = 16 Hz), 6.10 (d, 1, J = 16 Hz), 1.1 (s, 9); mass spectrum m/e 160 (28.1), 145 (100), 117 (32.6), 91 (33.6), 77 (13.2). An identical procedure was performed using Ni(acac)$_2$–Dibah–4PPh$_3$ and Ni(acac)$_2$–**6**. In the former case PPh_3 was weighed into the flask together with Ni(acac)$_2$ prior to reduction with Dibah. In the latter case **6** and Ni(acac)$_2$ were weighed into the flask and dissolved in THF.

Acknowledgment. The authors acknowledge generous support for this work provided by the National Science Foundation (Grant No. CHE-79-00996). They also thank Professor M. F. Semmelhack for the use of his electrochemical equipment and Professor A. Bocarsly for helpful discussions.

Thermochemical Studies of Carbonyl Reactions. 2. Steric Effects in Acetal and Ketal Hydrolysis[1]

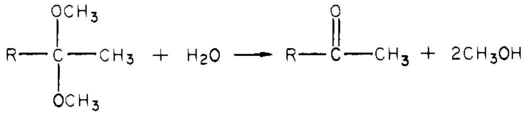
Kenneth B. Wiberg* and Robert R. Squires[2]

Contribution from the Department of Chemistry, Yale University, New Haven, Connecticut 06511. *Received November 14, 1980*

Abstract: A calorimetric determination of the enthalpies of hydrolysis of a series of alkyl-substituted dimethyl acetals is reported. These data are critically compared with the enthalpies of hydrolysis from an analogous set of aliphatic dimethyl ketals derived from 2-alkanones. The acetals exhibit a significantly attenuated range in their enthalpies of hydrolysis relative to that for ketal hydrolysis. The free energies of acetal formation in solution were modeled by measurements of the corresponding free energies of hemiacetal formation from the aldehydes in neutral methanol. The observed free-energy differences are satisfactorily correlated with the Taft E_s steric substituent constant scale, but the corresponding acetal enthalpy data vary in a complex manner. The role of entropy in determining kinetic and equilibrium steric effects in a variety of other systems is discussed. Preliminary molecular mechanics calculations on these systems indicate the importance of bond angle bending in evaluating the torsional potential at a carbonyl group. Many of the compounds were found to possess several conformations having comparable energies.

Steric effects on rates and equilibria are commonly observed in reactions that involve the interconversion of a trigonal carbon and a more crowded tetrahedral carbon. Examples of this type of reaction include the hydrolysis of aliphatic esters,[3] addition reactions of carbonyl compounds and olefins,[4] oxidations of secondary alcohols,[5] and the solvolysis of tertiary alkyl halides.[6] For many of these reactions the rate or equilibrium differences among the members of a reaction series correlated with the relative size of the substituent groups attached to the reaction center.[3,7]

We have obtained information on the enthalpy component of steric effects associated with trigonal–tetrahedral transformations by an examination of the enthalpies of hydrolysis of dimethyl ketals derived from alkyl methyl ketones[1] (eq 1). Through a combi-



$$R{-}C(OCH_3)_2{-}CH_3 + H_2O \longrightarrow R{-}C({=}O){-}CH_3 + 2CH_3OH \quad (1)$$

nation of calorimetric results with equilibrium constant mea-

---

[1] Part I: Wiberg, K. B.; Squires, R. R. *J. Am. Chem. Soc.* **1979**, *101*, 5512.

[2] Taken in part from the Ph.D. Thesis of RRS, 1980.

[3] Taft, R. W. In "Steric Effects in Organic Chemistry"; Newman, M., Ed.; Wiley: New York, 1956; Chapter 13.

[4] Newman, M. S. ref 3, Chapter 4.

[5] Wiberg, K. B. "Oxidation in Organic Chemistry"; Academic Press: New York, 1965.

[6] Fry, J. L.; Badger, R. C. *J. Am. Chem. Soc.* **1979**, *101*, 1680.

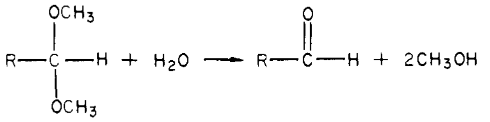
[7] Hine, J. "Structural Effects on Equilibria in Organic Chemistry"; Wiley-Interscience: New York, 1975.

Table I. Physical Properties of Dimethyl Acetals and Aldehydes

compd	bp, °C	*d* (20 °C) g/mL
acetal		
1,1-dimethoxyethane	67-69	0.850
1,1-dimethoxypropane	88-89	0.865
1,1-dimethoxybutane	115-116	0.845
1,1-dimethoxy-2-methylpropane	105-106	0.839
1,1-dimethoxy-2-methylbutane	133-134	0.849
1,1-dimethoxy-3-methylbutane	132-133	0.841
1,1-dimethoxy-2,2-dimethylpropane	120-121	0.844
1,1-dimethoxy-3,3-dimethylbutane	145-146	0.839
aldehyde		
2-methylbutanal	93-94	0.803
3-methylbutanal	94-95	0.797
3,3-dimethylbutanal	108-109	0.805

surements, we showed that the entropy term is dominant in determining the changes in free energy of hydrolysis.

We have now extended the study to the hydrolysis of aliphatic acetals (eq 2). A comparison of calorimetric and equilibrium



$$R-\overset{OCH_3}{\underset{OCH_3}{C}}-H + H_2O \longrightarrow R-\overset{O}{\overset{\|}{C}}-H + 2CH_3OH \qquad (2)$$

data for similarly substituted ketals and acetals may tell us whether the thermochemical trends are general for related systems and, further, may provide information on the role of the methyl group of the ketals in determining the magnitudes of the substituent effects.

Experimental Section

Materials. Each of the dimethyl acetals examined in this study was prepared from the corresponding aldehyde according to the standard methods previously described.[1] Pure acetal samples were obtained by repeated fractional distillation in an inert atmosphere from metallic sodium until the high-resolution NMR spectrum and IR spectrum showed no spurious signals attributable to anticipated impurities. Our previous work with dimethyl ketals showed these spectral assay techniques to be sensitive to approximately 0.1% impurity, and 100% purity was considered to have been achieved in each case.

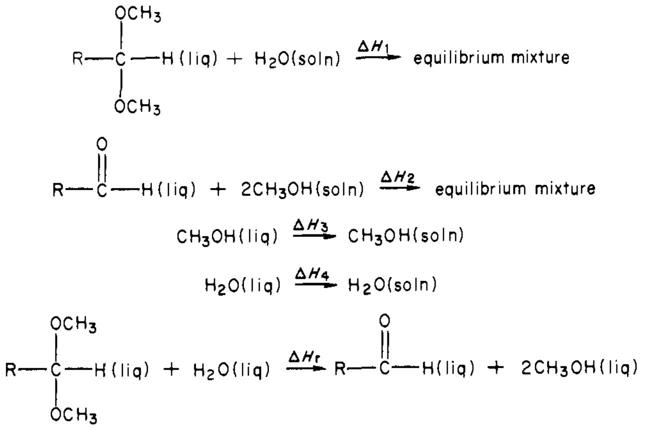
2-Methylbutanal, 3-methylbutanal, and 3,3-dimethylbutanal were prepared from the corresponding primary alcohols via pyridinium dichromate oxidation.[8] Samples of the eight aldehydes used for calorimetric and equilibrium measurements were purified immediately before use by drying with calcium chloride and distilling under nitrogen from a trace amount of hydroquinone. Gas chromatograms of each of the aldehydes purified in this fashion showed no impurities, reliable to <0.1%. The physical properties of the dimethyl acetals and the three synthesized aldehydes are presented in Table I. Methanol (Fisher) was purified by distillation under nitrogen from a mixture of methyl benzoate and sodium methoxide. A 1:1 (v/v) aqueous methanol reaction solvent[10] proved to be satisfactory for all of the acetals in the present study. It was prepared by mixing the appropriate amounts of methanol (Fisher, Spectranalyzed, used with no further purification), distilled water, and 70% perchloric acid (Fisher) to give a 50% (v/v) aqueous methanol solution which was approximately 0.25 N in $HClO_4$. A slightly alkaline methanol solution for the hemiacetal equilibrium studies was prepared by combining pure sodium methoxide and anhydrous methanol to yield a solution which was approximately 0.005 M in MeONa.

Calorimetic Measurements. All enthalpy measurements were performed with the automated reaction calorimetry system previously described.[11] Freshly purified samples of the acetals were sealed in thin-walled glass ampules and broken into the reaction solvent at precisely 25.000 °C. The reaction produces an equilibrium mixture of acetal, hemiacetal, hydrate, and aldehyde. The same mixture may be obtained by adding the corresponding aldehyde to the reaction solvent under identical conditions. Therefore, a combination of the enthalpies of reaction of the acetal and aldehyde with the reaction solvent along with the enthalpies of solution of methanol and water permits the calculation of the net enthalpy change corresponding to all components in the pure liquid phase.

Table II. Reaction of 2-Methylbutanal Dimethyl Acetal with 50% (v/v) Aqueous Methanol, 0.25 N in $HClO_4$, 25 °C

run no.	*E*,[a] cal/°C	Δ*T*, °C	*Q*, cal	sample wt, g	mol × 10^3	Δ*H*, cal/mol
1	90.292	0.126 88	11.456	0.485 88	3.675	3113
2	90.082	0.128 82	11.605	0.499 54	3.779	3068
3	89.866	0.114 09	10.253	0.443 89	3.358	3057
4	90.278	0.124 85	11.271	0.483 72	3.659	3084
5	90.330	0.120 87	10.918	0.462 71	3.500	3123
				mean value		3089 ± 25[b]

[a] Effective heat capacity of the reaction cell and contents based on an electrical calibration. [b] Uncertainty is twice the standard deviation of the mean ($2\bar{s}$).



$$R-\overset{OCH_3}{\underset{OCH_3}{C}}-H(liq) + H_2O(soln) \xrightarrow{\Delta H_1} \text{equilibrium mixture}$$

$$R-\overset{O}{\overset{\|}{C}}-H(liq) + 2CH_3OH(soln) \xrightarrow{\Delta H_2} \text{equilibrium mixture}$$

$$CH_3OH(liq) \xrightarrow{\Delta H_3} CH_3OH(soln)$$

$$H_2O(liq) \xrightarrow{\Delta H_4} H_2O(soln)$$

$$R-\overset{OCH_3}{\underset{OCH_3}{C}}-H(liq) + H_2O(liq) \xrightarrow{\Delta H_r} R-\overset{O}{\overset{\|}{C}}-H(liq) + 2CH_3OH(liq)$$

$$\Delta H_r(\text{pure liq}) = \Delta H_1 + \Delta H_4 - \Delta H_2 - 2\Delta H_3$$

Separate electrical calibrations were automatically performed for each of the chemical reaction runs. At the end of the experiment the data are transferred from the microprocessor to a larger computer for final analysis. A typical dataset for the exothermic heat of reaction of 2-methylbutanal with the aqueous methanol solvent is shown in Table II. In the case of the hydrolysis of 1,1-dimethoxyethane, Skinner and Birley[10] found ΔH_r = 8540 ± 70 cal/mol. Our value is in agreement with this result within the combined uncertainty intervals of the two determinations.

Equilibrium Measurements. Equilibrium mixtures of hemiacetal and aldehyde in slightly alkaline anhydrous methanol were assayed with a HA-100 NMR spectrometer as previously described.[1] Samples were prepared by weighing alkaline methanol and freshly purified aldehyde into a volumetric flask. The mixtures were allowed to stand for 1-3 h, after which time they were pipetted into NMR tubes for analysis at 25 °C. The achievement of true equilibrium was established by noting a constant area ratio over several hours time for NMR signals corresponding to analogous protons on the hemiacetal and aldehyde. The general approach for determining the equilibrium concentrations of the various components in the mixtures was to measure the areas of proton signals corresponding to groups of both the aldehyde and hemiacetal. The equilibrium composition may then be derived by a simultaneous solution of a set of constraining equations written in terms of mass action, the area ratios, and the fixed internal proton ratios of the reactants and products.[12] In a few cases it was possible to determine more than one independent area ratio corresponding to different types of protons on the aldehyde and hemiacetal. This made possible additional measurements of the equilibrium constant from a single NMR spectrum. A sample dataset from the analysis of 3,3-dimethylbutanal in alkaline methanol is given in Table III.

Results and Discussion

The reactions of acetals and aldehydes with 1:1 (v/v) $MeOH/H_2O$ were rapid in the presence of 0.25 M $HClO_4$. Half-lives for the total temperature change on the order of 60 s were calculated from computer simulations of the observed

---

(8) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

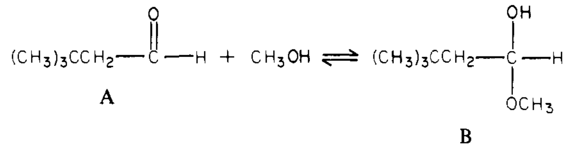
(9) Smith, E. L. *J. Chem. Soc.* **1927**, 1288.

(10) Skinner, H. A.; Birley, G. I. *Trans. Faraday Soc.* **1970**, *66*, 791.

(11) Wiberg, K. B.; Squires, R. R. *J. Chem. Thermodyn.* **1979**, *11*, 773.

(12) (a) Kasler, F. "Quantitative Analysis by NMR Spectroscopy"; Academic Press: New York, 1973; (b) Diehl, P.; Kellerhals, H. "Computer Assistance in the Analysis of High Resolution NMR Spectra"; Springer: New York, 1972.

Table III. Hemiacetalization of 3,3-Dimethylbutanal in Anhydrous Methanol, 0.005 M in Sodium Methoxide at 25 °C



initial concn (mole fraction)		NMR results (arbitrary units)		
aldehyde	CH_2OH	area A	area B	K_{hemi}
0.128 39	0.871 61	351 661[b]	576 174[b]	2.069
		16 958[a]	26 414[a]	1.963
0.151 36	0.848 64	75 562[a]	112 831[a]	1.970
		493 069[b]	756 859[b]	2.028
0.141 05	0.858 95	103 036[a]	164 379[a]	2.066
		409 094[b]	624 535[b]	1.973
0.127 18	0.872 82	87 757[a]	141 789[a]	2.034
		mean value		2.015 ± 0.035
		$\Delta G^{\circ c} = -415.1 \pm 10.0^{d}$ cal/mol		

[a] Area of signal corresponding to α-methylene protons. [b] Area of signal corresponding to *t*-Bu protons. [c] Standard state refers to dilute hemiacetal and aldehyde with pure methanol having unit activity. [d] Uncertainty is twice the standard deviation from the mean.

Table IV. Enthalpies of Hydrolysis of Acetals, 25 °C

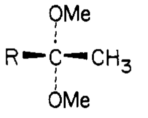
$$RCH(OCH_3)_2 + H_2O \rightarrow RCHO + 2CH_3OH$$

R	ΔH_r(acetal)[a,f]	ΔH_r(aldehyde)[b,f]	ΔH_r(liq)[c,g]
Me	532 ± 6 (5)[e]	−7795 ± 13 (5)	8622 ± 15
Et	991 ± 5 (4)	−7213 ± 16 (5)	8499 ± 17
n-Pr	1647 ± 13 (4)	−6790 ± 18 (5)	8732 ± 23
i-Pr	1829 ± 7 (5)	−6574 ± 14 (8)	8698 ± 16
i-Bu	2273 ± 18 (6)	−5774 ± 15 (4)	8342 ± 23
2-Bu	3089 ± 25 (5)	−4749 ± 21 (6)	8134 ± 33
t-Bu	3997 ± 5 (4)	−3633 ± 18 (4)	7925 ± 19
neopent	4013 ± 30 (3)	−3660 ± 18 (5)	7968 ± 35
CH_3OH		−246.5 ± 1.9 (5)	
H_2O		−198.0 ± 0.5 (4)	

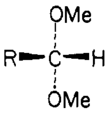
[a] Enthalpy of reaction of liquid acetal with 1:1 aq MeOH. [b] Enthalpy of reaction of liquid aldehyde with 1:1 aq MeOH. [c] Enthalpy of conversion of acetal to aldehyde with all components in the pure liquid state. [d] Enthalpy of solution in 1:1 aq methanol. [e] Number of runs is shown in parentheses. [f] Uncertainties are $2\bar{s}$. [g] Uncertainties are the root mean square sum of the component uncertainty intervals.

time/temperature profiles. High-resolution proton spectra of the final calorimetric reaction mixtures showed no signals other than those which may be assigned to the aldehyde and the acetal, hemiacetal, and/or hydrate. The enthalpy data for the series of eight acetals and aldehydes are summarized in Table IV.

The pure liquid phase enthalpies of hydrolysis of the acetals are compared with those for the corresponding ketals[1] in Table V. Taft's steric substituent constants (E_s)[3,13] are also shown in column 6 of Table V. The difference between these two closely related reactions is striking. The total range of enthalpy changes in columns 3 and 5 differs between the two series by more than 3 kcal/mol. The smaller effect observed with the acetals might be expected since the replacement of the methyl group in the ketals with a hydrogen would relax the steric interactions in the tetrahedral intermediate more than in the trigonal product.

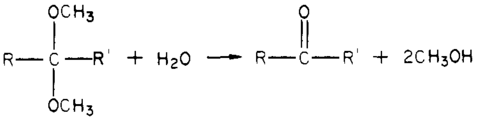


$$R-C(OMe)_2-CH_3$$



$$R-C(OMe)_2-H$$

Table V. Enthalpies of Hydrolysis of Ketals and Acetals, 25 °C[a]



$$RC(OCH_3)_2R' + H_2O \rightarrow RCOR' + 2CH_3OH$$

	ketals, R′ = CH_3		acetals, R′ = H		
R	ΔH_r	$\Delta\Delta H$	ΔH_r	$\Delta\Delta H$	E_s[3,13]
Me	4884 ± 7[b]	0	8622 ± 15	0	0.00
Et	4620 ± 8	−264	8499 ± 17	−123	−0.20
n-Pr	4666 ± 14	−218	8732 ± 23	110	−0.36
i-Pr	4858 ± 9	−26	8698 ± 16	79	−0.47
i-Bu	3284 ± 13	−1600	8342 ± 23	−280	−0.93
2-Bu	4762 ± 11	−122	8134 ± 33	−488	−1.13
t-Bu	819 ± 13	−4065	7925 ± 19	−697	−1.54
neopent	1642 ± 21	−3242	7968 ± 35	−654	−1.74

[a] Enthalpy of reaction in the pure liquid state. [b] Uncertainties are $2\bar{s}$.

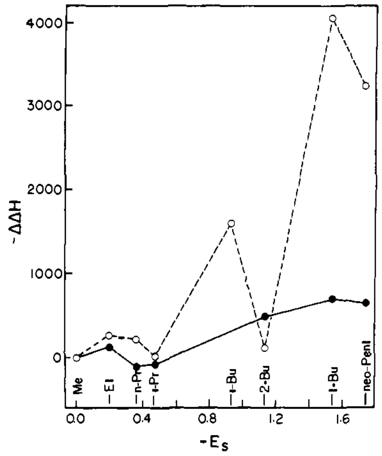


Figure 1. Relationship between the enthalpies of hydrolysis (cal/mol) of ketals (open circles) and of acetals (closed circles) and the Taft steric parameter, E_s.

Taft's E_s values and their many variations have been widely used in studying steric effects on free energies of activation and of reaction.[14,17] Currently, there are few examples in the literature in which enthalpies of reaction have been compared with these steric substituent constants.[18] Therefore, we have plotted the changes in enthalpy of acetal and ketal formation from aldehydes and ketones vs. E_s in Figure 1. It can be seen that although the acetal data do not give a good linear correlation with E_s, they at least do not give large fluctuations. Indeed, the data suggest that the enthalpy of acetal hydrolysis is remarkably insensitive to changes in the substituent alkyl group (approximate slope of acetal ΔH_r vs. E_s plot = 0.4). There are marked deviations in the ordering of the ketal data vs. E_s, with the greatest anomalies occurring in the cases where R = 2-butyl and R = neopentyl.

The small effect observed with the acetals is important with regard to the question of steric vs. polar effects of alkyl substituents in these reactions. If hyperconjugation or other polar interactions between alkyl groups and a carbonyl group were an important component of the apparent effect of the alkyl substitution, it should be more important for aldehydes than for methyl ketones. The aldehydes have only one alkyl group which may interact with the carbonyl, whereas the ketones have two, leading to a smaller effect per alkyl group. The small effect of alkyl substituents observed

---

(13) The Taft values[3] were used with the exception of that for the ethyl group. A considerable body of experience suggests that the ethyl group is roughly midway between methyl and propyl in its steric effect. Therefore we have arbitrarily used the value −0.2.

(14) Hancock, C. K.; Meyers, E. A. *J. Am. Chem. Soc.* **1961**, *83*, 4211.

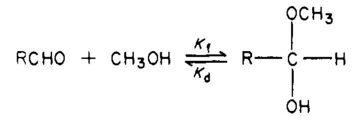
(15) Palm, V. A. "Fundamentals of the Quantitative Theory of Organic Reactions", Khimya: Leingrad, 1967; Chapter 10.

(16) MacPhree, J. A.; Panaye, A.; Dubois, J.-E. *Tetrahedron* **1978**, *34*, 3553.

(17) Charton, M. *J. Am. Chem. Soc.* **1975**, *97*, 1552.

(18) Brown, H. C. "Boranes in Organic Chemistry"; Cornell University Press: Ithica, NY, 1972; Part 2.

Table VI. Equilibrium Constants and Free Energies of Formation and Decomposition of Methyl Hemiacetals, 25 °C



$$\mathrm{RCHO} + \mathrm{CH_3OH} \underset{K_d}{\overset{K_f}{\rightleftharpoons}} \mathrm{R{-}C(OCH_3)(OH){-}H}$$

R	K_f[a]	$10^2 K_d$	$\Delta G_f^\circ = -\Delta G_d^\circ$
Me	18.85 ± 0.91 (7)[c]	5.306 ± 0.256	−1739 ± 29[b]
Et	14.09 ± 1.45 (5)	7.097 ± 0.730	−1567 ± 61
n-Pr	12.01 ± 0.60 (8)	8.326 ± 0.416	−1473 ± 30
i-Pr	9.177 ± 0.232 (4)	10.89 ± 0.28	−1313 ± 15
i-Bu	6.868 ± 0.199 (9)	14.56 ± 0.42	−1142 ± 17
2-Bu	4.659 ± 0.177 (3)	21.46 ± 0.82	−912 ± 23
t-Bu	2.387 ± 0.196 (4)	41.89 ± 3.44	−515 ± 49
neopent	2.105 ± 0.035 (7)	49.63 ± 0.86	−415 ± 10

[a] Standard state refers to dilute hemiacetal aldehyde in pure liquid methanol. [b] Uncertainty is twice the standard deviation from the mean. [c] Number of runs are shown in parentheses.

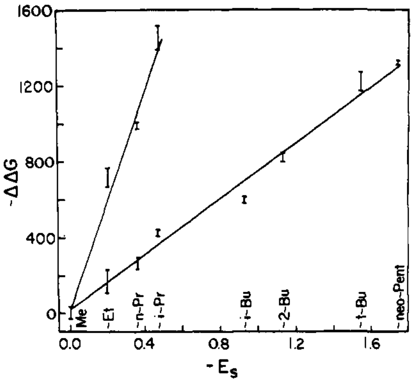


Figure 2. Relationship between the free energies of hydrolysis (cal/mol) of ketals (upper line) and of acetals (lower line) and the Taft steric parameter, E_s.

with the acetals suggests that polar interactions are negligible and that the larger effects seen with the ketals represent true steric effects.

The Taft steric parameters are derived from the relative free energies of activation for acid-catalyzed ester hydrolysis rather than from enthalpies.[3] It was therefore of interest to examine whether or not the free energies of acetal formation from aldehydes were linearly related to E_s. Solutions of aldehydes in dry methanol containing an acid catalyst were found to contain essentially no free aldehyde. The addition of water to the solution allowed an observable amount of aldehyde to be formed, but here there is a complex equilibrium among free aldehyde, acetal, hemiacetal, and hydrate.[19] We were unable to find a reliable analytical method which could give the concentrations of each these species and permit a satisfactory evaluation of the acetal formation equilibrium constant. For this reason we have examined the more easily determine case of the equilibrium between aldehyde and hemiacetal in dry neutral methanol.[20] The steric effects should be similar for hemiacetal and acetal formation, and the free-energy changes in the former system should provide a reasonable model for those in the latter. The equilibrium constants and corresponding free-energy changes for the series of eight aldehydes are shown in Table VI.

A plot of ΔG° for hemiacetal formation vs. E_s (Figure 2) shows a rather good linear correlation. The equilibrium data for ketal formation which we reported in our earlier work[1] are also shown in Figure 2, and the ratio of the two slopes is on the order of 1:4.

It can be seen in Table VII that the entropy contribution to the free-energy substituent effect for ketal hydrolysis is considerably larger than the enthalpy component. An analogous determination of the entropy contribution to the substituent effects in acetal hydrolysis could not be achieved for two reasons. First, it was not possible to correct the enthalpy data for the pure liquid phase hydrolysis to that in methanolic solution because the enthalpy of solution of the aldehyde (without reaction) cannot be measured. Second, we were not able to measure equilibrium constants for acetal hydrolysis directly or indirectly. In order to obtain a rough idea of the relative magnitudes of the entropy component, we have combined the pure liquid phase enthalpies of acetal hydrolysis with solution phase free energies for hemiacetal decomposition. These data are shown in Table VIII. Obviously, a combination of the irregularly changing acetal hydrolysis enthalpies with the E_s linear hemiacetal data will yield irregular entropy differences. However, it is instructive to note that while the entropy terms generally increase with increasing substituent size, this increase is attenuated with the largest of the groups.

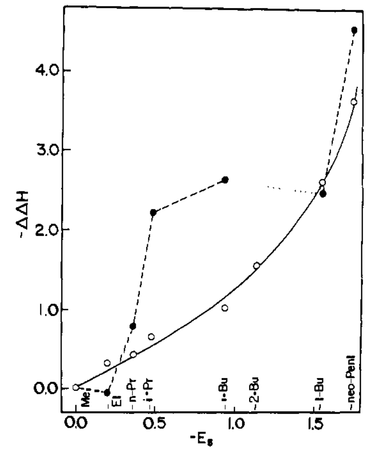
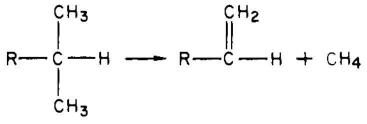
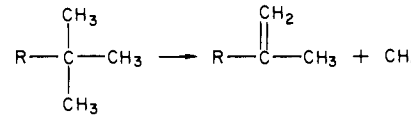


Figure 3. Relationship between the enthalpies of the hydrocarbon reactions 3 and 4 (kcal/mol) and the Taft steric energy parameter, E_s.

In order to put these results into perspective, we should like to compare them with thermochemical data from other reactions involving similar structural changes. A pair of hypothetical reactions which are formally related to ketal and acetal hydrolysis are shown in eq 3 and 4. Taft had previously examined these

 (3)

$$\mathrm{R{-}C(CH_3)_2{-}H} \longrightarrow \mathrm{R{-}C({=}CH_2){-}H} + \mathrm{CH_4} \quad (3)$$

 (4)

$$\mathrm{R{-}C(CH_3)_2{-}CH_3} \longrightarrow \mathrm{R{-}C({=}CH_2){-}CH_3} + \mathrm{CH_4} \quad (4)$$

reactions,[3] but improved data on the enthalpies of formation of the hydrocarbons have subsequently becomes available.[21] The calculated heats of reaction are recorded in Table IX and are plotted against E_s in Figure 3. The first reaction, which corresponds to acetal hydrolysis, does not correlate with E_s but at least gives a smooth curve. The second, which corresponds to ketal hydrolysis, gives no correlation with E_s and varies from substituent to substituent in a complex manner. Interestingly, the difference in the total range of enthalpy changes between the two series is only 1 kcal, as compared to a 3-kcal difference between the acetals and ketals. This must be due at least in part to the differences in conformational requirements between carbonyl groups and carbon–carbon double bonds.[22]

---

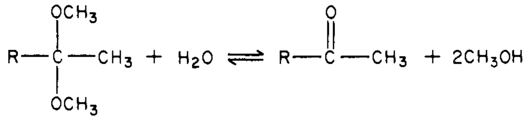
[19] (a) Bell, R. P. *Adv. Phys. Org. Chem.* **1966**, *4*, 1; (b) Schmitz, E.; Eichorn, I. "The Chemistry of the Ether Linkage"; Patai, S., Ed.; Interscience: New York, 1967; Chapter 7.

[20] Jencks, W. P. *Prog. Phys. Org. Chem.* **1964**, *2*, 63.

[21] Cox, J. D.; Pilcher, G. "Thermochemistry of Organic and Organometallic Compounds"; Academic Press: London, 1970.

[22] In propanal (Butcher, S. S.; Wilson, E. B. *J. Chem. Phys.* **1964**, *40*, 1641), the cis conformation is preferred by 900 cal/mol, whereas in 1-butene (Kondo, S.; Hirota, E.; Morino, Y. *J. Mol. Spectrosc.* **1968**, *28*, 471) the cis and gauche conformations have about equal energies.

Table VII. Thermodynamic Profile of Substituent Effects for Ketal Hydrolysis in Methanol Solution at 25 °C[a]

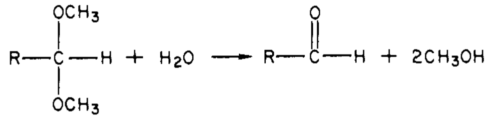


$$R{-}C(OCH_3)_2{-}CH_3 + H_2O \rightleftharpoons R{-}C(=O){-}CH_3 + 2CH_3OH$$

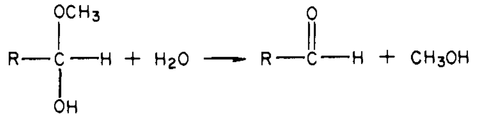
R	$E_s^{3,13}$	ΔG_r, cal/mol	$\Delta\Delta G$, cal/mol	ΔH_r, cal/mol	$\Delta\Delta H$, cal/mol	ΔS, eu	$\Delta(T\Delta S)$, cal/mol
Me	0.00	-780	0	5483	0	21.00	0
Et	-0.20	-1502	-722	5184	-299	22.42	423
n-Pr	-0.36	-1784	-1004	5132	-351	23.20	656
i-Pr	-0.47	-1475	-1475	5325	-158	25.42	1318

[a] The data are taken from ref 1. The equilibrium constants have been recalculated taking the standard state as dilute ketal and ketone in methanol, with pure methanol having unit activity. The changes in free energy are essentially unaffected.

Table VIII. Acetal Hydrolysis and Hemiacetal Decomposition



$$R{-}CH(OCH_3)_2 + H_2O \longrightarrow R{-}C(=O){-}H + 2CH_3OH \quad (1)$$

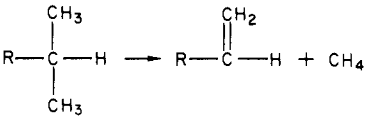


$$R{-}CH(OCH_3)(OH) + H_2O \longrightarrow R{-}C(=O){-}H + CH_3OH \quad (2)$$

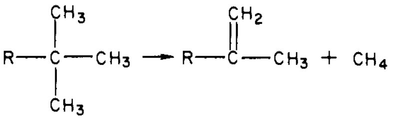
	$\Delta G(2)$,[a] cal/mol	$\Delta H(1)$,[b] cal/mol	ΔS,[c] eu	$\Delta\Delta H$, cal/mol	$\Delta(T\Delta S)$, cal/mol
Me	1740	8622	23.08	0	0
Et	1567	8499	23.25	-123	51
n-Pr	1473	8732	24.35	110	378
i-Pr	1313	8698	24.77	76	504
i-Bu	1142	8342	24.15	-280	319
2-Bu	912	8134	24.22	-488	340
t-Bu	515	7925	24.85	-697	528
neopent	415	7968	25.33	-654	671

[a] Free energy of hemiacetal decomposition, 25 °C. [b] Enthalpy of acetal hydrolysis, liquid phase, 25 °C. [c] Calculated entropy change from *a* and *b*.

Table IX. Enthalpies of Hypothetical Reaction of Methane with 1-Alkenes, 25 °C[a]



$$R{-}CH(CH_3)_2 \longrightarrow R{-}C(=CH_2){-}H + CH_4 \quad (1)$$



$$R{-}C(CH_3)_3 \longrightarrow R{-}C(=CH_2){-}CH_3 + CH_4 \quad (2)$$

R	$\Delta H(1)$, kcal/mol	$\Delta\Delta H$, kcal/mol	$\Delta H(2)$, kcal/mol	$\Delta\Delta H$, kcal/mol	$E_s^{3,13}$
Me	19.09	0.00	18.08	0.00	0.00
Et	18.77	-0.32	18.15	0.07	-0.20
n-Pr	18.66	-0.43	17.29	-0.79	-0.36
i-Pr	18.44	-0.65	15.86	-2.22	-0.47
i-Bu	18.08	-1.01	15.46	-2.62	-0.93
2-Bu	17.53	-1.52	*b*	*b*	-1.13
t-Bu	16.48	-2.61	15.62	-2.46	-1.54
neopent	15.45	-3.64	13.51	-4.57	-1.74

[a] Enthalpy of formation data from ref 19. [b] The enthalpies of formation for 2,2,3-trimethylpentane and 2,3-dimethyl-1-pentene are presently unknown.

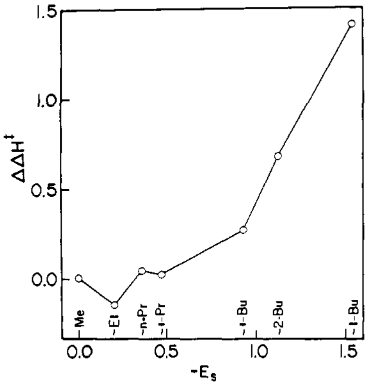


Figure 4. Relationship between the enthalpies of activation for ester hydrolysis (kcal/mol) and the Taft steric energy parameter, E_s.

It would be interesting to examine the equilibrium constants for these reactions so that the relative importance of entropy and enthalpy might be ascertained. Unfortunately, the entropies of all the compounds have not been determined and the estimated values[23] for the remaining compounds are not sufficiently reliable for the present purpose.

The E_s scale was derived from the kinetics of acid-catalyzed ester hydrolysis.[3] Data are available on the corresponding enthalpies and entropies of activation,[24-26] which also might be compared with our calorimetric results. Although kinetically derived thermochemical properties such as these are usually characterized by large uncertainties,[27] a simple plot of $\Delta H^\ddagger$ vs. E_s (Figure 4) does not even suggest a linear relationship. Further, the entropy components of the relative free energies of activation are generally larger than the enthalpy terms.

In summary, for reactions involving tetrahedral–trigonal interconversions, free-energy changes are generally well correlated with the E_s scale. However, the same is not true with the corresponding enthalpy changes. It is clear that an understanding of the role of entropy changes in determining the magnitudes of steric effects is needed.

A reaction entropy may change in response to structural modification in the reactants for two principal reasons. With reactions in solution which involve polar species, the solvation of the reactants and products may be subject to steric constraints.[28] Therefore, changing substituents may influence the entropy of solvation term in the overall free energy of reaction.[29] Most of the reactions of ketones, aldehydes, and esters for which free-energy changes have been measured have been studied in hydroxylic solvents. Here, hydrogen bonding with the carbonyl

---

(23) (a) Benson, S. W. "Thermochemical Kinetics"; Wiley: New York, 1968; (b) Stull, D. R.; Westrum, E. F., Jr.; Sinke, G. C. "The Chemical Thermodynamics of Organic Compounds"; Wiley: New York, 1969.

(24) Smith, H. A. *J. Am. Chem. Soc.* **1939**, *61*, 254.

(25) Smith, H. A.; Myers, R. R. *J. Am. Chem. Soc.* **1942**, *64*, 2362.

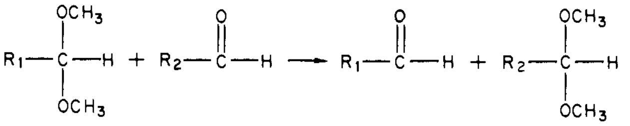
(26) Smith, H. A.; Burn, J. *J. Am. Chem. Soc.* **1944**, *66*, 1494.

(27) Ritchie, C. D.; Sager, W. F., *Prog. Phys. Org. Chem.* **1964**, *2*, 323.

(28) Taft, R. W.; Beauchamp, J. L.; Arnett, E. M. *J. Am. Chem. Soc.* **1978**, *100*, 1240; Schubert, W. M.; Sweeney, W. A. *J. Org. Chem.* **1956**, *21*, 119.

(29) Cf. Arnett, E. L.; Reich, R. *J. Am. Chem. Soc.* **1980**, *102*, 5901, for another example of a reaction in which entropy changes due to solvation are important.

carbon would be important and this interaction would be subject to steric effects. The best way to determine the effects of solvation would be to measure the corresponding thermochemical properties in the gas phase. Enthalpies of hydrolysis in the vapor phase could be obtained through a knowledge of the heats of vaporization of each of the reactants and products. While measurements of this type are fairly routine,[30] the corresponding free energies for transfer of the reaction components between methanol and the vapor phase would be experimentally difficult to obtain.[31] One partial solution to the problem would be to minimize the effects of solvation by measuring the relative free energies of hydrolysis via an acid-catalyzed transacetalization reaction. Such a reaction



$$R_1-\overset{OCH_3}{\underset{OCH_3}{C}}-H + R_2-\overset{O}{\overset{\|}{C}}-H \longrightarrow R_1-\overset{O}{\overset{\|}{C}}-H + R_2-\overset{OCH_3}{\underset{OCH_3}{C}}-H$$

could be examined either with pure reactants (i.e., no solvent) or in a nonhydroxylic solvent, which leads to relatively ideal solutions. Although there are analytical problems in determining such equilibrium constants, preliminary results in our laboratory suggest that they can be overcome.

The second factor which might lead to changes in entropy through the above series arises from internal contributions. These are most likely a function of internal rotational characteristics. Increasing the steric bulk of a substituent at a reaction center can cause not only an increase in the potential energy due to compressing together the atoms of the groups, but also a significant hindrance to internal motions. The latter effect will show up largely as an entropy term.[32] The internal motion problem is not readily susceptible to direct experimental study. However, in principle, it may be attacked by molecular mechanics calculations.[33] These calculations, if properly parameterized, will give the geometry needed to derive the rotational partition function. Many of the modern force fields can provide estimates of the vibrational frequencies[34] which are generally adequate to allow the calculation of the vibrational partition function. The contribution from internal rotation frequently may be estimated from the calculated low-frequency vibrations.[35] With these quantities in hand, the absolute entropies of the species involved in the steric interactions may be calculated.

The successful application of molecular mechanics requires physically realistic potential functions for each of the valence and nonbonded interactions in the molecule. Acetals, ketals, ketones, and aldehydes thus require suitable parameters for representing the interactions about an oxygen.[36] Unfortunately, there are not adequate data for reliable parameterization of all of these terms. In order to see what problems may arise in using this method for the estimation of equilibrium geometries, energies, and entropies of the compounds discussed above, we have used the nonbonded parameters for a carbon as a rough approximation to those for oxygen. A torsional potential function was developed[37] which satisfactorily reproduced the known "anomeric effect"[38] operative in the ketals and acetals. A separate form of the torsional potential function had to be parameterized for the ketones and aldehydes in order to account for the preferred conformations which eclipse the α substituents and the carbonyl oxygen.[39]

Table X. Effect of Alkyl Substituents on the Bond Angles in Ketals, Acetals, and Carbonyl Compounds[a]

R	acetals[c]	aldehydes[b]	ketals[c]	ketones[b]
Me	110.4	110.4	110.6	110.4
Et	112.7	113.6	115.1	113.7
n-Pr	112.7	113.6	115.2	113.7
i-Pr	111.5	112.4	113.5	112.5
i-Bu	114.9	114.6	117.8	115.0
2-Bu	111.4	111.9	113.5	111.9
t-Bu	110.9	111.3	112.3	110.9
neopent	117.1	117.5	121.4	118.0

[a] The bond angle is that for the most stable conformer. [b] C-C-C or H-C-C angle for bond eclipsed to carbonyl. [c] C-C-C or H-C-C angle for bond gauche to hydrogen or methyl on acetals and ketals, respectively.

Calculations of this sort have recently been applied to a series of ketones by Suter.[40] However, he maintained fixed bond angles and distances for all values of the R-C-CO torsional angle. We have allowed these parameters to vary, constrained only by ordinary bond angle bending and stretching potentials. We have found that large changes in these so-called "hard" valence coordinates are calculated as the R-C-CO torsional angle is varied.

In order to demonstrate that bond angle deformation is an important conformational relaxation mechanism with the sterically congested alkyl groups,[41] we have presented in Table X the calculated C-C-C and H-C-C bond angles for the bonds α to the acyl carbon in ketones, ketals, aldehydes, and acetals. The data show a wide variation in the valence angle for the different groups, with the β-branched substituents (*n*-propyl, isobutyl, neopentyl) exhibiting the largest deviations from the normal tetrahedral value. This relaxation mechanism appears to provide a means by which neopentyl may exhibit a smaller steric enthalpy effect than *tert*-butyl, as was observed in this investigation. The replacement of the acetal hydrogen by a methyl to form the ketals makes this relaxation mechanism less favorable because of the interaction with the methyl group and accounts for the larger range of effects found with the ketals.

The second result obtained from these molecular mechanisms calculations was that most of the ketals, acetals, and carbonyl compounds were found to have many conformations which appeared to be significantly populated. This is a key finding in the context of the eventual development of the correct nonbonded parameters for oxygen. Because of the large number of conformers which must be treated, it is impractical to use our hydrolysis calorimetric data to directly parameterize the the oxygen nonbonded interactions. It would be better to attempt to derive realistic oxygen parameters through optimization of the agreement between calculated and experimental results for more rigid systems. For example, if calorimetric data were available for the hydrolysis of alicyclic or bicyclic ketals wherein only one significant conformation of the reactants and products would be present, then one might reasonably carry out a complete refinement of the calculated enthalpies of reaction as a function of the oxygen nonbonded parameters. A study of this type is currently being implemented, using the norbornanone–2,2-dimethoxynorbornane system with alkyl substituents at the 1, 3, 5, 6, or 7 positions. The ultimate test of the oxygen potentials derived in this way would be to apply them to a recalculation of the heats of hydrolysis for the acyclic acetals and ketals. If they reproduce the trends in the observed heats of reaction correctly, one may have confidence that they are correct.

Acknowledgment. This investigation was supported by the Office of Basic Energy Science, Department of Energy.

---

(30) Reference 19, Chapter 4.

(31) Leo, A.; Hansch, C.; Elkins, D. *Chem. Rev.* **1971**, *71*, 525.

(32) Reference 3, p 652.

(33) For recent reviews, see (a) Allinger, N. L., *Adv. Phys. Org. Chem.* **1976**, *1*, 13; (b) Stang, P. J.; Williams, J. E.; Schleyer, P. v. R. *Annu. Rev. Phys. Chem.* **1968**, *19*, 531.

(34) Boyd, R. H.; Breitling, S. M.; Mansfield, M. *AIChE J.* **1973**, *19*, 1016.

(35) Janz, G. J. "Estimation of Thermochemical Properties of Organic Compounds"; Academic Press: New York, 1958, p 26ff; ref 23b.

(36) For other reports of molecular mechanics calculations on ketals, acetals, and carbonyl compounds, see (a) Allinger, N. L.; Chung, D. Y. *J. Am. Chem. Soc.* **1976**, *98*, 6798; (b) Allinger, N. L.; Tribble, M. T. *Tetrahedron* **1972**, *28*, 1173.

(37) The potential function was composed of 1-fold, 2-fold, and 3-fold barriers and was fit to the available data on the torsional potential for acetaldehyde, propanal, 2-methylpropanal, and pivaldehyde. The details of the torsional potential as well as the other parameters used in the calculations are available in the Ph.D. thesis of RRS.

(38) (a) Zefirov, N. S.; Shekhtman, N. M., *Russ. Chem. Rev.* **1971**, *40*, 315; (b) Jeffrey, G. A.; Pople, J. A.; Binkley, J. S.; Vishveshwara, S. *J. Am. Chem. Soc.* **1978**, *100*, 373.

(39) Jorgenson, W.; Allen, W. C. *J. Am. Chem. Soc.* **1971**, *93*, 567.

(40) Suter, V. W. *J. Am. Chem. Soc.* **1979**, *101*, 6481.

(41) Charton, M. *J. Am. Chem. Soc.* **1979**, *101*, 7356.