138. Steric Effects on Reaction Rates. IV. Evaluation of the Ketone Model for the Solvolysis Transition State of Secondary *p*-Toluenesulfonates

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Summary

The rates of solvolysis of secondary *p*-toluenesulfonates in acetic acid or 97% trifluoroethanol are interpreted in terms of strain changes between substrate and the corresponding ketone. Such strain changes are obtained from force-field calculations (ΔE_{st}) and from equilibration of alcohols and ketones (ΔG_{ox}). This simple model reproduces the behaviour of substrates reacting by k_c-pathways to afford unstrained carbenium ions. Anchimeric assistance and leaving group hindrance in the transition state are recognized in clear-cut cases by deviations from the expected reactivity. However, the model breaks down when highly strained carbenium ions of the cyclobutyl or 7-norbornyl type are involved.

Introduction. – The rates of solvolysis of tertiary halides and sulfonates are determined by the strain changes associated with the change of hybridization of the reacting C-atoms from sp^3 to sp^2. These strain changes can be calculated by means of molecular mechanics (empirical force-field calculations). The rates of solvolysis of tertiary substrates correlate well with the calculated strain differences between the halide or sulfonate and the corresponding tertiary carbenium ion [1]. The situation is more complex with secondary substrates, where in addition to these strain differences other factors such as solvent participation [2] (k_s-process), anchimeric assistance [3] (k_Δ-process) or leaving group hindrance [4] may increase or decrease the reaction rate. During almost 20 years the *Foote-Schleyer*-correlation [5] was the only rational approach to explain the rate variations during solvolysis of secondary substrates in quantitative terms. Since these changes relate only to the simple ionization pathway (k_c-process) anchimeric assistance and steric inhibition to ionization could be estimated from deviations of the experimental from the expected rate constant. More recently, *Schleyer*'s force-field approach to solvolysis of tertiary substrates has been extended to secondary *p*-toluenesulfonates by *Harris* [6]. The steric requirements of the tosyloxy group were simulated by those of CH_3, the strain of the transition state by that of the secondary carbenium ion.

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The strain differences (ΔE_{st}) were successfully correlated with the rate constant of acetolysis of six rigid, polycyclic *p*-toluenesulfonates which are believed to react *via* a simple carbenium ion mechanism (k_c-process). Similarly, the rate variations produced by 1-alkyl substituents in solvolysis of 2-adamantyl *p*-toluenesulfonates were rationalized with the same approach [7]. A slightly different procedure was adopted by *Schneider & Thomas* [8] who approximated the properties of the transition state with a carbonyl group. An excellent correlation was obtained for solvolysis of cycloalkyl *p*-toluenesulfonates in 97% trifluoroethanol (TFE) from C_5 to C_{11} in function of the strain differences between a methylcycloalkane and the corresponding cyclanone. With the possible exception of cyclooctyl *p*-toluenesulfonate [8] all compounds used react without anchimeric assistance and are non-controversial. The solvent, TFE, is a poor nucleophile [2] so that differential solvent assistance should be weak. The slope of the correlation indicates that an increase in strain differences ΔE_{st} yields almost the same numerical decrease in activation energies of solvolysis [8]. The success of this correlation suggests that the carbonyl group could be a better model than the carbenium ion for the transition state of solvolysis of secondary substrates. Accordingly, we have investigated the general applicability of this model. The strain energies for methyl-substituted hydrocarbons and ketones required for this investigation have been reported in communications related to steric effects on chromic acid oxidations of alcohols [9]. In addition, relative strain differences of alcohols and ketones have been determined [10]. The latter data should be useful to assess the calculated strain energies and the validity of the CH_3-surrogate for the tosyloxy substituent, and are summarized in *Table 1*. The rate constants are expressed in terms of ΔG^+ relative to cyclohexyl *p*-toluenesulfonate (**4**). ΔG_{ox} is derived from the experimentally determined equilibrium constant [11] of the reaction

$$\text{alcohol} + \text{cyclohexanone} \overset{K}{\rightleftarrows} \text{ketone} + \text{cyclohexanol}$$

$\Delta\Delta E_{st}$ is the calculated strain difference between ketone and the corresponding CH_3-substituted alkane [8] [10] diminished by ΔE_{st} (cyclohexanone-methyl cyclohexane). This correction allows for direct comparison for the ΔG_{ox} and ΔE_{st} scale.

Results and discussion. – ΔG_{ox} correlates well with ΔG^+ for solvolysis of cycloalkyl *p*-toluenesulfonates from C_5 to C_{11} in 97% TFE with a slope of 0.99 ($r = 0.95$) [11]. *Figure 1* shows an extension of this plot to include acyclic and bicyclic substrates (data from *Table 1*, entry 2). Whenever possible ΔG_{ox} was used for the strain changes occurring between substrate and transition state, but for **9**, **15**, **16** and **19** we used $\Delta\Delta E_{st}$, ΔG_{ox} being unavailable. This substitution should not be important for the present discussion. *Figure 1* shows that the correlation is satisfactory (slope 1.02, $r = 0.94$). We were somewhat surprised to find cyclobutyl *p*-toluenesulfonate (**1**) very close to the regression line. The ketone model for the transition state is in good agreement with the experimental rate constant, and there is no indication for a particular rate enhancement of **1** [24]. A more detailed discussion of this question will follow.

The acetolysis of cycloalkyl *p*-toluenesulfonates from C_4 to C_{11} correlates with ΔG_{ox} with a slope of 0.82 ($r = 0.987$) [25]. *Figure 2* shows an extension of this plot

Table. *Strain changes and rates of solvolysis of secondary* p-*toluenesulfonates* (in kcal/mol)

No.	*p*-toluenesulfonate	$-\Delta G^{\neq}_{AcOH}$[a])	$-\Delta G^{\neq}_{TFE}$[l])	$-\Delta G_{ox}$[q])	$-\Delta\Delta E_{st}$[r])
1	Cyclobutyl	1.34	2.20[m])	1.67	−0.34
2	3-Pentyl	0.92[b])	0.94[n])	1.99	2.67
3	Cyclopentyl	2.05	1.90	2.16	1.35
4	Cyclohexyl	0.00	0.00	0.00	0.00
5	2-Bicyclo[2.1.1]hexyl	−0.50		0.77	−0.23
6	5-*exo*-Bicyclo[2.1.1]hexyl	−4.53			−7.54
7	Cycloheptyl	2.42	2.52	2.60	3.13
8	2-*exo*-Norbornyl	3.67	4.79[o])		0.67
9	2-*endo*-Norbornyl	0.24	0.81		1.56
10	7-Norbornyl	−8.65[c])		−3.70	−4.05
11	Cyclooctyl	3.75	4.80	3.75	5.55
12	2-Bicyclo[2.2.2]octyl	2.51		1.97	2.42
13	2-*ax*-Bicyclo[3.2.1]octyl	2.19			1.21
14	2-*eq*-Bicyclo[3.2.1]octyl	0.64			0.21
15	3-*endo*-Bicyclo[3.2.1]octyl	2.90[d])	3.82[p])		3.43[s])
16	3-*exo*-Bicyclo[3.2.1]octyl	1.51[d])	1.99[p])		1.25
17	8-*endo*-Bicyclo[3.2.1]octyl	(−5.57)			−1.38
18	8-*exo*-Bicyclo[3.2.1]octyl	−0.28			−1.95
19	Di-*t*-butylmethyl	2.78[e])	4.29[e])		4.91
20	Cyclononyl	3.66	4.60	4.61	5.40
21	2-*endo*-Bicyclo[3.3.1]nonyl	2.53[f])			2.22
22	2-*exo*-Bicyclo[3.3.1]nonyl	0.03[f])			1.23
23	3-*endo*-Bicyclo[3.3.1]nonyl	5.53[g])			6.45
24	3-*exo*-Bicyclo[3.3.1]nonyl	4.18[g])			5.08
25	9-Bicyclo[3.3.1]nonyl	0.65		−0.34	0.33
26	Cyclodecyl	4.04	4.72	4.84	6.58
27	3,3,5,5-Tetramethylcyclohexyl	0.47[d])		1.35	2.06
28	2-Adamantyl	−1.60	−0.06[m])	−0.32	−0.08
29	*endo*-5,6-Trimethylene-*endo*-2-norbornyl	(−1.00)[h])			6.55
30	*endo*-5,6-Trimethylene-*endo*-8-*norbornyl*	(−0.66)[i])			2.38
31	*endo*-5,6-Trimethylene-*exo*-8-norbornyl	0.35[i])			2.38
32	Cycloundecyl	2.78	5.35	4.26	4.67
33	Cyclododecyl	–	1.35	3.20	3.13
34	*endo-endo*-Tetracyclo[6.2.1.1.^{3,6}0^{2,7}]-*endo*-4-dodecanyl	(2.13)[h])			9.53
35	*endo-endo*-Tetracyclo[6.2.1.1.^{3,6}0^{2,7}]-*exo*-4-dodecanyl	(4.58)[k])			2.56

[a]) Rel. to cyclohexyl *p*-toluenesulfonate, in AcOH, 25°, data from [5]. [b]) [12]. [c]) [6]. [d]) [13]. [e]) [14]. [f]) Estimated from rate in 80% EtOH, 40° [15]. [g]) [16]. [h]) [17]. [i]) [4b]. [k]) Calc. from bromobenzenesulfonate [18]. [l]) Rel. to **1** in 97% TFE, 25° [8]. [m]) 100% TFE [19]. [n]) [20]. [o]) [21]. [p]) [22]. [q]) [11]. [r]) From [8] and [10a], rel. to **4**. [s]) From value of **16** and experimental ax./eq. energy difference [23].

to include acyclic and bicyclic substrates for which ΔG_{ox} has been measured. Again, agreement is good (slope 0.88, r = 0.91). For this particular series differential solvent participation or contribution by anchimeric assistance must be weak. Further, our omission of the correction for polar substituent effects owing to variation of the substitution pattern at the C(β)-atom has no serious consequences despite of the

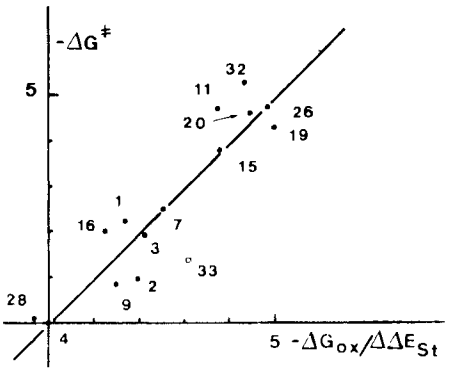

Fig. 1. *Plot of* ΔG^{+} *for solvolysis of* p-*toluenesulfonates in 97% TFE* vs. ΔG_{ox} *or* $\Delta\Delta E_{st}$

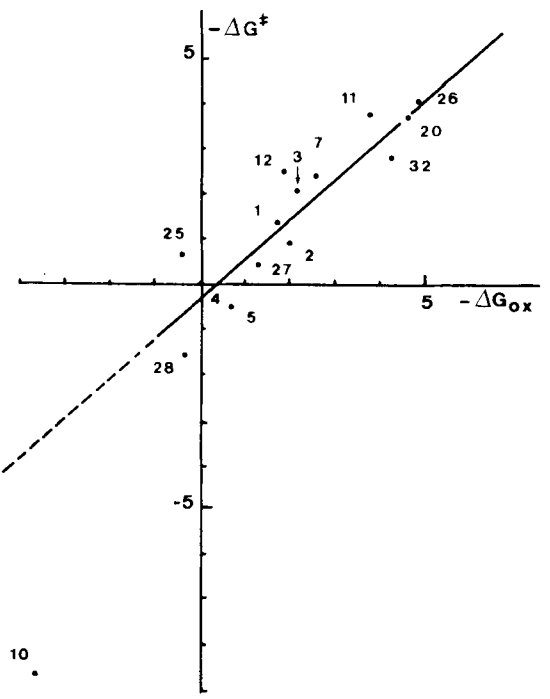

Fig. 2. *Plot of* ΔG^{+} *for acetolysis of* p-*toluenesulfonates* vs. ΔG_{ox}

p-value of -2.10 [2a]. Again, the cyclobutyl derivative **1** fits well with the correlation. A serious deviation occurs however with 7-norbornyl p-toluenesulfonate (**10**) which deviates by several kcal/mol from the regression line. If the ΔG_{ox} values are reliable, something must be wrong with the approach unless some special rate-retarding effect can be found operating in **10**. Since we have shown that the equilibration data form a consistent set that can be correlated with other thermodynamic and kinetic properties [11], the difficulty must arise from an inadequate transition state model. The carbonyl group as model probably leads to an underestimation of angle strain in the transition state of solvolysis. Therefore despite of *Figures 1* and *2* the cyclobutyl derivative **1** must react at enhanced rate. The fact that it fits the correlation is an artefact and has no significance.

These considerations are further corroborated by comparison of ΔG^{+} for acetolysis with the calculated strain difference ($\Delta\Delta E_{st}$) between ketone and methyl derivative *(Fig. 3). Figure 3* differs from the others by the use of CH_3 as leaving group; however, the transition state model is the same in all cases.

Examining the left side of the y-axis of *Figure 3*, we find four compounds (**6**, **10**, **17**, **18**) leading to highly strained carbenium ions. An unbiased observer would consider the reactivities of 5-*exo*-bicyclo[2.1.1]hexyl (**6**) and 8-*exo*-bicyclo-[3.2.1]octyl (**18**) p-toluenesulfonates as 'normal' and would try to explain the 'unexpectedly low reactivity' of 7-norbornyl (**10**) and 8-*endo*-bicyclo[3.2.1]octyl (**17**) p-toluenesulfonates. Two arguments can be invoked: *Hoffmann et al.* [26] explained the low reactivity of **10** by a special destabilizing factor in the cation due to sym-

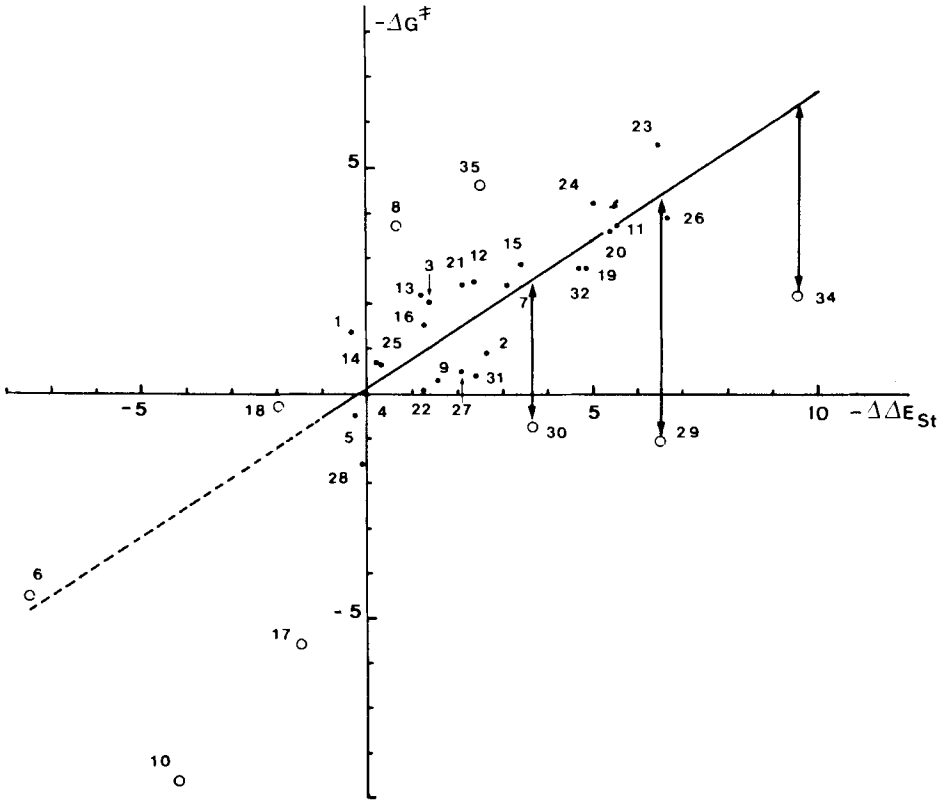

Fig. 3. *Plot of* $\Delta G^{\neq}$ *for acetolysis of* p-*toluenesulfonates* vs. $\Delta\Delta E_{st}$. Open circules are not included in the correlation

metry-imposed absence of interaction between the vacant *p*-orbital and the high lying σ-orbitals of the molecular framework. However, the magnitude of this effect would be difficult to evaluate and the concept has not been applied to compounds such as **17** or **18** where the σ-framework has different nodal properties. The second argument is leaving group hindrance in the transition state. We have studied by molecular mechanics [27] steric hindrance for perpendicular attack on, or departure from a carbonyl group. 7-Norbornanone has about the same hindrance as 9-bicyclo-[3.3.1]nonanone; the *exo* face of 8-bicyclo[3.2.1]octanone is *ca.* half hindered and the *endo* face *ca.* a quarter more. 2-Adamantanone is in the same range as is the *endo* face of 2-norbornanone. It is very difficult to evaluate the magnitude of these effects in solvolysis, since they depend considerably from the model used for the calculations. However, since 2-*endo*-norbornyl *p*-toluenesulfonate (**9**) deviates little from the plot in *Figure 3*, steric hindrance of the leaving group in the transition state should not retard the reaction by more than 1 kcal/mol. Similarly, rate retardation of **10** and **18** should be in this order of magnitude. This stands in contrast to leaving group hindrance in the U-shaped molecules **29**, **30** and **34** which

deviate by 3–5 kcal/mol from the plot. Clearly, the steric situation is not comparable with **10** and **17**, and the low reactivity of these compounds does not seem to be due significantly to leaving group hindrance in the transition state. On the other hand anchimeric assistance has been recognized in solvolysis of **6** [6] [28] and **18** [29] [30].

Scheme

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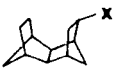

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We are aware that the assignment of 'enhanced' and 'reduced' reactivity to a particular molecule is very much a question of a suitable reference system acceptable to everybody, and that the selection of this reference system is to a certain degree determined by tradition. For our present case, unless evidence to the contrary becomes available, **10** and **17** should be considered 'normal' while **6** and **18** are anchimerically assisted. Accordingly, *the ketone model for the transition state of solvolysis must be rejected for substrates which lead to strained carbenium ions.* On the contrary, the model works quite well for the majority of the secondary *p*-toluenesulfonates used in this study. It reproduces leaving group hindrance in the transition state (**29**, **30** and **34**) and anchimeric assistance in typical cases like the 2-*exo*-norbornyl derivatives **8** and **35**. Anchimeric assistance is at the limits of detection for 2-axial-bicyclo[3.2.1]octyl *p*-toluenesulfonate (**13**) [31]. Similarly, leaving group hindrance is not reliably demonstrated for the 2-*endo*-norbornyl compound **9**. For the majority of substrates the model works reasonably well. The final correlation, which includes 25 substrates is characterized by a slope of 0.67 and a correlation coefficient $r = 0.86$ (intercept 0.11). In view of the uncertainties concerning the appropriate choice of the leaving group for the calculation [32], the error in the calculated strain energies and, in particular, the continuing discussion on the contribution of k_s, k_Δ and k_c pathways to the solvolysis, we consider it premature to extract more subtle information from the plot. The model is appropriate for description of k_c-processes in acetolysis of secondary substrates leading to unstrained or weakly strained carbenium ions. It breaks down when highly strained cations of the cyclobutyl or 7-norbornyl type are involved, and the 2-adamantyl cation is about at the limits of reliability of the model.

An explanation for this breakdown has been provided by *Schneider & Thomas* [8], who found that within their series of cycloalkyl *p*-toluenesulfonates the strain changes between the sp^3-hybridized starting compound and the sp^2-hybridized transition state model (ketone) are mainly due to release of torsional and nonbonded interactions, but not to angle strain in the ketone. As long as the latter are relatively small, their inadequate treatment will only lead to some scatter in the plot, but not to systematic deviations. As soon as this term becomes predominant, the model necessarily breaks down. For these cases, the model of *Harris* [6]

which has recently been applied to several severely strained 7-norbornyl derivatives [33] is more reliable. The ketone model, although limited in its applicability, has the advantage of producing strain energies which can be verified experimentally by thermochemical methods. This is not the case for carbenium ions; their force-field contains several terms [34] which had to be estimated. From the quality of the fit of the correlations shown in *Figures 1–3* we conclude that ΔG_{ox} is more representative for the strain changes occurring during solvolysis than $\Delta\Delta E_{st}$. Therefore either OH is a better leaving-group model for OTs than CH_3, or the experimental data (ΔG_{ox}) are more reliable than the calculated ones ($\Delta\Delta E_{st}$). Furthermore solvolysis in TFE is better reproduced (slope 1.0) than in acetic acid (slope 0.88). However, more data are needed before these trends can be safely interpreted.

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