Steric Effects on Reaction Rates: Correlation Analysis of Solvolysis Data for Tertiary Carbon Substrates**

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Abstract: Rate constants for solvolysis of tertiary chlorides and *p*-nitrobenzoates are compared and converted to *Bentley*'s unified reactivity scale. For the majority of structures consistent behavior is observed. Deviations are interpreted in terms of F-strain or, to a minor extent, of leaving group hindrance. The reactivity of the tricyclic compound **31**-OPNB can be rationalized by strain calculations if F-strain due to the presence of the OPNB substituent is taken into consideration.

The solvolytic reactivity of organic substrates is dependent from a variety of factors, some of them steric, some electronic, while yet others are due to environmental causes. In the series of bridgehead substrates steric effects predominate[1] while all others are remarkably constant. In particular, relative rates of bridgehead derivatives are essentially independent from leaving groups and solvents. On these grounds a unified reactivity scale for solvolysis of bridgehead derivatives under standard conditions (OTs leaving group, solvolysis in 80% EtOH, 70°C) was recently proposed by *Bentley*[2]. The mechanistic simplicity of these substrates provides a unique test ground for mechanistic concepts. Molecular-mechanics calculations have been applied to the problem of solvolytic bridgehead reactivity as early as 1967[3] and repeatedly since then[1,4]. *Bentley*'s unified reactivity scale[2] can be rationalized in terms of strain changes between the bridgehead substrate (R–X) and the respective carbenium ion ($R^{\oplus}$)[5].

The existence of a similar set of unified reactivity data is a prerequisite for wider application of molecular mechanics to solvolysis of non-bridgehead tertiary substrates. The existence of such a reactivity scale is note self-evident; tertiary substrates do not exhibit the same mechanistic uniformity as do bridgehead derivatives. The solvolysis mechanism may involve solvent participation[6], anchimeric assistance[7], F-strain[4,8,9], or leaving group hindrance[10] in addition to release or build-up of steric strain in the molecular skeleton. Some of these complicating effects may be dependent upon the leaving group, others on the solvent or even on both. In this communication we compare rate data for solvolysis of tertiary *p*-nitrobenzoates (OPNB's) and chlorides under standard conditions. The objective is to establish consistent behavior, wherever it exists or on the contrary, identify and if possible rationalize deviations from «normal» solvolytic reactivity.

The data are collected in Table 1. For chlorides all rate constants are converted to standard conditions (80% EtOH, 70°C) as follows: Data were extrapolated from other temperatures to 70°C by means of the Arrhenius equation if rate constants at two or more temperatures were available; otherwise the rate constant relative to *t*-BuCl or another suitable reference compound was determined and extrapolated to 70°C assuming constant *A* factors. The same procedure was adopted for conversion of rate constants from other solvents. Details are given in the footnotes of Table 1. The rate constants of chlorides are converted to *Bentley*'s unified reactivity scale ($\lg k_{calc}$ (OTs)) using the conversion factor: $\lg 1.6 \times 10^5$ (= 5.20)[2]. For OPNB derivatives the standard conditions are 80% acetone, 70°C. The data available from the

Table 1. Kinetic data for solvolysis of chloride and *p*-nitrobenzoate derivatives, R–X (X = Cl, OPNB).

No	Substrate R =	$\lg k$[a] X = Cl	$\lg k$[b] X = OPNB	$\lg k_{calc}$[c, d] X = OTs from Cl	$\lg k_{calc}$[e] X = OTs from OPNB
1	*t*-Butyl	–2.82[f]	–7.22[g]	2.38	2.46
2	*t*-Butyl(dimethyl)methyl	–2.75[h]	–6.61[g]	2.45	3.12
3	Di-*t*-butyl(methyl)methyl	–1.72[i]	–5.11[k]	3.48	4.94
4	Tri-*t*-butylmethyl		–3.52[h]		6.81
5	1-Methylcyclopentyl	–1.40[l]	–6.55[g]	3.80	3.25
6	1,2,2,5,5-Pentamethylcyclopentyl	0.33[m]		5.53	
7	1-Methylcyclohexyl	–3.15[l]	–7.29[g]	2.05	2.38
8	1-Methylcycloheptyl	–1.43[l]	–5.71[g]	3.77	4.24
9	*cis*-1-Hydrindanyl	–1.82[n]	–6.16[o]	3.38	3.71
10	*trans*-1-Hydrindanyl	–0.94[n]	–5.56[o]	4.26	4.41
11	*cis*-1-Decalinyl	–3.13[p]	–7.13[o]	2.07	2.57
12	*trans*-1-Decalinyl	–3.24[p]	–7.75[f]	1.96	1.83
13	2-Methyl-2-*endo*-norbornyl	–2.79[q]	–7.97[g]	2.49	1.58
14	2-Methyl-2-*exo*-norbornyl	–0.62[f]	–5.43[g]	4.58	4.57
15	2-*t*-Butyl-2-*endo*-norbornyl		–3.87[g]		6.40
16	2-*t*-Butyl-2-*exo*-norbornyl		–1.92[r]		8.69
17	7-Methyl-7-norbornyl	–6.86[s]		–1.66	–2.42[x]
18	1,2-Dimethyl-2-*endo*-norbornyl	–1.83[t]	–7.07[u]	3.37	2.64
19	1,2-Dimethyl-2-*exo*-norbornyl	0.12[t]	–4.67[u]	5.32	5.46
20	2,3,3-Trimethyl-2-*endo*-norbornyl		–7.64[g]		1.97
21	2,3,3-Trimethyl-2-*exo*-norbornyl	0.78[m]	–4.45[g]	5.98	5.72
22	2-*t*-Butyl-3,3-dimethyl-2-*endo*-norbornyl		–2.42[g]		8.11
23	9-Methyl-9-bicyclo[3.3.1]nonyl		–6.69[g]		3.08
24	9-*t*-Butyl-9-bicyclo[3.3.1]nonyl		–2.33[g]		8.21
25	1-Adamantyl	–5.61[f]	–9.52[f]	–0.41	–0.25
26	2-Methyl-2-adamantyl	–1.99[f]	–6.86[g]	3.21	2.88
27	2-*t*-Butyl-2-adamantyl		–2.33[g]		8.21
28	1-Homoadamantyl	–5.00[v]	–9.38[v]	0.20	–0.08
29	3-Homoadamantyl	–3.29[w]	–7.72[v]	1.91	1.87
30	*t,t,t*-1-Tricyclo[7.3.1.$0^{5,13}$]-tridecanyl	–3.71[f]	–8.07[f]	1.49	1.46
31	*t,t,t*-13-Tricyclo[7.3.1.$0^{5,13}$]-tridecanyl	–4.36[f]	–5.08[f]	0.84	4.98
32	*c,c,t*-13-Tricyclo[7.3.1.$0^{5,13}$]-tridecanyl	–3.12[f]	–7.93[f]	2.08	1.62

[a] Converted to 80% EtOH, 70°C from other temperatures and, in part, other solvents. [b] Converted to 80% acetone, 70°C. [c] Conversion factor 1.6×10^5. [d] Ref.[2]. [e] OPNB rates converted to chloride rates with Eq. (1), the latter converted according to [c]. [f] Ref.[9]. [g] Ref.[11]. [h] Ref.[12]. [i] Ref.[13]. [k] Converted from 70% acetone [14] via $k(t\text{-BuOPNB}) = 6.81 \times 10^{-6}\ s^{-1}$ (100°C)[15]. [l] From data relative to *t*-BuCl[16] and rate of *t*-BuCl reported in Ref.[9]. [m] From relative rates in EtOH, 25°C[17]. [n] Ref.[18]. [o] Extrapolated from 60% acetone, 100°C[19]. [p] Ref.[20]. [q] Calculated from rate of **14**-Cl in EtOH and *exo/endo* rate ratio of 1,2-dimethyl-2-norbornyl chlorides[21]. [r] Ref.[22]. [s] Extrapolated from 80% acetone[23]. [t] In EtOH[21]. [u] In 80% acetone[21]. [v] Extrapolated from 70% CH_3CN, 150°C (X = OPNB) and from 80% EtOH, 25°C (X = Br)[24]; relative rates of perfluorobutyrates are slightly different[25]. [w] Ref.[1]. [x] From rate of *p*-toluenesulfonate in AcOH, 70°C[26]; conversion factor to 80% EtOH = 3.5[2].

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literature were converted to these conditions in the same way as the chloride data. The last column of Table 1 contains calculated rate constants for standard conditions (80% EtOH, X = OTs) calculated from OPNB reactivities via conversion to chlorides (see below).

Comparison of Chlorides with OPNB Derivatives (Fig. 1):

The rate constants for solvolysis of chlorides (80% EtOH) and *p*-nitrobenzoates (OPNB's, 80% acetone) are in general remarkably consistent as revealed by Fig. 1. Only two compounds (**3** and **31**) fall out of the correlation. The remaining data correlate by means of Equation (1):

$$\lg k(\mathrm{OPNB}) = 0.839 \lg k(\mathrm{Cl}) - 4.95; \quad r = 0.966 \qquad (1)$$

If, for reasons discussed below, **2**, **13**, and **18** are excluded from the plot, the relationship becomes:

$$\lg k(\mathrm{OPNB}) = 0.85 \lg k(\mathrm{Cl}) - 4.89; \quad r = 0.984 \qquad (2)$$

We note that contrary to the situation in the restricted series of bridgehead compounds[2] the slope of the correlation line is different from the expected value of 1.0. The OPNB rates are slightly compressed in comparison to the chloride rates, but we believe that this discrepancy should not be mechanistically significant. It may well be due to our conversion of the rate data. The unreactive OPNB's are extrapolated from 125–150 °C to 70 °C, the very reactive ones from 25 °C, but very often data were available only at two temperatures, sometimes even only at one. Such extrapolations could lead to systematic distortions. In the case of chloride solvolysis the extrapolations involve a smaller temperature range (25–70 °C). We believe therefore that the chloride data are more reliable and they are used in preference for conversion to *Bentley*'s unified reactivity scale[2] (X = OTs. 80% EtOH, 70 °C; second last column of Table 1). The OPNB rates are converted to standard conditions via the chlorides by means of Equation (2). We are rather surprised to find that mechanistically so different compounds like adamantyl, *tert*-butyl or *exo*-norbornyl respond similarly to solvent and leaving group change, but it is clear that this common behavior must break down in limiting solvents[6].

Upwards deviations from the plot in Fig. 1 can be attributed to F-strain. This effect has been recognized in the case of **31**-OPNB[9] and **3** [12], but it could also play some role in **2**-OPNB. Since the steric requirements of Cl and OPNB groups are obviously different, some of the small scatter in the plot should be due to this difference. Nevertheless, in a first approximation F-strain is almost negligible in uncrowded substrates.

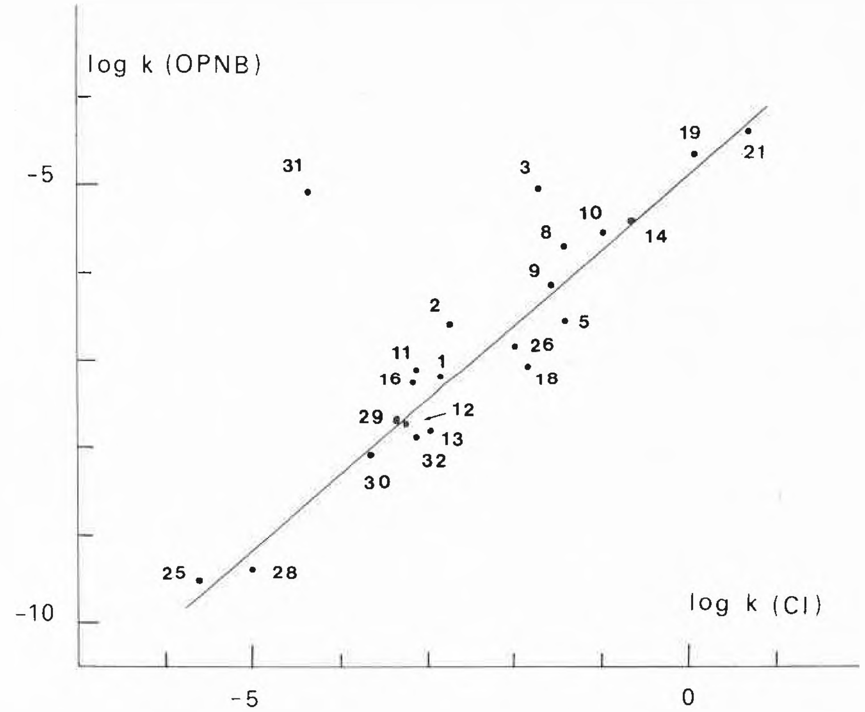


Fig. 1. *Plot of rate constants for solvolysis of p-nitrobenzoates (80% acetone, 70 °C) vs. chlorides (80% ethanol, 70 °C). Data from Table 1.*

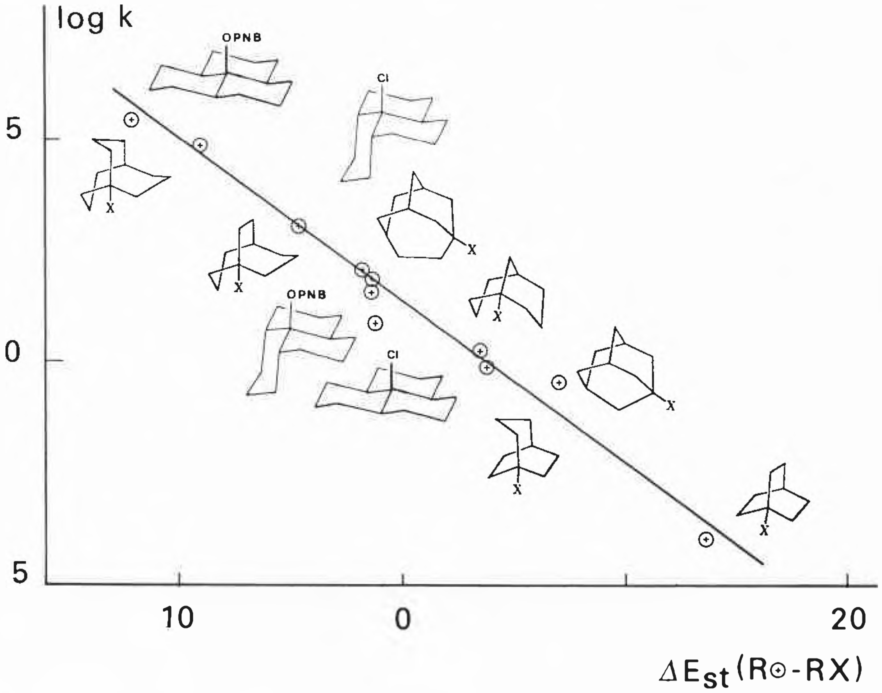


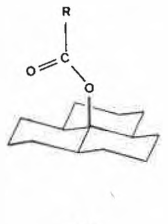
Fig. 2. *Plot of rate constants for solvolysis of bridgehead halides and p-nitrobenzoates vs. ΔE_{st} ($R^{\oplus}$ – RCl) with correction for **31**-OPNB and **32**-OPNB (see text and Table 2). Correlation equation: lg k_{calc} = – 0.36 ΔE_{st} ($R^{\oplus}$ – RCl) + 1.32; r = 0.9833.*

The most significant downwards deviations in Fig. 1 occur with the *endo*-norbornyl derivatives **13** and **18**. Following *Brown*'s suggestion, these should be ascribed to leaving group hindrance[27] which is expected to be more pronounced with OPNB's than with chlorides because of the higher steric requirements of the former. However, the effect is disappointingly small.

A Model for Molecular-Mechanics Treatment of F-Strain in p-Nitrobenzoates:

The recognition of different types of strain effects (B-strain, F-strain, I-strain) represented a significant step for the development of the concept of strain, but their nature is in principle identical. F-strain is due to steric interaction between the leaving group and the rest of the molecule; this interaction can be evaluated with molecular mechanics if the corresponding leaving group or an appropriate surrogate is used for the calculations.

One of the classical examples of rate enhancement in solvolysis owing to F-strain is the *t,t,t*-9b-phenalenyl derivative **31**[9]. The reactivity of the chloride **31**-Cl like that of bridgehead chlorides in general is satisfactorily correlated with the steric energy difference ΔE_{st} ($R^\oplus$ – RCl) (Fig. 2). If the chloro substituent of **31** is replaced by OPNB a significant rate enhancement occurs; the rate constants extrapolated from **31**-Cl and **31**-OPNB differ by ca. 4 log units (see Table 1). The rate enhancement of **31**-OPNB can be rationalized by force-field calculations using a simplified leaving group model (acetate) instead of OPNB. This simplification is justified, because in the most stable conformations of **31**-OAc (and also of **32**-OAc) the principal F-strain interactions occur between the carbonyl group and the molecular skeleton, while the bulkier CH_3 group points away from the latter. In a first approximation, extra strain due to the presence of the group R (R = CH_3 or $C_6H_4NO_2$) may be neglected.



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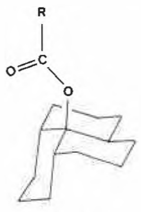

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Steric energies of chlorides are not directly comparable with those of acetates, but comparable numbers may be obtained as follows: The strain difference between **31**-Cl and **31**-OAc is – 7.78 kcal/mol. Adding this difference to ΔE_{st} ($R^\oplus$ – RCl) (– 1.34) we arrive at – 9.12 kcal/mol for ΔE_{st} ($R^\oplus$ – ROPNB) (Table 2). The same procedure applied to the *c,c,t* derivative **32** gives a strain difference between **32**-Cl and **32**-OAc of 0.48 and ΔE_{st} ($R^\oplus$ – ROPNB) increases to – 1.29 kcal/mol. Fig. 2 shows that the data for OPNB solvolysis fit almost perfectly the strain-reactivity correlation of bridgehead chlorides. It remains to be seen if this approach is applicable to OPNB solvolysis in general.

Table 2. Steric energy differences and solvolytic reactivity of bridgehead halides and *p*-notrobenzoates, R–X (X = Cl, OPNB).

No	Compound R =	ΔE_{st} ($R^\oplus$ – RCl)[a)]	lg *k*[b)]
25	1-Adamantyl	7.17	–0.40
29	3-Homoadamantyl	–1.69	1.97
31-Cl	*t,t,t*-13-Tricyclo[7.3.1.$0^{5,13}$]tridecanyl	–1.34	0.84
31-OPNB	*t,t,t*-13-Tricyclo[7.3.1.$0^{5,13}$]tridecanyl	–9.12[c)]	4.91[d)]
32-Cl	*c,c,t*-13-Tricyclo[7.3.1.$0^{5,13}$]tridecanyl	–1.77	2.08
32-OPNB	*c,c,t*-13-Tricyclo[7.3.1.$0^{5,13}$tridecanyl	–1.29[c)]	1.62[d)]
33	1-Bicyclo[2.2.2]octyl	13.58	–4.00
34	1-Bicyclo[3.3.1]nonyl	3.50	0.51
35	1-Bicyclo[3.2.2]nonyl	3.74	–0.13
36	1-Bicyclo[3.3.2]decyl	–4.66	3.08
37	1-Bicyclo[3.3.3]undenyl	–12.13	5.45

a) Calculated with force-field UNICAT 1[4,5]. b) Calculated for X = OTs, 80% EtOH[2]. c) Calculated for R-$OCOCH_3$, see text. d) Calculated from rate of OPNB derivative (Table 1).

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