ABSENCE OF HETEROATOM KINETIC EFFECTS IN π-ROUTES TO CARBOCATIONS

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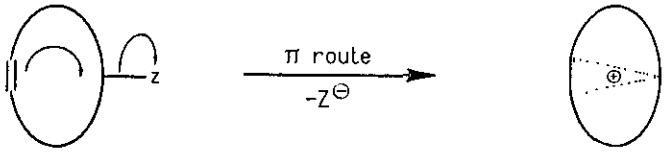
Respectfully dedicated to Sir Derek H. R. Barton on the occasion of his 70th birthday.

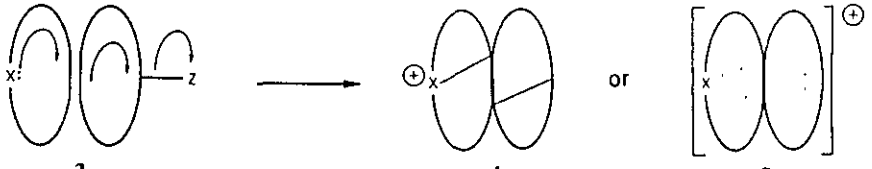
Abstract - In solvolyses of prototypical tricyclic and bicyclic heterocycles, suitably positioned oxygen, nitrogen, or sulfur ring-atoms have little net kinetic influence on π routes to carbocations.

It is well established that a suitably located double bond can accelerate departure of a remote nucleofuge (**1** → **2**) by providing additional delocalization for the derived carbocation.[1] The precise nature of the ion produced by this so-called π route depends on many structural and experimental factors, and is inextricably meshed with the ongoing discussions about "nonclassical" ions.[2]



1 **2**

When a "π route" substrate also contains a properly placed heteroatom X, (eg. **3**) the question arises whether X can provide additional anchimeric assistance by exerting its own nucleophilicity via the π bond. Such kinetic assistance might originate through repulsion between heteroatom lone pairs and the π cloud with a consequent increase in the ground state nucleophilicity of the double bond in **3**. Alternatively, a heteroatom might stabilize the transition state for ionization of Z by dispersal of incipient charge beyond that possible in the absence of X. In either case, the nature of the derived cation (eg. **4**, **5**, or related structure) could depend upon substrate structure, experimental conditions, etc.

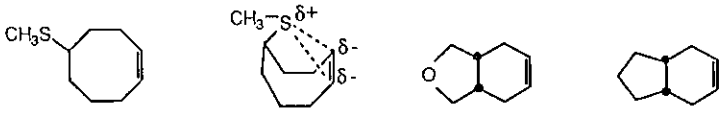


3 **4** **5**

Heteroatom involvement in π routes is a potentially important consideration in heterocyclic chemistry; and the concept could even be extended to some enzymic reactions of alkenes (eg. intramolecular

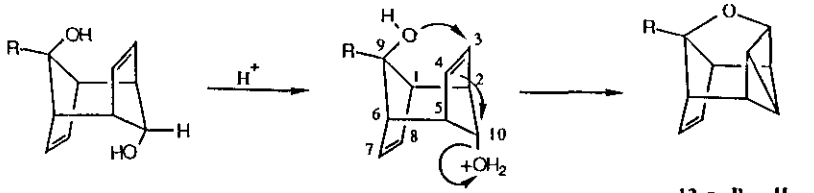
cyclization of squalene oxide, of polyene pyrophosphates, etc.).[3] Thus, in an enzyme-substrate complex a suitably poised nitrogen, sulfur, or oxygen in the enzyme might influence double bond activity in the substrate during cyclization.

It is not uncommon for researchers to involve heteroatoms to interpret behavior of unsaturated molecules. For example, to account for an observed enhanced reactivity of the π bond in **6** toward external electrophilic additions, Mueller proposed a transannular π bond activation by the sulfur, symbolized in **7**.[4] Mundy *et al.* accounted for some differences in the oxymercuration behavior of **8** and **9** on the basis of remote participation by the oxygen; but further work with other substrates led them to question this interpretation.[5]



6 **7** **8** **9**

In the field of polycyclics, research groups led by Garratt[6] and by Ganter[7] independently found that acid converts diol **10a** in high yield to the pentacyclic ether **12a**. Parallel studies with the less symmetrical analog **10b** led Garratt's team to propose that the **10a** → **12a** cyclization proceeds by simultaneous action of both the free OH and the π bond in the early stages of heterolysis at C-10 (**11**).



10 a, R = H
b, R = CH_3

11

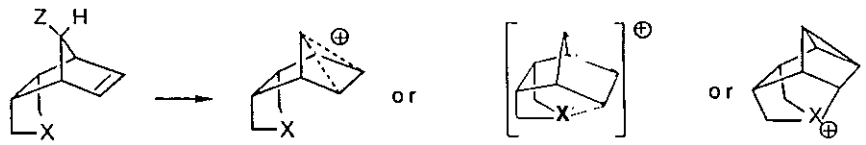
12 a, R = H
b, R = CH_3

Ganter *et al.* also investigated **10b**, and various mechanistic considerations led them to suggest that the major product (**12b**) arose through concerted action of the OH at C-9 and the 3,4-π bond (see **11**).[7]

Notwithstanding that researchers often invoke heteroatom participation during π route ionizations, the important question of whether the heteroatom actually accelerates such ionizations has received hardly any attention.[8] We now report kinetic studies of several bridged polycycles designed to test whether a suitably juxtaposed oxygen, nitrogen, or sulfur can enhance the π route participation of a double bond in solvolysis. We examined two classes of structures, which differed in the degree of conformational flexibility of a heterocyclic ring relative to the rest of the molecule. Also, our substrates possess a symmetry that could enhance the opportunities for charge delocalization.[9]

In our first structural class (tricycle **13**; X = O, NCH_3, or S) a departing group Z (Z = OTs) is anti to a π bond that can assist ionization to a delocalized ion **14** by analogy to the well-known anti-7-norbornenyl tosylate (which ionizes ca. 10^{11} times faster than its saturated counterpart, 7-norbornanyl tosylate).[10] The issue here is whether the X heteroatom in **13** can further assist C-Z cleavage by producing a cation that

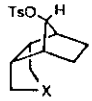
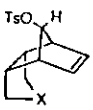
could gain additional stability through dipole effects, through more extensive delocalization (**15**), or through bond readjustment that transfers charge almost completely to the heteroatom (**16**). As reference standards, we also prepared and solvolyzed the corresponding saturated heterocycles as well as the unsaturated carbocyclic analog, (**13**, with X = CH_2) and its saturated counterpart.[11]



13 **14** **15** **16**

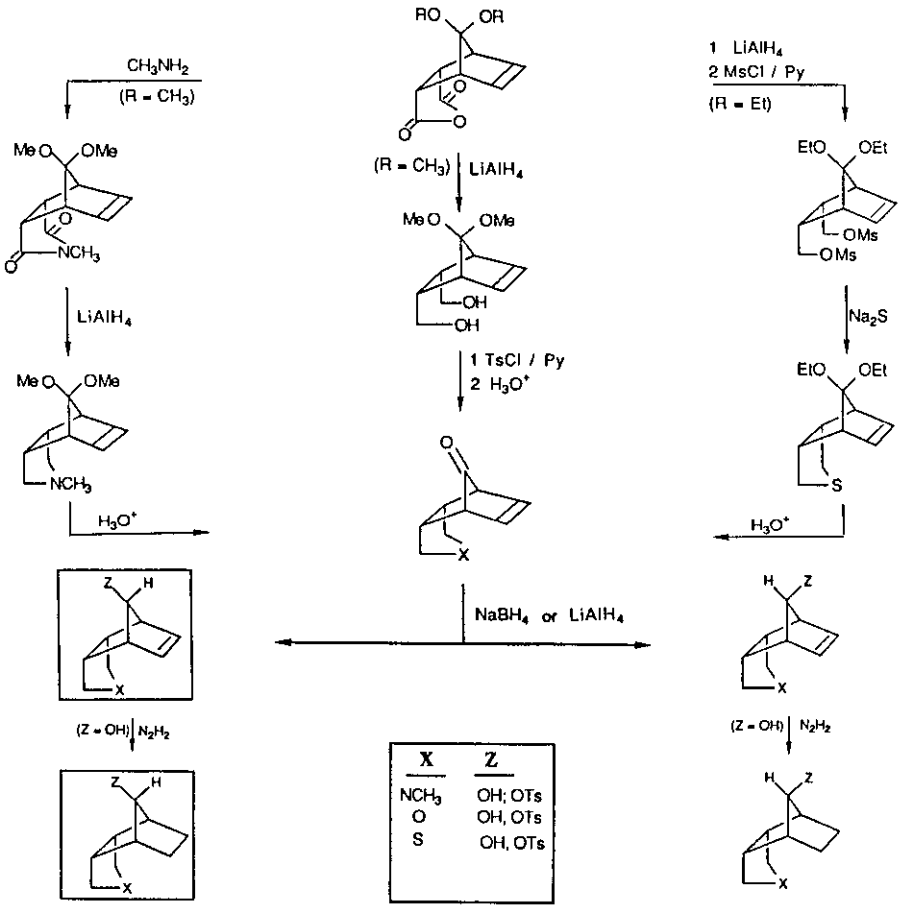
Scheme 1 outlines our syntheses of the series of unsaturated alcohols **13** (Z = OH; X = NCH_3; O; S) from a known[12] cyclic anhydride; and Scheme 2 summarizes our route to the carbocyclic analogs from known[12] precursors.[13] We converted our alcohols to tosylates, which were solvolyzed in buffered aqueous dioxane and, except for the amino series, also in buffered HOAc. Kinetics were measured by established titrimetric and spectrophotometric techniques.[14] Good first-order plots were obtained, and activation enthalpies and entropies were calculated from temperature dependency studies.[15] The results appear in Table 1, which also includes published data for acetolysis of anti-7-norbornenyl tosylate and 7-norbornanyl tosylate.

Table 1. Solvolysis Data for Tricyclic Tosylates Adjusted to 25 °C[a].

			HOAc / KOAc				Dioxane / H_2O (70.30)[b]			
	Entry	X	k sec^{-1}	ΔH‡ kcal/mol	ΔS‡ e.u.	k rel	k sec^{-1}	ΔH‡ kcal/mol	ΔS‡ e.u.	k rel
	1	—	6.4×10^{-15}	35.7	-3.5	1.0	—	—	—	—
	2	CH_2	1.6×10^{-14}	35.6	-2.2	2.5	1.3×10^{-13}	33.1	-6.3	20.3
	3	O	3.9×10^{-15}	34.5	-8.9	0.6	6.6×10^{-14}	31.0	-14.8	10.3
	4	NCH_3	—	—	—	—	5.4×10^{-14}	32.2	-11.2	8.4
	5	S	3.3×10^{-15}	36.3	-3.2	0.5	1.4×10^{-14}	34.5	-6.0	2.2
	6	—	9.0×10^{-4}	23.3	5.7	1.4×10^{11}	—	—	—	—
	7	CH_2	3.6×10^{-3}	21.2	1.4	5.6×10^{11}	1.3×10^{-2}	11.3	-29.2	20.3×10^{11}
	8	O	7.6×10^{-4}	18.8	-9.7	1.2×10^{11}	6.9×10^{-3}	12.7	-25.7	10.8×10^{11}
	9	NCH_3	—	—	—	—	5.9×10^{-3}	14.2	-21.2	9.2×10^{11}
	10	S	2.5×10^{-3}	20.6	-1.2	3.9×10^{11}	4.9×10^{-3}	21.0	1.4	7.7×10^{11}

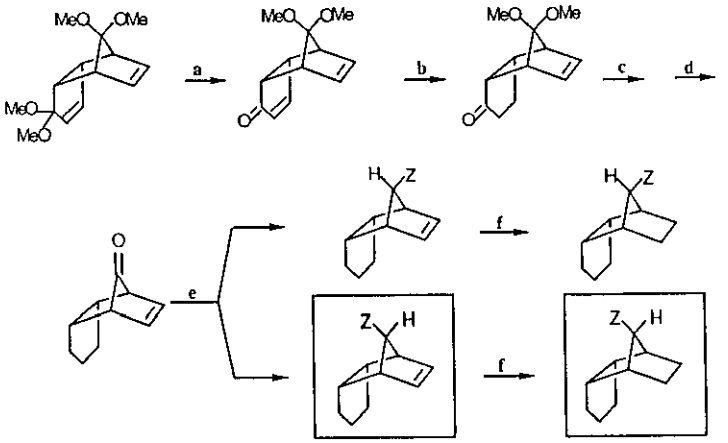
(a) For the saturated heterocycles, rates were calculated from data at higher temperatures.
(b) NaOH buffer for unsaturated compounds; $(iPr)_2NH$ buffer for saturated compounds.

Scheme 1



X	Z
NCH_3	OH; OTs
O	OH, OTs
S	OH, OTs

Scheme 2



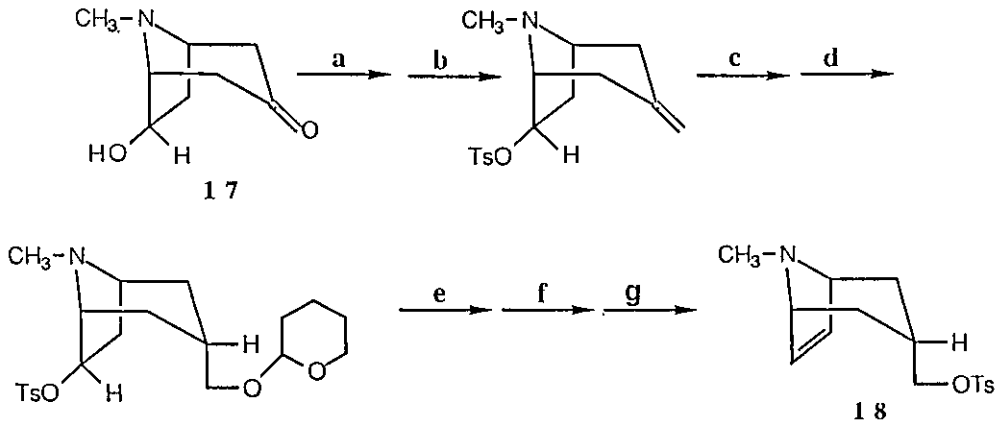
a, 6% HCl; **b**, $Li(OtBu)_3AlH$; **c**, Wolff-Kishner reduction; **d**, H_3O^+; **e**, $NaBH_4$; **f**, N_2H_2

Note first that the acetolysis rate constants for all our *saturated* tricyclics (entries 2-5) are close (within a factor of 2.5) to that for 7-norbornanyl tosylate (entry 1). Consequently, the endo-fused 5-membered ring with or without a heteroatom has little net effect (inductive, strain, etc.) on the ease of ionization at the norbornyl bridging carbon.

Note next that the unsaturated tosylates (entries 7-10) in HOAc solvolyze at rates that are similar (within a factor of 4) to that of anti-7-norbornenyl tosylate (entry 6). Therefore, the endo-fused carbocyclic ring does not much perturb the anchimeric assistance by the π bond and, significantly, *neither does the presence of the O, N, or S ring atom.* Parallel conclusions may be drawn from the data on hydrolysis in aqueous dioxane, where again the overall kinetic effect of the heteroatom is minor. Clearly, in these unsaturated tricycles, relative to the saturated ones, the π bond provides a degree of anchimeric assistance (factor of 2.0 - 7.8 x 10^{11}) comparable to that in anti-7-norbornenyl tosylate (1.4 x 10^{11}), and so the heteroatom exerts little net kinetic effect.

The second structural class we examined is typified by the tropane alkaloid derivative **18.** This bicyclic system has considerable conformational mobility near the ionization site but far less so within the unsaturated pyrrolidine ring. We synthesized **18** from a known precursor (**17**)[16] as outlined in Scheme 3. As reference standards, we also prepared and studied **19** and **20** (see Table 2) which are, respectively, the saturated and carbocyclic analogs of **18.** The three substrates **18, 19,** and **20** displayed good first-

Scheme 3

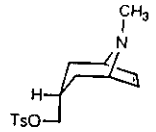
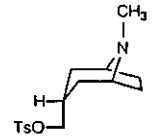
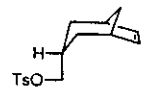
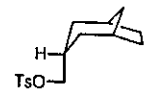


a, Wittig reaction; **b**, TsCl / Py; **c**, B_2H_6, then H_2O_2, OH^-;
d, dihydropyran / H^+; **e**, KOtBu / BuOH; **f**, H_3O^+; **g**, TsCl / Py

order kinetics in aqueous dioxane; Table 2 summarizes the data as well as activation enthalpies and entropies. Solvolysis of tosylate **20** was accompanied by 13 % isomerization (by internal return) to noradamantyl tosylate (**22**),[17] which is 2700 times less reactive and so does not perturb the linearity of the kinetic plots. (For completeness we also examined **22** and included the results in Table 2.) The un-

saturated heterocycle **18** likewise partly isomerizes by internal return (16 %) to an inert tosylate. Therefore the k's listed for **20** and **18** are *ionization* rate constants which include isomerization by internal return plus conversion to solvolysis products (i.e. $k_{ioniz} = k_{isom} + k_{solv}$).[18] Some acetolysis data are derivable for carbocycles **20, 21,** and **22** from work in our laboratory and from other sources, and these estimates are also included in Table 2 for comparison.

Table 2. Solvolysis Data for Bicyclic Tosylates Adjusted to 25 °C.

		Hydrolysis (Dioxane / H_2O 70:30)				Acetolysis	
		k [a] sec^{-1}	ΔH‡ kcal / mol	ΔS‡ e.u.	k rel.	k sec^{-1}	k rel.
	**18**	43.7×10^{-5}	18.9	-10.5	2.1×10^{5}	—	—
	**19**	2.1×10^{-9}	31.7	8.1	1.0	—	—
	**20**	348×10^{-5}	19.0	-6.0	16.6×10^{5}	2.3×10^{-3} [b]	1.9×10^{5}
	**21**	—	—	—	—	1.2×10^{-8} [c,d]	1.0
	**22**	0.129×10^{-5}	23.7	-5.9	614	8.4×10^{-7} [e]	70

(a) For unsaturated compounds, the buffer was NaOH; for saturated ones the buffer was $(iPr)_2NH$ and rates are calculated from data at higher temperatures.
(b) Calculated (see text).
(c) E. R. Johnson, B. A. Thesis, Amherst College, 1973 (copy kindly provided by the late G. D. Sargent) reported acetolysis of the brosylate.
(d) Adjusted from the usual relationship $k_{OBs} / k_{OTs} \sim 3$. L. A. Paquette and P. C Storm, *J. Am. Chem. Soc.*, **1970**, *92*, 4295; S. Winstein, C. R. Lindegren, and L. L. Ingraham, *ibid.*, **1953**, *75*, 155.
(e) A. Nickon and P. G. Kotcher, unpublished results on brosylate adjusted as in d.

Note that the unsaturated heterocycle **18** ionizes 2.1 x 10^5 faster than does its saturated counterpart **19**. Consequently we have here another example of substantial π assistance to heterolysis. That nitrogen plays little net role in this assistance in **18** is indicated by the comparable reactivity of its carbocyclic analog **20.** In fact the N analog **18** is modestly (a factor of 8) less reactive than the carbocycle **20** perhaps through inductive[19] or slight distortion effects. A precise value for the π assistance in **20** (defined as k_{unsat}/k_{sat}) cannot be specified because data are not available for hydrolysis in aqueous dioxane for the reference saturated derivative **21**. However, we can estimate the π assistance for *acetolysis* of **20** as follows. Assume that the **20**:**22** rate ratio (namely 2700) observed for *hydrolysis* holds also for *acetolysis*, and use the available acetolysis rate for **22** (Table 2) to calculate an approximate *acetolysis* rate (2.3 x 10^{-3} sec^{-1}) for **20**. This k_{unsat} is 1.9 x 10^5 greater than k_{sat} reported for acetolysis of **21**[20] and is in line with our hydrolysis ratio of 2.1 x 10^5 for the amines **18**:**19**. Clearly, in this tropane system, as in our tricyclic series, the heteroatom does little to slow or speed the kinetics, despite apparently favorable spatial proximity.

ACKNOWLEDGEMENTS

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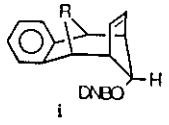

i

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11. Our full paper will also report the findings with epimers of **13** in which Z has the opposite configuration. Those data are not critical to our present conclusions.
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20. Table 2, footnote c.

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