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The Electromeric Effect in Polar 1,2-Elimination is a Myth. A Revised Version and a Unified Rule for Elimination.

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Abstract: The orientation rules for elimination reactions are discussed. Currently accepted explanations of the Saytzev eliminations and the exceptions to it which have been found, based on electromeric efffects, are not soundly based. A Unified Rule for Elimination (URE) is proposed, by which the regioselectivity of eliminations can be explained for a wide range of substrates and reaction conditions.

1. INTRODUCTION

The currently accepted explanation for the Saytzev and Hofmann rules for orientation of 1,2-elimination is amongst the most general tenets in organic chemistry, having been initially suggested by Ingold[1] in the first half of the present century. Typically, if elimination is controlled by electromeric effects, then the thermodynamically more stable olefin is formed, whereas if the inductive effect dominates, then the less stable regioisomer, or so-called kinetic product, is formed (*e.g.* Eq. 1). Ingold's view, without alteration or somewhat modified, has been generally recognised and widely applied in organic chemistry.[2-14]

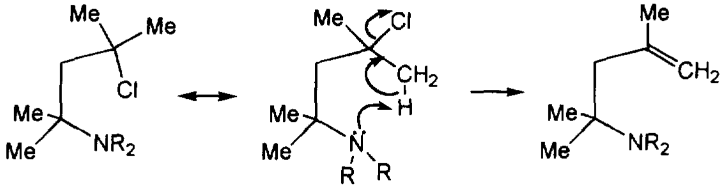
$$\mathrm{MeCH_2CHXMe} + {}^{-}\mathrm{OR} \longrightarrow \underset{\text{Saytzev product}}{\mathrm{MeCH{=}CHMe}} + \underset{\text{Hofmann product}}{\mathrm{MeCH_2CH{=}CH_2}} \qquad \text{(Eq. 1)}$$

However, the number of exceptions to these rules has continued to increase as an increasing variety of organic molecules, reaction conditions, and leaving groups X, has been investigated, such that it is more justified to treat these exceptions as a general phenomenon in their own right. The principal goal of this paper is to sharpen the definitions and to propose an extended version to explain the regioselectivity of eliminations over a broader range of substrates and reaction conditions.

2. THE P-EFFECT IN ELIMINATION REACTIONS

The derivatives of substituted and unsubstituted hydrocarbons, amino compounds, ethers, acids, and others do not eliminate in accordance with the Saytzev and Hofmann rules.[15-17] Retrospective examination highlights the key role in these "abnormal" eliminations of p-electrons (lone pairs) in adjacent groups.

Grob and his co-workers[18] initially noticed that dehydrochlorination of the γ-chloroisoamyl amines (**1**, Eq. 2) by alcoholic base forms not a mixture of unsaturated amines but exclusively the γδ-unsaturated amine **2**. The chloro-amines also eliminated much faster than the corresponding chloro-hydrocarbons, a fact explained by an intramolecular E2H-type of interaction between the p-electrons of the amino group and the δ-hydrogen, as indicated in Eq. 2 for 3-chloro-1,1,3-trimethylbutylamines.

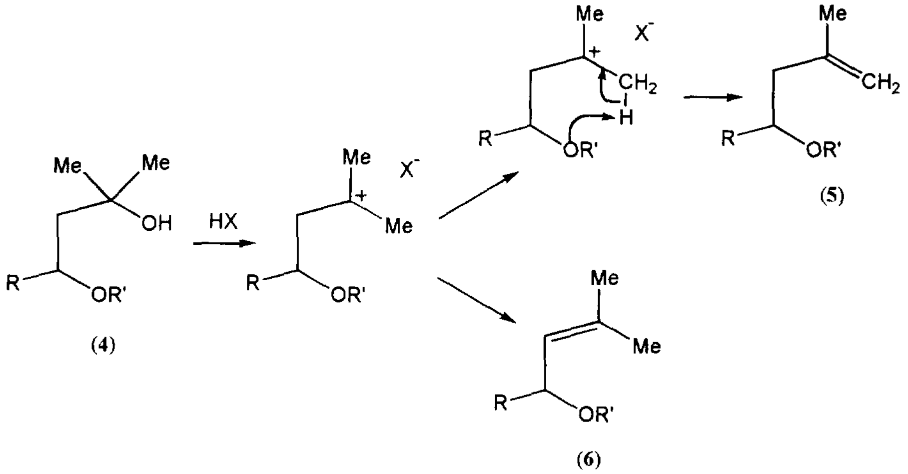


(1) (2) (3)

(Eq. 2)

However, some years later Grob[19] admitted that, in the molecules investigated by him earlier, the anomalous elimination may be attributed also to the steric effect of the two α-methyl groups, hindering the approach of a base to the protons of the inner parts of the molecules.

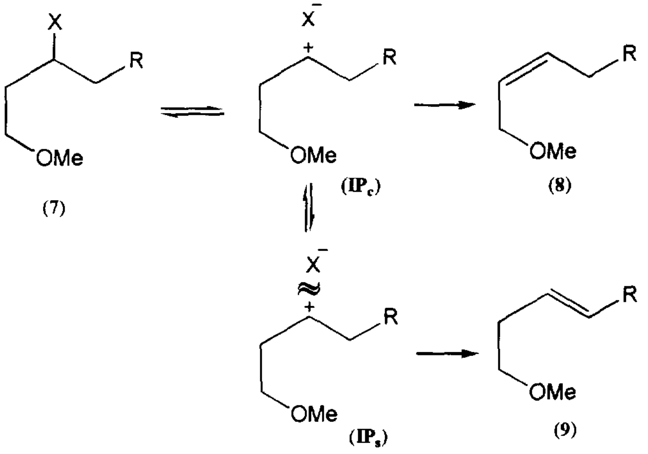
During ten subsequent years of study[20-25], unquestionable evidence for the participation of the p-electrons was obtained[23, 24] in the acid dehydration of ethers of several primary-tertiary and secondary-tertiary 1,3-glycols **4** (Scheme 1). These substrates and reaction conditions were selected to exclude steric effects. Normally in dehydration reactions the more substituted alkene would be formed, but the predominant formation of homoallylic alcohols **5**, in preference (ratio 7:3) to **6**, supports the proposal of p-electron interaction, aiding elimination from the carbocation intermediate as indicated.[23]



Scheme 1

It has been assumed that the intramolecular p-effect operates as the nucleofuge leaves the carbocationic intermediate[24], in agreement with the earlier proposal of Grob and co-workers[18]. The main product, **5**, is equivalent to the Hofmann elimination product, whereas carbocationic species normally eliminate in accordance with the Saytzev rule.

A further clarification of the relationship between heterolysis and regioselectivity of elimination can be found in the reactions of γ-X-substituted ethers **7**, in which X is a nucleofuge, and in particular of secondary γ-halo ethers and the corresponding ammonium salts[17] (Scheme 2). The halides are substrates with a 'good' leaving group, in contrast to the 'poor' nucleofugal properties of the ammonium groups. In the series chosen, it is possible to select groups in both branches with similar steric but differing electronic properties. In **7** there is a three-carbon system (C carrying X and its two neighbours) attached to an electron-donating group R, and an electron-withdrawing methoxymethyl group CH_2OMe. Reaction conditions were varied from polar aprotic (water, methanol, ethylene glycol) to aprotic solvents (DMSO), which should encourage varying degrees of C-X bond cleavage in intermediate transition states and/or varying solvation of ion pairs.



7	a	b	c	d	e	f
R	Pr	Bu	Pr	Bu	Pr	Bu
X	Cl	Cl	Br	Br	$NMe_3^+X^-$	$NMe_3^+X^-$

Scheme 2

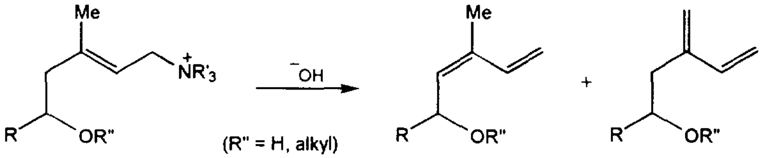
Table 1 summarizes the results. In protic solvents, which promote greater extension of the *C*-halogen bond, ethers **9** are the predominant products, probably formed *via* solvated ion pairs (**IP_s**), or a transition state with considerable C-X bond extension. In contrast, the ammonium salts yield only the ethers **8**, presumably *via* transition states with minimal C-X bond cleavage. Finally, a change to an aprotic solvent causes the halides to eliminate with an increased preference for formation of ether **8** over ether **9**, this being slightly more pronounced when the nucleofuge is chloride rather than bromide.

Clearly, as the ease of extent of cleavage of the C-X bond increases, there is a greater preference for formation of ethers **9**, consistent with an increasing contribution of the p-electrons of the methoxy group in promoting a greater role of solvated ion-paired intermediates compared to tighter contact ion-pair intermediates. This is consistent with similar findings in hydrocarbon derivatives[2-10], as well as literature data on ethers similar to **8** (produced from contact ion pairs) and **9**, produced from solvated ion pairs.[26-33]

Table 1. Regioselectivity of Base-induced Elimination of Ethers 7[17]

Compd.	Solvent	Base	% **8**:**9**	Compd.	Solvent	Base	% **8**:**9**
7a	MeOH	MeONa	84:16				
	water	NaOH	85:15	**7c**	MeOH	MeONa	92:8
	ethylene glycol	Na glycolate	83:17		DMSO	MeONa	47:53
	DMSO	MeONa	36:64	**7d**	MeOH	MeONa	90:10
7b	MeOH	MeONa	82:18		DMSO	MeONa	45:55
	water	NaOH	83:17	**7e**	water	NaOH	100:0
	ethylene glycol	Na glycolate	88:12	**7f**	water	NaOH	100:0

Related to the fragmentation of the ammonium salts 7 ($X = \overset{+}{N}Me_3$) is the allylic 1,4-elimination in **10** (Eq. 3), which yields the homoallylic alcohol and ether **12** predominantly (**12** : **11** ratio is >7:3).[34] In this case the least acidic hydrogen is preferentially abstracted, although stereochemical considerations may also play a significant part.[4]



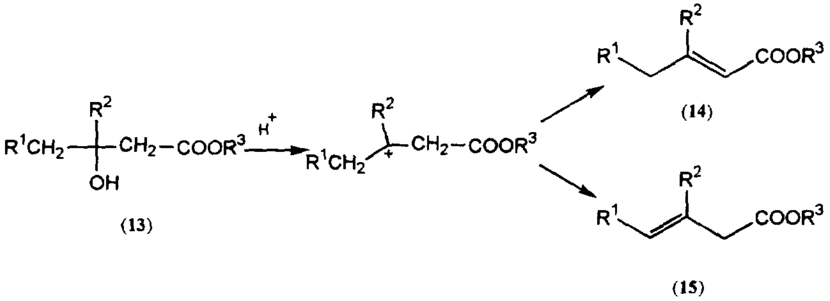
(10) (11) (12)

(Eq. 3)

The acid-catalyzed fragmentation of γ-acetoxyalkyl ethers 7 (X = OAc) results in almost exclusive formation of homoallylic ethers 9, with the allylic products of type 8 being formed in only trace amounts.[35] In this case, with no base to abstract the β-hydrogen, the influence of the adjacent p-electrons of the methoxyl group is clearly apparent and much greater than for the partially formed carbocation centres with the comparatively good nucleofuges (X = Cl, Br).

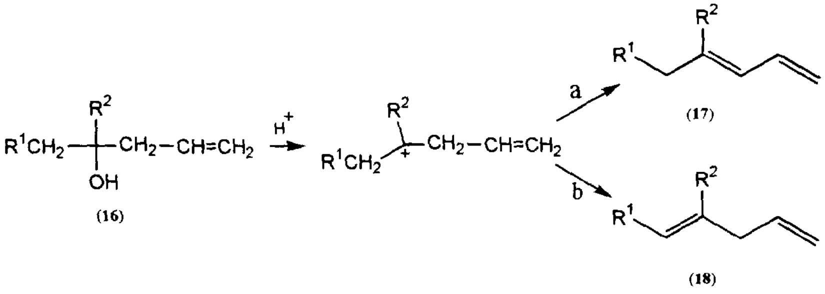
3. A RE-ANALYSIS OF THE DRIVING FORCES OF SAYTZEV'S ELIMINATION

The preferential regioselectivity of elimination of molecules 7 may simply be attributed to the normal Saytzev rule, in which electromeric effects control the direction of orientation of elimination.[1-14] However, this fails to explain the significant shift in orientation which takes place with a mere change of solvent, and also does not account for the marked contrast in elimination of closely related ethers **4**, nor for the many earlier literature reports[36-43] of other discrepancies. For instance, in the dehydration of the β-hydroxy ester **13** (Scheme 3) the ester **14** should be the main product, being the more stable conjugated unsaturated ester, but in fact the non-conjugated ester **15** is the predominant product by a factor of >7:3.[40]



Scheme 3

A reexamination of the literature data is merited to explain this divergence and that of several other related examples listed below.[38,39,41,42] Because of the apparently increased stabilization of partially conjugated cations (or ion pairs) compared to the cationic stabilization with an associated γ-CH bond, allyl dialkyl carbinols **16** would be expected to produce preferentially the conjugate diene product **17**, but again a 7:3 preference is shown for the 1,4-diene product **18** (Scheme 4). Thus the cationic decomposition pathway b is favoured over pathway a, when R^1 = H and R^2 = Me (or other alkyl group).



Scheme 4

Comparison of the dehydration of **16** with that of its saturated analogue, dimethyl propyl carbinol, shows that the Saytzev product is favoured more in the saturated molecule. Substitution of an additional methyl group in **16** (R^1 = Me) increases the unconjugated product to 90% and reaches 100% for R^1 = i-Pr (Scheme 4). Even allyl methyl phenyl carbinol produces the unconjugated pentadiene **18** (R^1 = H; R^2 = Ph).[38]

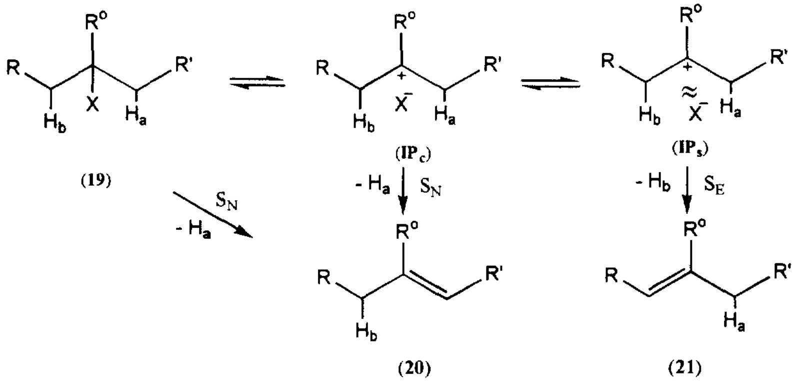
From these facts, it is clear that a β-vinyl (or phenyl) group does *not* facilitate abstraction of an adjacent hydrogen, and even tends to discourage it. Thus, it would appear that the commonly-held interpretation of the Saytzev rule, which states that elimination takes place *via* an intermediate represented by a (partially) pre-formed double bond, in which conjugation with a substituent may lower the transition state energy, is *little more than a myth*. Furthermore, the range of molecules and reaction conditions in which the Saytzev rule of elimination correctly predicts the outcome of the reaction is so limited as to be of little or no practical value.

The eliminations in the unsaturated alcohols above is similar to those of other molecules in which p-electrons are present on atoms adjacent to the eliminating groups. An explanation may lie in the elimination of the hydrogen *via* an intramolecular E2H type interaction. But a wider explanation is required to allow for the concurrent inclusion of saturated hydrocarbon derivatives in an overall explanation.

Quantum mechanical calculations imply that the most important factor influencing the orientation of elimination is the nucleophilicity of the electrons in the C-H bond. This can be realized by adjacent electron-donating substituents or by the abstraction of a proton by an external or internal base. For this stage of the reaction, thermodynamic factors play a less important role.

4. A UNIFIED RULE FOR ELIMINATION (URE)

In 1962 Ingold implied that elimination may be characterized by both nucleophilic as well as electrophilic indications.[44] However, this view was not specifically spelt out, and later authors have always presented elimination as a nucleophilic substitution process.[1-6] However, taking both options into account, the orientation of elimination may be predicted or explained in terms of ordinary substitution reactions using guidelines which are common to all structural units, independent of the presence or absence of p-electrons on a nearby group in the substrate. In Scheme 5 the three-carbon central unit of the model system **19** carries the substituent groups as indicated. If the substrate or reaction conditions retard the heterolysis of the C-X bond, then ethylenes **20** are formed, either *via* contact ion pairs (**IP**$_c$), or directly, without ion pair formation. On the other hand, if substituents and/or reaction conditions promote heterolysis of the C-X bond, then ethylenes **21** result, *via* solvated ion pairs (**IP**$_s$). The equilibrium between ion pairs moves towards increased **IP**$_s$ with better nucleofuges and/or greater solvating power.[29] **IP**$_c$ reacts *via* a nucleophilic substitution (or 'nucleophile-led' elimination, tending to E2 in the spectrum of mechanism), whereas **IP**$_s$ decomposes *via* an electrophilic substitution ('electrophile-led', or elimination tending to the E1 extreme). The direct transformation of (**19**) to (**20**) is also a 'nucleophile-led' reaction (tending to E1cb). (The alternative descriptions in parentheses follow the usage of other groups of workers.)



R = Electron donating substituent
X = Nucleofuge
H$_a$ = More acidic hydrogen

R' = Electron withdrawing substituent
R° = Group with variable electronic properties
H$_b$ = Less acidic hydrogen

Scheme 5

This striking difference in behaviour between the two cationic particles is caused by the continuing close proximity of the departing leaving group X in the case of $\mathbf{IP}_c$. The poorer nucleophiles merit greater interaction from the adjacent β-CH bond to effect collapse of the cationic ion pair, and therefore the more acidic hydrogen H_a is preferentially eliminated, giving products **20**. The cationic intermediate effectively undergoes a nucleophilic substitution (at the hydrogen atom). In contrast, the solvated ion pair $\mathbf{IP}_s$ collapses *via* an electrophilic substitution with the more hydride-like β-hydrogen H_b, leading to the preferential formation of the ethylenes **21**.

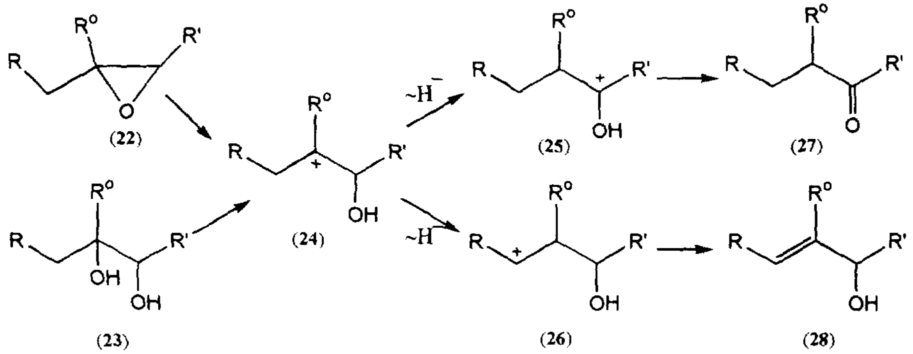
We believe that the concept that we describe above has general application to a wide range of elimination reactions, and we have therefore termed it as a "Unified Rule of Elimination" (URE).

5. SOME EXAMPLES OF THE APPLICATION OF THE URE CONCEPT

The elimination of 2-haloalkanes in alkoxide/alcohol media[14] shows increasing proportions of the 1-ene in the products along the series I < Br < Cl << F. Relative to model **19**, R = Me or Et, R^o = R' = H. R' is more electronegative than R, and promotes elimination of H_a with increasing difficulty of C-X bond cleavage, and greater involvement of contact ion pairs $\mathbf{IP}_c$.

The acid-catalyzed dehydration of β-hydroxy carboxylic acids, and their esters **13**, do not accord with the previous Saytzev-Hofmann theories.[1-7]. However, molecules with a secondary hydroxyl group (R^2 = H) form αβ-unsaturated products **14**, while the tertiary hydroxy derivatives (R^2 = alkyl) produce the βγ-unsaturated compounds **15**. In the tertiary alcohols, heterolysis is more likely to lead to a greater presence of the $\mathbf{IP}_s$ ion pair, and subsequent elimination of the less acidic hydrogen to yield the non-conjugated product.

It is well known that, in the acid-catalyzed isomerization of epoxides (**22**), and of 1,2-glycols (**23**), carbonyl compounds **27** are formed. (Scheme 6) This transformation occurs in the presence of weak acids, or on heating. The corresponding allylic alcohols (**28**) are usually not produced or are formed in only trace amounts. The driving force for isomerization is the formation of the more stable hydroxy-carbocation (**25**), which is then deprotonated

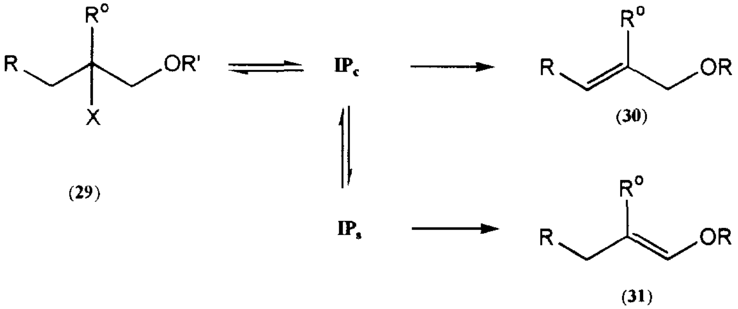


Scheme 6

to the carbonyl product **27**. The alternative transformation *via* the less stable carbocation **26** and subsequent formation of the allylic alcohol **28** has been regarded as almost impossible. However, using the guiding principles of the URE, it is possible to predict the conditions under which epoxides **22** (even with R = H and R^0 = Me) can be transformed into allylic alcohols (**28**) or their derivatives, and these reactions can be effected in yields of up to 90%.[46,47]

6. THE MASKED α-EFFECT

The URE concept gives the incorrect prediction of regioselectivity for elimination in molecules with a substituent carrying a lone pair of electrons on a carbon atom adjacent to that bearing the nucleofugal group (Scheme 7). Thus, **29**, under conditions favouring the generation of $\mathbf{IP_s}$, yields the olefin **30** rather than **31**. Furthermore, the opposite orientation results from conditions expected to favour $\mathbf{IP_c}$.[45,48]



Scheme 7

Literature data show that an interaction takes place between the lone pair of electrons on the α-alkoxy group and the electrons on the adjacent C-H bond.[49] The net effect is that the alkoxy group acts as a stronger electron donor, compared to a simple alkyl group[50,51], and this leads to the reverse regioselectivity to that normally expected from the URE concept for the different ion pairs $\mathbf{IP_c}$ and $\mathbf{IP_s}$.

CONCLUSION

At this stage, the URE concept offers a good explanation for many of the regioselectivities of elimination so far recorded in the literature, which are either in agreement or disagreement with the Saytzev rules of orientation. However, rather like the masked α-effect above, there may yet be other discrepancies to uncover. Not all elimination reactions occur *via* ion-pair intermediates; there are many well-known examples in which isotope effects clearly show, for relatively acidic β-hydrogen atoms and good α-leaving groups, that bimolecular E2 eliminations occur with basic reagents *via* transition states in which significant bond cleavage of both eliminating fragments occurs in the transition state without the advanced formation of ion pairs at the nucleofugal centre – the direct conversion **19** → **20** indicated in Scheme 5. The eliminations of 2-phenylethyl derivatives with alkoxide bases are typical examples of concerted E2 eliminations.[4] However, for the less acidic C-H bonds in the hydrocarbon and related examples cited in this article, the URE concept, through contact and solvent-separated ion pairs, affords an excellent explanation of the known facts of regioselectivity.

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