Chelating Agents and Urinary Calculi

Preliminary experiments with chelating agents such as ethylenediamine tetraacetic acid (Sequestrene, generously supplied by the Alrose Chemical Co., Providence, R. I.) and allied substances indicate a definite applicability to clinical problems. These compounds form strong unionized complexes with calcium, barium, strontium, zinc, lead, and other divalent ions, as well as some of the trivalent metallic ions. Each Sequestrene molecule bonds a molecule of the metal so that the product is quantitatively more effective against the heavier metals than the lighter. This differential affinity may be useful clinically.

Experiments *in vitro* have been run comparing the solubility of various urinary calcium calculi in a 3% solution of Sequestrene (pH 7.0) with that in Suby's solution G (pH 4.0), at present the most effective of the available clinical solvents. Sequestrene was found to be consistently much more effective with all types of stones used (calcium oxalate, calcium phosphate, and calcium carbonate). It has the additional advantage of a maximum efficiency at a neutral pH compared to the acid pH of Suby's solution. When used to irrigate the bladder, however, it was found to be fairly irritating. Whether this is due to the removal of the calcium ion or to impurities in the product, is still to be determined.

Other studies have been made using Sequestrene injected intravenously in rabbits as a treatment for acute lead poisoning. Theoretically, the heavier lead ion should be sequestered more effectively than the calcium so that subtetanic doses can be used. The early results appear promising.

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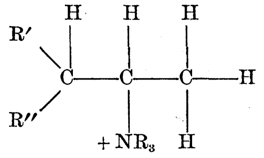
Steric Effects in Bimolecular Eliminations

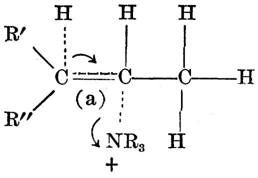
In a recent series of articles (*J. Chem. Soc.*, 1949, 2093), Hughes, Ingold, *et al.* have discussed bimolecular elimination reactions. Whereas attempts are made to explain the reasons for different products obtained in eliminations governed by Hoffman and Saytzeff rules, the reasons offered seem to be mere restatements of conditions necessary for the occurrence of the respective eliminations.

An explanation for the apparent anomality existing in eliminations that proceed by the Hoffman and Saytzeff rules may be based upon steric considerations (Schramm, Harvard University Seminar, Spring, 1949). In the case of elimination from quaternary salts (I), where $R' =$ alkyl, $R'' =$ alkyl or H,

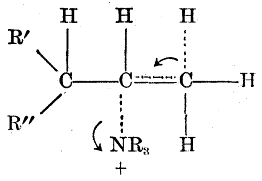
(I)



the transition state may be a priori either (II) or (III):

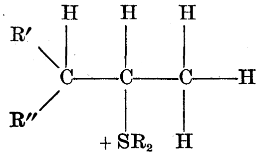


(II)



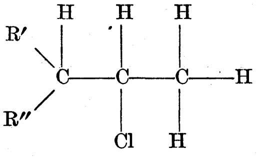
(III)

The transition state of (II) with electronic shifts as indicated would require groups R', R'', and $+NR_3$ to lie in one plane by virtue of the partial double bond character of the bond at (*a*). This would introduce a strong steric effect into the reaction, and elimination in the direction as indicated in (III) would be favored. Analogous reasoning would be applicable to the corresponding sulfonium salt (IV).



(IV)

When one considers the alkyl halide (V),



(V)

such steric limitations would, for the most part, be precluded. It may well be that the Saytzeff rule is the general rule that governs bimolecular eliminations, whereas the Hoffman rule is the exception, applying in cases where steric effects, such as outlined above, are involved.

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