approximately 850 units/mg of avian depressor activity[8] and 520 units/mg of oxytocic activity.[9] Thus the replacement of both sulfurs by selenium in deaminooxytocin yields a highly potent isolog. A further study of this isolog from various chemical, physical, and biological standpoints is indeed warranted.

Acknowledgments. The authors wish to thank the following members of this department for their cooperation: Dr. Theodore Mahowald and Mrs. Caroline Holzhauser for the amino acid analyses, and Dr. W. Y. Chan for the bioassays.

(8) R. A. Munsick, W. H. Sawyer, and H. B. van Dyke, *Endocrinology*, **66**, 860 (1960).

(9) Oxytocic assays were performed according to the method of P. Holton (*Brit. J. Pharmacol.*, **3**, 328 (1948)) on uteri from rats in natural estrus with the use of magnesium-free van Dyke–Hastings solution as employed by R. A. Munsick (*Endocrinology*, **66**, 451 (1960)).

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Chemistry of Conjugate Anions and Enols. VII. Rates of Formation and Equilibria of Enolate Anions[1,2]

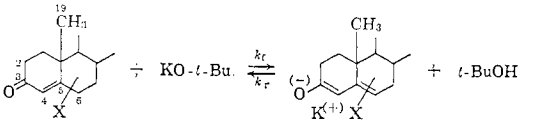
Sir:

Because of their high stability, solubility, and relatively fixed stereochemistry, the potassium enolate anions of Δ^4-3-keto steroids in *t*-butyl alcohol offer an ideal model for a systematic study of the factors that control the rate of formation and the stability of enolate anions as well as the nature of the transition state. Utilizing androst-4-ene-3,17-dione as primary substrate, the effects on enolization rate and equilibrium of alkyl and fluoro substitution have been measured and reveal a number of novel relationships not readily apparent in simple enolate systems.

The rate and extent of anion formation was best determined by quenching the *t*-butyl alcohol solution of steroid and potassium *t*-butoxide at various time periods with excess acetic anhydride.[3] Since only the enolate anion reacted under these conditions to form the $\Delta^{3,5}$-enol acetate, determination by gas chromatography of the ratio of enol acetate to unreacted ketone provided a semiquantitative measure of anion formation[4] that agreed well with values obtained by 4,4-dialkylation[5] or formation of the β,γ-unsaturated ketone by kinetically controlled protonation.[6] Table I lists the second-order rate constants for anion formation (k_f), the over-all equilibrium constants (K_{eq}), and the reverse rate (k_r) determined indirectly from K_{eq} and k_f.[7]

Entries 1 and 7 of the table, derived from a study of 6β-deuterioandrost-4-ene-3,17-dione *vs.* the nondeuterated compound, give the rates for axial and equatorial proton loss and gain from C-6 and demonstrate that 6β-(axial) proton loss is 53 times faster than 6α-(equatorial) loss ($k_{6\beta\text{-H},6\alpha\text{-H}}/k_{6\beta\text{-D},6\alpha\text{-H}} = 9$; 6$\beta$-deuterium loss 83% in enol acetate formation). The profound preference for axial proton loss despite greater steric hindrance from the β face strikingly emphasizes in a rigid system the importance of continuous $\sigma-\pi$ overlap of the departing (or entering) proton.[8] Since the C-19 angular methyl group is the major steric impediment to loss of the 6β proton to base, the 5- to 6-fold enhanced rate of protonation and of proton loss in the 19-nor compound (entry (4)) indicates an angular methyl *t*-butoxide interaction of *ca.* 1 kcal. Although the axial–equatorial preference has not been measured in (4) it is apparent that, in the absence of the angular methyl group, the true "stereoelectronic" axial preference should be approximately 300-fold, a magnitude much greater than previously suspected. In view of this preference, *cases of "equatorial" protonation in conformationally mobile systems must be considered in terms of axial protonation via nonchair conformations.*

Table I. Rates of Anion Formation and Reprotonation



		k_f,[a,b] l. mole^{-1} sec^{-1}	k_r,[c] l. mole^{-1} sec^{-1}	K_{eq} (27°)[a]
	Axial (6β) Proton Loss			
(1)	Androst-4-ene-3,17-dione	8.0×10^{-3}	1.6×10^{-5}	5.0×10^{2}
(2)	6α-Methyl-	2.9×10^{-3}	4.6×10^{-7}	6.3×10^{3}
(3)	6α-Fluoro	7.4×10^{-1}	3.1×10^{-5}	2.4×10^{4}
(4)	19-Nor-	4.0×10^{-2}	1.0×10^{-4}	4.0×10^{2}
(5)	4-Methyl-	1.8×10^{-3}	1.2×10^{-5}	1.5×10^{2}
(6)	2α-Methyl-	2.8×10^{-3}	5.6×10^{-5}	5.0×10^{1}
	Equatorial (6α) Proton Loss			
(7)	Androst-4-ene-3,17-dione	1.5×10^{-4} [d]	3.1×10^{-7}	5.0×10^{2}
(8)	6β-Methyl-	1.7×10^{-3}		
(9)	6β-Fluoro-	1.9×10^{-3}		

[a] Average value of three or more determinations. Average error *ca.* ±10%. [b] Forward rates are not corrected for the reverse reaction [c] Determined indirectly from k_f and k_{eq}. [d] Determined indirectly from $k_{6\beta\text{-H},6\alpha\text{-H}}/k_{6\beta\text{-D},6\alpha\text{-H}}$ and from 6β deuterium loss in enol acetate formation.

Entries (2) and (3) demonstrate that *either a 6-methyl or 6-fluoro substituent stabilizes the enolate anion* (13- and 48-fold, respectively). The 6α-fluorine effect is due primarily to a 90-fold increase in the rate of enolization, while the 6α-methyl group actually slows

(1) Supported by American Cancer Society Grant T-185.

(2) Previous paper in this series: T. D. J. D'Silva and H. J. Ringold, *Tetrahedron Letters*, 4487 (1965).

(3) H. J. Ringold and S. K. Malhotra, *J. Am. Chem. Soc.*, **84**, 3402 (1962); H. O. House and V. Kramer, *J. Org. Chem.*, **28**, 3362 (1963); S. K. Malhotra and F. Johnson, *J. Am. Chem. Soc.*, **87**, 5492 (1965).

(4) Product examination by thin layer chromatography showed only enol acetate and unreacted ketone except in the cases of the 6-fluoro derivatives where trace quantities of 6-dehydrosteroids were detected. The extent of dehydrohalogenation was not sufficient to significantly affect the results. The peak areas in gas chromatography were calibrated in each case with the authentic standard ketones and analytical specimens of the enol acetates which were prepared *via* the described anion quenching method.

(5) H. J. Ringold and S. K. Malhotra, *J. Am. Chem. Soc.*, **84**, 3402 (1962).

(6) H. J. Ringold and S. K. Malhotra, *Tetrahedron Letters*, 669 (1962).

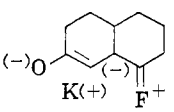
(7) For rate and equilibrium determinations, the unsubstituted and methylated steroids were studied at concentrations of 0.033 *M*, the 6α-fluoro compound at 0.0021 *M*, and the 6β-fluoro compound at 0.0167 *M*. The concentrations of potassium *t*-butoxide varied from 1 to 5 equiv based on steroid while the reaction time allowed for equilibration ranged from 1 (6α-fluoro) to 72 hr for the 4-methyl compound. In order to prevent autoxidation, all reactions were carried out in an atmosphere of nitrogen.

(8) E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **78**, 6269 (1956).

the rate of enolization by a factor of about 3 but reprotonation is slowed by a factor of 35. The forward rates, which involve axial proton loss in (1), (2), and (3), correspond to the anticipated inductive effect of fluorine *vs.* methyl; in the over-all reaction, it is apparent that the transition state in (3) reflects anion stability, while in (2) the reverse is true and the transition state must resemble the ketone.

A different pattern emerges with equatorial proton loss, as seen in the forward rates of the 6β-methyl (entry 8) and 6β-fluoro (entry 9) steroids. Either substituent increases the rate of enolization by a factor of about 10-fold relative to the unsubstituted steroid and, while k_f for 6β- and 6α-methyl are of the same magnitude, the rate of 6α-fluoro is 390× that of 6β-fluoro. As noted previously,[9] the 6β-methyl compound is highly unstable relative to the 6α isomer, and a close resemblance of the transition state in both cases to the common enolate anion would dictate a much faster enolization rate for the β-methyl isomer. The enhanced rate of (8) relative to the nonsubstituted compound may be due to a slight relief of strain in the transition state, or the diaxial 6β-19 methyl–methyl interaction may lead to deformation of the C-6 methylene in the ketonic ground state so that the 6α-proton is not strictly equatorial.

The 6β-fluoro rate increase of 13-fold is very likely primarily an inductive effect, although, as in (8), steric effects may play a small role. Since the over-all K_{eq} for anion formation must be even greater for the unstable isomers (8) and (9) than for the corresponding 6α-substituted compounds, it is clear from the small rate enhancement that the transition state of (9), in contrast to (3), cannot reflect the favorable free-energy factor for anion formation and must resemble the starting ketone. Yet, in enolization the inductive effect of either axial or equatorial fluorine must be essentially equal with respect to the departing proton; therefore, a resonance role must be invoked for fluorine that is operative in the transition state only when fluorine is equatorial. Such a contribution may be formally depicted as



which requires fluorine in the plane of ring B (equatorial) for continuous overlap. We believe the enhanced k_f of (3) relative to (9) and the shift toward enolate anion character in the transition state are due to this resonance contribution while a combination of this effect with inductive delocalization of charge explains the great stability of the fluoro enolate anion.

Enolate stabilization by the 6-methyl group may be attributed to hyperconjugation in common with the usual increased stability of a more substituted olefin. The failure to enhance k_f even with an equatorial methyl group in position for continuous participation may be a general phenomenon as evidenced by the equal enolization rates of nitromethane and nitroethane despite the much greater anion stability of the latter.[10] The parallel between anion stability and enolization rate with equatorial but not axial 6-fluoro suggests that *deviations from a free-energy relationship in other anionic systems* (in particular alicyclic) *containing strong electron-withdrawing groups such as halogen, double bond, nitrile, or carbonyl may be due to favored conformations that do not allow continuous participation of the resonating group.*

The important question of the direction of solvation of the potassium–oxygen ion pair and the extent of this interaction with adjacent methyl groups may be approached from the following observations. The 4-methyl group destabilizes the enolate anion by ~0.7 kcal (3-fold, entry (5)) while a 2α-methyl group (entry (6)) causes a 1.4 kcal destabilization. The equatorial 2α-methyl is essentially in the plane of oxygen in either the ketone or enolate anion; therefore, the effect of 1.4 kcal must arise completely as the result of a marked steric interaction between the solvated ion pair and that methyl group[11] (the electronic effect of methyl at C-2 should be negligible). With respect to the 4-methyl compound the decreased K_{eq} represents a summation of electronic and steric factors. If electronic stabilization of the double bond by methyl is more effective in the neutral unsaturated ketone than in the enolate anion, as appears most likely, the steric interaction of the 4-methyl with the ion pair must be less than 0.7 kcal. *This indicates that the steric requirement of the ion pair may be unsymmetrical about C-2 and C-4 with the greatest bulk directed away from the double bond and the C-4 position and toward C-2.*[12]

(9) S. K. Malhotra and H. J. Ringold, *J. Am. Chem. Soc.*, **86**, 1997 (1964).
(10) R. G. Pearson and R. L. Dillon, *ibid.*, **75**, 2439 (1953).
(11) See also S. K. Malhotra and F. Johnson, *ibid.*, **87**, 5513 (1965).
(12) It should be noted that with *t*-butyl alcohol as solvent, the oxygen–potassium ion pair of the enolate is undissociated and the degree of negative charge on ring carbons may be minimal. Studies are in progress to determine if the same resonance and steric interaction effects pertain in dissociating solvent systems.

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Reversible Addition of Sulfur Dioxide to Four-Coordinated Metal Complexes[1]

Sir:

The discovery of a synthetic oxygen-carrying system[1b] has led us to a study of the factors which are responsible for reversible oxygenation of metal complexes, both synthetic and natural. A part of this program has been concerned with finding analogies for molecular oxygen in its reversible reaction with the square-planar iridium complex, *trans*-[IrCl(CO)(Ph_3P)$_2$].[1b,2] Thus, we have been searching for reactions of the latter with small molecules which would remain *undissociated* in their adducts with the metal complex. These investigations have produced reversible addition compounds of [IrCl(CO)(Ph_3P)$_2$] with ethylene,[3] carbon monoxide,[4] and sulfur dioxide, the subject of this paper.

Prior to this investigation, the only known complexes containing SO_2 as ligand were those of the ruthenium–

(1) (a) Activation of Molecular Oxygen and Related Molecules by Transition Metal Complexes. II. (b) For part I, see L. Vaska, *Science*, **140**, 809 (1963).
(2) L. Vaska and J. W. DiLuzio, *J. Am. Chem. Soc.*, **83**, 2384 (1961).
(3) L. Vaska and R. E. Rhodes, *ibid.*, **87**, 4970 (1965).
(4) L. Vaska, submitted for publication.