G and V and albumin mixture shows slightly less broadening of the V peak and much less broadening of the G peak compared with their controls. Thus there is a competition for the binding sites on the albumin molecule.

Table VIb gives the results of an experiment carried out with 6-aminopenicillanic acid (6APA), the penicillin nucleus. 6APA does not interact with albumin itself, and does not inhibit the penicillin G interaction.

A similar experiment was carried out with the acetyl derivative of 6APA which was synthesized specifically for this purpose, since it has the shortest possible side chain while also containing the characteristic amide linkage. The results in Table VIc show this compound is not bound to albumin and does not inhibit the binding of penicillin G.

Tables VId and e show the results of inhibition with two analogs of the penicillin V side chain, phenoxyacetic acid (POAAc) and phenoxyacetamide (POAAm). These were chosen rather than the corresponding penicillin G analogs to prevent overlap in the spectra. The limited solubility of these compounds made it necessary to use a lower concentration range than was used in the preceding three experiments, i.e., 0.01 M penicillin G and 0.04 M inhibitor. Both of the

compounds tested were bound to the albumin (as judged by the increase in width of their methylene peaks) and also inhibited the binding of penicillin G.

The specificity of the inhibition agrees with the results of the experiments reported in the preceding section.

6APA, the nucleus of the penicillin molecule, does not bind or inhibit binding, indicating that its contribution to the observed binding is negligible. Furthermore, acetylpenicillin does not bind or inhibit. It is a complete penicillin containing the characteristic amide linkage but only a very short side chain. If the amide linkage were the binding site, this molecule should be the strongest inhibitor for there would be no possibility of steric hindrance interfering with bond formation.

Penicillin V binds and inhibits, as do the two small analogs of its side chain, POAAm and POAAc. These inhibition experiments clearly demonstrate, by a second, independent method, that the ring structure is the binding site.

Communications to the Editor

An Understanding of the Stereoselectivity of Base-Catalyzed Olefin Isomerization Based on a Thermodynamically More Stable cis-Allylic Anion

Sir:

Base-catalyzed prototropic shifts are often accompanied by unexpected kinetic control to the less stable *cis* form.[1-4]

Existing explanations to account for these stereoselectivities in the homogeneous base-catalyzed isomerizations of ethers, amines, and olefins are not wholly adequate. For example, the observation that 4,4-dimethyl-1-pentene shows considerable kinetic control to a *cis* product[5] makes it highly unlikely that an extension of the proposed metal cation bonding to a hydrogen[1] can account for the data. Similarly, Price's[6] explanation based on the energy difference of conformers is incompatible with the subsequent conclusion that all conformers of 1-butene are equally populated at room temperature.[7]

The rate of base-catalyzed olefin isomerization is a marked function of variations in the base and solvent.[8] In contrast, as reported here, the stereoselectivity shows a pronounced insensitivity to these factors.

The stereoselectivity was examined in a variety of bases and solvents. The pertinent data are summarized in Table I. Cation variations produce rate factors of 450 in going from sodium *t*-butoxide to cesium *t*-butoxide, an effect discussed in a forthcoming publication.[8] Of particular interest to the present study is the fact that the stereoselectivities are essentially the same for all the cations.

In addition, similar ratios of stereoselectivity are obtained with potassium methoxide and *t*-butoxide, although the rates of isomerization are markedly dependent on the anion (KO-*t*-Bu/KOMe = 125).

A striking resemblance to the results of the effect of base is observed in the study of the effect of solvent variations upon the stereoselectivity. Addition of the hydroxylic species *t*-butyl alcohol has essentially no effect upon the stereoselectivity. Indeed the factors which account for the rate decreases[9] cannot have direct bearing upon the stereoselectivity. Finally, base-catalyzed isomerization in several dipolar solvents proceeding at various relative rates once more produces similar stereoselectivities. The effect of solvent

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Base	Solvent	$10^{+3} k$, sec.$^{-1}$	(cis/trans) $t \to 0$[b]
	1-Butene, 55°		
NaO-t-Bu	DMSO[c]	0.01	37
KO-t-Bu	DMSO	1.16	26
RbO-t-Bu	DMSO	2.84	16
CsO-t-Bu	DMSO	4.47	25
KO-t-Bu	TMU[d]	0.0174	23
KO-t-Bu	N-Methyl-2-pyrrolidone	0.0785	26
KO-t-Bu	HMPA[e]	0.201	19
	1-Pentene, 55°		
KOMe	DMSO	0.00569	14
KO-t-Bu	DMSO	0.717	13
KO-t-Bu	DMSO + 0.5% t-BuOH	0.605	11
KO-t-Bu	DMSO + 1% t-BuOH	0.493	10
KO-t-Bu	DMSO + 2% t-BuOH	0.433	10
KO-t-Bu	DMSO + 4% t-BuOH	0.256	10
KO-t-Bu	DMSO + 8% t-BuOH	0.044	10

[a] Experimental details will be presented in a future publication.
[b] The uncertainty in these values is ±10% of the ratios. At least five points at low conversions were taken in each run.
[c] DMSO, dimethyl sulfoxide. [d] TMU, tetramethylurea. [e] HMPA, hexamethylphosphoramide.

upon the rate of isomerization will be discussed in a future publication.

The work reported here shows clearly that there is no correlation between the stereoselectivities and the rates, the cation, the anion, or the solvent involved in the isomerization. Therefore any explanation for the stereoselectivity must evolve from a property that is common to all of these systems, that is, a fundamental or intrinsic property of the system. We propose that this intrinsic property of the system is that for simple olefins the cis-allylic anion is thermodynamically more stable than the trans form.

That such an assumption can explain the kinetic results is seen by the following kinetic scheme. For simplicity ion pairs have been neglected in the formulation; their inclusion does not affect the over-all conclusion. With $k_{-5} > k_5$ the cis-allylic anion is more
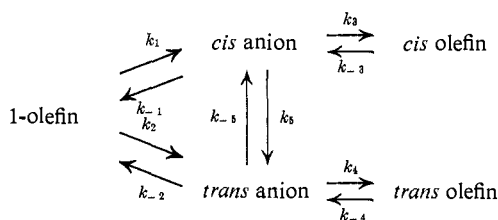
stable than the trans form. Both k_{-5} and k_5 are expected to be small, perhaps insignificant, for the eventual cis to trans olefin conversion; nonetheless the allylic anions once formed are expected largely to maintain their geometry.[10] The reprotonation of the anions is probably diffusion controlled and most reasonably the same for both anions. Then with $k_{-3} > k_{-4}$ the reaction initially produces more cis olefin, but with time the more stable trans olefin predominates.

While the kinetics are amply accounted for by the assumption that the cis-allylic anion is more stable than the trans form, some external justification is desirable. For this purpose halo-substituted olefins and Grignard reagents are used as models for the allylic

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anion formed in the base-catalyzed isomerization of simple olefins.

Recent data[11,12] have shown that halo-substituted propenes show unusual thermodynamics, namely, the cis form is more stable than the trans. Favorable dipole–dipole van der Waals interactions present only in the cis form have been invoked to account for the results.

The halopropenes are a better model for the allylic anions than the parent olefin for several reasons. First, the electronegativity of the anionic system is better represented both directionally and in magnitude by the halo-substituted compounds. Second, the dipole of the anionic system is expected to be as great or greater than that of the halo compounds. From these considerations the cis-allylic anion, in analogy with the cis-halopropenes and unlike the parent olefin, is expected to be more stable than the trans form. In addition, U-shaped pentadienyl anions are more stable than other planar forms although the corresponding transoid dienes are more stable than the cisoid dienes.[13]

Equally convincing support is found in the fact that a preference for the cis form is found in quenching butenyl Grignard reagents.[14] As a model, the fact that Grignard reagents are solvated and agglomerated makes them an excellent choice for the highly solvated anion formed in the isomerization reaction.

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Thermodynamic Stability of Allylic Intermediates

Sir:

A previous communication presents evidence that the stereoselectivity observed in the base-catalyzed olefin isomerization is the result of the fact that the cis-allylic anion is thermodynamically more stable than the trans form.[1] Favorable dipole attractive forces in the cis form were offered to account for the thermodynamic reversal relative to the parent hydrocarbons. In the present communication the extension of this simplified scheme to other reactive intermediates is considered. Of compelling interest is the conclusion that the thermodynamic stabilities of these intermediates can be derived from charge and dipole considerations.

There will be interactions of the dipole of a methyl group and the dipoles of the various allylic intermediates, Ia–c and IIa–c (where a, b, and c are 0, 1, and 2 π-electrons).
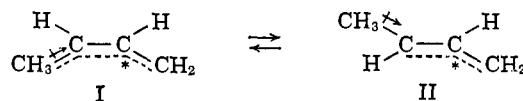
It is the purpose of this communication to demonstrate that the thermodynamic isomeric preferences can be predicted by a consideration of these interations.

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