column chromatography over silica gel: ^{1}H NMR δ 7.5–7.0 (5 H, m), 3.10 (4 H, s broad), 2.35 (3 H, s); MS, m/z (%) 212 (13), 136 (100), 123 (26), 110 (74), 109 (27).

General Procedure for the Acetolysis of Tosylates 1 and 3. The reactions were performed on 1.5 g of the substrates dissolved in 50 mL of anhydrous AcOH, and the solutions were kept at 40 °C under a N_2 atmosphere. Samples were taken after 30, 60, 120, 180, 240, 300 min and treated as follows: dilution with 30 mL of cold CH_2Cl_2, repeatedly washings at 0 °C with H_2O, $NaHCO_3$ solution, and again with H_2O until neutral. The organic layers, dried over Na_2SO_4, were evaporated to dryness under reduced pressure at 20 °C. The progress of the reaction was followed by ^{1}H NMR analysis ($CDCl_3$). In particular, with tosylate 1 it was evaluated by the decay and/or the disappearance of the signals at δ 2.45 (arom CH_3) and 4.10 (CH_2OTs) and the appearance of the signals at δ 2.01 (CH_3COO), 3.10 (CH_2S), and 4.25 (CH_2OAc). With tosylate 3, the calculations were analogously made by measuring the decay and/or the disappearance of the signals at δ 2.45 (arom CH_3) and 3.10 (CH_2S) and the appearance of those at δ 2.01 (CH_3COO), 4.10 (CH_2OTs), and 4.25 (CH_2OAc). The final reaction mixtures were purified by chromatography over silica gel; elution by *n*-hexane gave mixture of acetates 4 and 5. When present, the tosylate 1 and 3 were obtained by elution with hexane–ethyl acetate, 1:2. MS/GC analyses were also performed on the final mixtures.

1-Acetoxy-2,2-dideuterio-2-(phenylthio)ethane (4): oil; ^{1}H NMR δ 7.5–7.0 (5 H, m), 4.25 (2 H, s), 2.01 (3 H, s); MS, m/z (%) 198 (12), 137 (100), 125 (27), 110 (11), 109 (22).

1-Acetoxy-1,1-dideuterio-2-(phenylthio)ethane (5): oil; ^{1}H NMR δ 7.5–7.0 (5 H, m), 3.10 (2 H, s), 2.01 (3 H, s); MS, m/z (%) 198 (13), 138 (100), 123 (22), 110 (5), 109 (15).

General Procedure for the Thioacetolysis of Tosylates 1 and 3. The reactions were run on 1.5 g of the substrates dissolved in 50 mL of CH_3COSH (Fluka) at 40 °C under stirring and in N_2 atmosphere, following the above described procedure for the acetolysis. In the thioacetolysis of 1 the ^{1}H NMR analysis of the samples (taken after 15, 30, 60, 90, 120, 180 min) was based on the decay of the signal at δ 4.10 (CH_2OTs) and the appearance of the signals at δ 3.10 (due to $CH_2SC_6H_5$ and/or CH_2SCOCH_3) and 4.25 (CH_2OCSCH_3), without considering the remaining signals at δ 2.00 (CH_3CSO), 2.35 (CH_3COS), and 2.45 (arom CH_3). Instead, ^{1}H NMR analysis did not result as a very effective tool in following the progress of the thioacetolysis of 3 except for the absence, through out the reaction, of the signals at δ 4.25 (due to the methylene on oxygen) and 4.10 (due to the rearranged tosylate 1). The crude mixtures were chromatographed over a silica gel column; elution with *n*-hexane gave first the thiol acetates 8 and 9 (in 1:1 ratio) and subsequently the pure thionoacetate 6 in the thioacetolysis of 1 and 7 in that of 3. The results are reported in Table IV. The thioacetolysis of 1, when performed at 90 °C, was completed after 15 min. In this case the final mixture, according to the above procedure, gave only a 1:1 mixture of the thiolacetates 8 and 9.

2,2-Dideuterio-2-(phenylthio)-1-thioacetylethane (6): oil; ^{1}H NMR δ 7.5–7.0 (5 H, m), 4.25 (2 H, s), 2.00 (3 H, s); MS, m/z (%) 214 (26), 137 (100), 136 (78), 125 (34), 110 (14), 109 (27).

1,1-Dideuterio-2-(phenylthio)-1-thioacetylethane (7): oil; ^{1}H NMR δ 7.5–7.0 (5 H, m), 3.10 (2 H, s), 2.00 (3 H, s).

2,2-Dideuterio-2-(phenylthio)-1-(acetylthio)ethane (8) and 1,1-dideuterio-2-(phenylthio)-1-(acetylthio)ethane (9) were obtained in a 1:1 ratio as an oily mixture: ^{1}H NMR δ 7.5–7.0 (5 H, m), 3.10 (2 H, s broad), 2.35 (3 H, s); MS, m/z 214 (19), 137 (100), 138 (76), 125 (16), 123 (15), 110 (45), 109 (30).

Dichloroacetolysis of Tosylate 1. The reaction was run on 0.5 g of substrate dissolved in 17 mL of $CHCl_2COOH$ (Fluka) at 40 °C with stirring and under a N_2 atmosphere. Samples were taken after 60 and 120 min and treated as for the above solvolyses. The progress of the reaction was followed by ^{1}H NMR analysis ($CDCl_3$), estimating the new signals at δ 3.20 ($C_6H_5SCH_2$), 4.40 (CH_2OCO), and 5.90 ($CHCl_2$) and the decay of those at δ 2.45 (CH_3 arom) and 4.10 (CH_2OTs). The conversion was 85% after 1 h and 100% after 2 h. Oily mixtures 1:1 of **2,2-dideuterio-2-(phenylthio)-1-(dichloroacetoxy)ethane (10)** and **1,1-dideuterio-2-(phenylthio)-1-(dichloroacetoxy)ethane (11)** were obtained: ^{1}H NMR δ 7.5–7.0 (5 H, m), 5.90 (1 H, s), 4.40 (1 H, s), 3.20 (1 H, s); MS, m/z (%) 266 (15), 139 (40), 138 (71), 137 (100), 125 (21), 123 (20), 110 (18), 109 (63).

Solvolytic Reactions of Ethyl *p*-Toluenesulfonate. Acetolysis, thioacetolysis, and dichloroacetolysis of the above tosylate were run at the refluxing temperature. After 18 h the relative conversion were 1%, 18%, and 25%, respectively.

Acknowledgment. We wish to acknowledge the helpful experimental assistance of Sonia Mini. Financial support by the National Research Concil (CNR) and Public Education Ministry (MPI) is also acknowledged.

Registry No. 1, 109244-24-8; 3, 109244-17-9; 4, 109244-23-7; 5, 109244-22-6; 6, 118298-67-2; 7, 118298-68-3; 8, 118298-69-4; 9, 118298-70-7; 10, 118317-79-6; 11, 118317-80-9; 2-(phenylthio)ethyl *p*-toluenesulfonate, 116047-07-5; 1-acetoxy-2-(phenylthio)ethane, 20965-30-4; 1-hydroxy-2-(phenylthio)ethane, 699-12-7; 2-(phenylthio)-1-thioacetyl ethane, 14476-42-7; ethyl *p*-toluenesulfonate, 80-40-0.

Mechanism of *E*/*Z* Stereoisomerization of Imidate Anions

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Kinetics of *E*/*Z* stereoisomerization of *N*-arylformimidate anions, HC(O$^-$)=NAr, in *N*-methylpropionamide solvent were determined by an NMR saturation-transfer method. A Hammett plot of the rate constants gives a slope ρ of +2.3 ± 0.2 or +2.1 ± 0.3. This value is very close to the ρ of 2.2 observed in similar imine stereoisomerizations known to proceed by nitrogen inversion. It is inconsistent with the ρ of 3.8 expected for stereoisomerization by C–N rotation. It is therefore concluded that *E*/*Z* stereoisomerization of imidate anions proceeds by nitrogen inversion, despite a high-level MO calculation that favored C–N rotation.

Introduction

Despite continual investigation into the dynamic stereochemistry of amides,[1] their conjugate bases—imidate anions—have been largely neglected. These are important as catalysts,[2] as ligands for metal ions,[3] including those at enzyme active sites,[4] and as intermediates in organic

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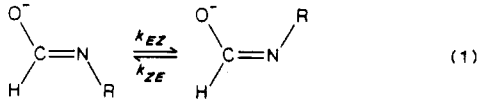
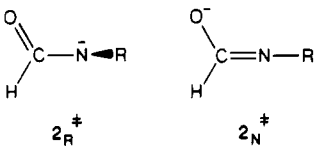
synthesis,[5] although their formation is sometimes only incidental.[6] However, only two studies of their stereochemistry have been reported. By ^{1}H NMR spectroscopy it was possible to characterize imidate anions, to detect both E and Z forms of N-alkylformimidate anions (1), and to determine the equilibrium between them (eq 1).[7] The



(1)

barrier to interconversion was determined to be 18–23 kcal/mol, depending on R. This is nearly the same as the barrier to E/Z interconversion by C–N rotation in amides even though amides have less C–N double-bond character. It was therefore concluded that E/Z interconversion of imidate anions (1) occurs by nitrogen inversion, rather than C–N rotation. Subsequently it was found[8] that N-(perfluoroalkyl)fluoroformimidate anions, $FCONR_F^-$, exist in two forms, but these interconvert by F^- dissociation.

Nguyen and Hegarty[9] have disputed the conclusion[7] that E/Z stereoisomerization of imidate anions occurs by nitrogen inversion. According to their MO calculations and a previous one,[10] the transition state for C–N rotation ($2_R^‡$) is of lower energy than that for nitrogen inversion ($2_N^‡$).



Relative to other imines, the O^- substituent greatly reduces the C–N double-bond character and lowers the barrier to C–N rotation. Yet it is not certain that this lowering is sufficient to render this barrier lower than the one for nitrogen inversion. We have therefore undertaken an experimental investigation to determine which mechanism of stereoisomerization is operative.

The two mechanisms can be distinguished through study of substituent effects on rates. If R = X-substituted phenyl, the Hammett equation (eq 2)[11] can be used to

$$\log k_X = \log k_H + \rho\sigma_X \quad (2)$$

correlate the rates. The transition state for the C–N rotation mechanism ($2_R^‡$) has the full negative charge on the nitrogen, without the possibility of delocalization into the carbonyl. Reaction by this mechanism should be greatly accelerated by electron-withdrawing substituents on nitrogen. This corresponds to a large positive slope ρ in a plot of eq 2. In contrast, the negative charge remains on oxygen in the transition state for the inversion mechanism ($2_N^‡$). Electron-withdrawing substituents should still accelerate the reaction, since the nitrogen lone pair in $2_N^‡$ is in a pure 2p atomic orbital and is thereby more delocalizable. However, the acceleration should be weaker, corresponding to a small positive ρ. This comparison is not so clear-cut as that with some imines,[12] where ρ is positive for inversion and negative for a (different) rotation mechanism. Indeed, an early study[13] erroneously inferred a rotation mechanism from acceleration by an electron-withdrawing substituent, and Herkstroeter[12] despaired of using substituent effects to distinguish mechanism when both show the same sign of ρ. However, the magnitude of ρ is significantly different for the two mechanisms. By comparison with suitable model reactions it is possible to estimate these magnitudes. We now report a ρ that is consistent with the inversion mechanism and too low to be consistent with the rotation mechanism.

Experimental Section

Formanilide was purchased from Aldrich. All of the substituted anilines used in the synthesis of the substituted N-phenylformamides were purchased from Aldrich, Mallinckrodt, or Matheson, Coleman and Bell. Formic acid was purchased from J. T. Baker Chemical. N-Methylpropionamide was obtained from Eastman Chemical. All starting materials were used without further purification.

N-Arylformamides were prepared by standard procedure.[14] Typically 5 g of the substituted aniline was refluxed in a 3- to 5-fold excess of formic acid for 2–4 h. The resulting formanilides were taken up in CH_2Cl_2, washed three times with 3 N HCl, and dried over $MgSO_4$. Evaporation of the CH_2Cl_2 under reduced pressure was followed by recrystallization from ethanol, chloroform, or cold ether. All melting points agree with literature values.

Formimidate anions were prepared by adding approximately 3×10^{-4} mol of amide to 1 mL of basic N-methylpropionamide solution. This stock solution was prepared by adding N-methylpropionamide dropwise to KH that had been washed three times with hexanes and dried with a stream of nitrogen. Titration verified that the resulting stock solution was approximately 0.4 M potassium N-methylpropionimidate in N-methylpropionamide. The excess of base forestalled the need for special precautions to exclude air or moisture.

FT-NMR spectra were obtained with a Nicolet 293B pulse programmer and 1180E computer interfaced to an Oxford 360-MHz magnet. Probe temperatures were calibrated[15] with methanol at temperatures below ambient and with ethylene glycol above ambient. Equilibrium constants (K_e = [E imidate]/[Z imidate]) were determined by integration of formyl CH peaks. Saturation–transfer studies were performed by measuring the steady-state intensity and spin–lattice relaxation time of the major formyl peak (H_E) while saturating the minor formyl resonance (H_Z). Spin–lattice relaxation times (T_1) were measured by the inversion–recovery method. The usual (nonselective) inversion method was complicated by biphasic relaxation owing to dipolar interactions with solvent protons and ortho protons. The Dante pulse[16] was chosen to provide selective excitation of only the major formyl resonance. Inversion was accomplished by approximately 300 1-μs pulses at low transmitter power and separated by 200-μs delays.

Rate constants were calculated[17] according to eq 3 and 4, where $M_E(Z)$ is the apparent spin–lattice relaxation rate constant of the formyl CH peak of the E isomer while holding the Z formyl CH saturated, and $t_E(Z)$ is the fractional decrease of intensity of the E formyl peak upon saturation of the Z peak. For optimum

$$k_{EZ} = M_E(Z)t_E(Z) \quad (3)$$

$$k_{ZE} = k_{EZ}K_e \quad (4)$$

accuracy the temperatures were chosen so that $t_E(Z)$ would be approximately 0.5. Inversion–recovery data were well fit to a single exponential by Nicolet's nonlinear least-squares routine, which

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(17) Equation 3 of ref 7 is incorrect. It should read as it appears in this paper. This error affects some of the values in Table VI of ref 7, but only slightly.

Table I. Saturation-Transfer Data for E/Z Interconversion of N-Arylformimidate Anions, $HC(O^-)=NAr$

X	K_e	T, °C	$t_E(Z)$	$M_E(Z)$, s^{-1}	k_{EZ}^T, s^{-1}	$\Delta G_{EZ}^{\ddagger}$, kcal/mol
3-nitro	3.8 ± 0.1	3.5	0.70 ± 0.02	4.0 ± 0.2	2.8 ± 0.1	15.58 ± 0.03
3-bromo	*a*	4.4	0.605 ± 0.01	2.85 ± 0.09	1.72 ± 0.06	15.90 ± 0.02
4-bromo	3.5 ± 0.2	8.5	0.35 ± 0.01	1.68 ± 0.03	0.60 ± 0.02	16.72 ± 0.02
3-methoxy	2.43 ± 0.09	15.2	0.41 ± 0.01	1.65 ± 0.04	0.68 ± 0.03	17.08 ± 0.02
H	2.7 ± 0.1	22.6	0.49 ± 0.01	1.64 ± 0.03	0.80 ± 0.03	17.42 ± 0.02
3-methyl	3.3 ± 0.3	23.9	0.425 ± 0.008	1.74 ± 0.05	0.74 ± 0.02	17.55 ± 0.02
3,5-dimethyl	4.5 ± 0.2	22.6	0.42 ± 0.02	1.80 ± 0.03	0.76 ± 0.04	17.46 ± 0.01
4-methyl	4.0 ± 0.2	31.5	0.52 ± 0.01	1.52 ± 0.03	0.79 ± 0.03	17.98 ± 0.02
4-methoxy	3.2 ± 0.2	41.6	0.48 ± 0.01	1.25 ± 0.06	0.60 ± 0.04	18.77 ± 0.04

[a] Not determined, owing to overlap with solvent NH peak.

provides error estimates (standard deviation), verified or augmented by repetitive measurement. Standard errors of $t_E(Z)$ were obtained from repetitive measurement. Errors in rate constants and activation free energies were calculated according to propagation of errors. Rate constants were extrapolated to 25 °C with the simplifying approximation that each observed $\Delta G^{\ddagger}$ is independent of temperature.

Results

Previously it has been shown[7] that N-phenylformimidate anion could be prepared with excess NaOH in hydroxylic media. However, rate constants for stereoisomerization were observed to depend on the concentration of NaOH, presumably because E/Z interconversion can also occur via the amide. Even though an excess of base shifts the equilibrium far toward the imidate anion, if the amide's barrier to interconversion is slightly lower,[7] even a small fraction of amide can contribute to the observed rate constant. Therefore a less acidic solvent was sought. This solvent must also be polar, not only so that imidate salts will be soluble but also so that the equilibrium will not be shifted strongly toward the E imidate, which predominates in THF.[7]

N-Methylpropionamide was found to be optimum. It is suitably polar (ϵ = 172.2).[18] By adjusting the concentration of base it is possible to arrange that no NMR signals interfere with any formyl CH resonance peaks (except for N-(3-bromophenyl)formimidate anion at 5 °C). This solvent can hydrogen bond to a formimidate anion and retard E/Z interconversion so that rates are conveniently measured near room temperature. Its NH proton can be readily removed with KH. However, its methyl is much less electron withdrawing than an aryl group, so that it is not expected to be acidic enough to protonate an N-arylimidate. Indeed the rate constants in N-methylpropionamide solvent are independent of the concentration of excess base.

The formyl region of the NMR spectrum of an N-arylformimidate anion shows two CH singlets near 8.7 and 8.3 ppm, corresponding to the E and Z isomer, respectively. These assignments are based on the general conclusion that the formyl CH resonance of the E isomer of imidate anions is found downfield of the Z isomer.[7] The E/Z ratio varies near 3 but with no apparent pattern. This is further evidence that even the less acidic amides have been converted completely to their conjugate bases, since otherwise the apparent E/Z ratio would be reduced toward the 0.4 of the amides. The equilibrium constants, saturation-transfer data, rate constants, and activation free energies are shown in Table I.

These results are in good agreement with previous work[7] in which it was found that $\Delta G^{\ddagger}_{EZ}$ for N-phenylformimidate in ethylene glycol is 18.5 kcal/mol. Since N-methylpropionamide is not as good as ethylene glycol at forming hydrogen bonds, the barrier to imidate isomerization is lower in the propionamide.

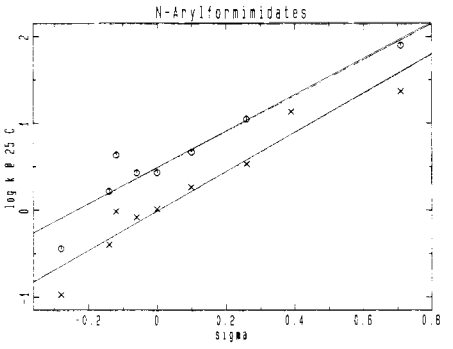

Figure 1. Hammett plot of rate constants for E/Z stereoisomerization of N-arylformimidate anions; k_{EZ} (×), k_{ZE} (○).

Figure 1 shows a Hammett $\rho\sigma$ correlation for the isomerization of the N-arylformimidate anions. Values of σ were taken from Exner's compilation.[11] The slope ρ is +2.3 ± 0.2 for k_{EZ} (correlation coefficient 0.96). The ρ value for k_{ZE}, +2.1 ± 0.3, is less reliable (correlation coefficient 0.95) because of the additional uncertainty in K_e.

Discussion

It is necessary to compare the observed ρ of +2.3 with the ρ for each of the two possible mechanisms. Neither ρ can be determined independently. Each must be estimated from ρ values observed in model reactions.

The transition state for the C–N rotation mechanism ($\mathbf{2_R}^{\ddagger}$) is characterized by localization of the negative charge on nitrogen. The simplest model for this is the pK_a of anilines, for which ρ is 4.9.[19] However, this does not take any account of electron withdrawal by the carbonyl in $\mathbf{2_R}^{\ddagger}$. Only an inductive effect can be exerted, since the carbonyl is orthogonal to the 2p lone pair on nitrogen. A more suitable model is thus the pK_a of N-arylanilines, for which ρ has been reported[19] as 4.07. However, it is necessary to omit the electron-donating substituents, since these force the negative charge to be delocalized into the unsubstituted phenyl ring. Then ρ can be recalculated as 4.3. Actually, this is an underestimate, since the electron-withdrawing power of a phenyl ring is slightly greater than the inductive effect of a carbonyl, as judged from the comparison of N,N-dimethylanilinium (pK_a 5.06[20]) with a protonated 1-azabicyclo[2.2.2]octan-2-one (pK_a 5.6[21]). It is further necessary to correct for the negative charge present in the reactant imidate 1. This negative charge is localized chiefly on the distant oxygen. The interaction between this charge and the aromatic ring may be modeled by ionization of

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arylacetic acids, for which $\rho = 0.56$.[11] This model is imperfect, but serious error would be introduced only if this ρ should approach 2. This entire argument may be summarized by the assertion that the equilibrium constant for the overall reaction of eq 5 should be nearly independent of Ar substituents. It leads to the conclusion that ρ for the rotation mechanism ought to be $4.3^{+} - 0.56$, or ca. +3.8.

$$HC(O^{-}){=}NAr + PhN\tilde{A}r + ArCH_2COOH \rightleftharpoons HC(=O)N\tilde{A}r^{*} + PhNHAr + ArCH_2CO_2^{-} \quad (5)$$

The inversion mechanism is well modeled by imine isomerizations known[22] to proceed by nitrogen inversion. Except for *N*-aryl ketenimines,[23] where delocalization of the nitrogen lone pair reduces ρ to 0.4, values of ρ, corrected to 25 °C, range from 1.3 to 2.2: (*N*-arylimino)dithiocarbonates ($\rho = 1.3$[24]), (*N*-arylimino)carbonates ($\rho = 1.4$[24]), benzophenone *N*-arylimines ($\rho = 1.9$[25]), benzoquinone *N*-arylimines ($\rho = 1.9$[26]) benzaldehyde *N*-arylimines ($\rho = 2.0$[27]), *N*-aryltetramethylguanidines ($\rho = 2.2$[28]). Moreover, ρ seems to increase as carbon substituents become more electron-donating. Guanidines are the closest model to imidate anions, which have a strongly electron-donating O^{-} substituent. Therefore in imidate anions ρ for the inversion mechanism ought to be ca. 2.2.

Conclusions

It is clear that the observed ρ of 2.3 ± 0.2 or 2.1 ± 0.3 is in good agreement with the ρ of 2.2 expected for the inversion mechanism. Moreover, the observed ρ does not agree with the ρ of 3.8 expected for the rotation mechanism. It is very difficult to reconcile so low an observed ρ with the rotation mechanism. We therefore conclude that E/Z stereoisomerization of imidate anions occurs by nitrogen inversion.

Why do the molecular-orbital calculations lead to the opposite conclusion? Calculations on anions are often unreliable, since orbitals are diffuse, so that even with large basis sets convergence can be slow.[29] The calculations of Nguyen and Hegarty[9] are certainly at a high level, with diffuse functions, and including electron correlation and configuration interaction. Nevertheless their best calculated value for the activation energy ΔE^{*} is 27.5 kcal/mol (29.6 kcal/mol with one water of solvation), whereas our experimental ΔG^{*} is 17.4 kcal/mol. If the calculated value (the energy difference between transition state and reactant) is subject to so large an error, the calculated difference between ΔE^{*} for C–N rotation and ΔE^{*} for nitrogen inversion may also be subject to such an error. An error of 7 kcal/mol would be sufficient to vitiate the calculations.

There is further reason to suspect the calculations. The 4-31G barrier to C–N rotation in formamide is 20.3 kcal/mol.[30] This is to be compared with the 4-31G barrier to rotation in formimidate anion, which is 30.3 kcal/mol.[9] This large increase on deprotonation is in accord with the increased C–N double-bond character in an imidate anion (as evidenced[7] by a larger $^{4}J_{HCNCH}$). Yet no increase is seen experimentally. Instead the barrier in an imidate anion is almost equal to that in the corresponding amide.[7] This equality does not fit with the rotation mechanism. The barrier to C–N rotation could well be 30 kcal/mol. However, our observed barrier of 17.4 kcal/mol is lower because it corresponds to the inversion mechanism.

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