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Stereochemistry of Thermal Chlorine-for-Bromine Substitution in Diastereomeric 3-Bromo-4-fluorohexane

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Synopsis. The stereochemistry of thermalized chlorine-for-bromine substitution was studied in gaseous (3*RS*,4*SR*)- and (3*RS*,4*RS*)-3-bromo-4-fluorohexane. While energetic chlorine-for-bromine substitution occurs by a two-channel substitution mechanism, one leading to retention, the other to inversion of configuration, thermal chlorine-for-bromine substitution at the sp^3-hybridized carbon of the diastereomers proceeds extensively, if not exclusively, via stereochemical inversion.

The stereochemistry of energetic homolytic bimolecular substitution reactions ($S_{HH}2$) by recoil halogen atoms at asymmetric carbon atoms employing substrate molecules possessing two chiral carbon centers[1–5] occur predominantly with retention of configuration. Subsequent studies on the gas phase substitution of energetic chlorine-for-halogen on substrate molecules possessing a single chiral center[6–10], have yielded significantly higher levels of inversion. The degree of stereospecificity of the substitution reaction depends on the nature of the chiral molecule. From earlier studies, Ingold and Roberts[11] concluded that available data could not provide unequivocal evidence for the existence of thermoneutral homolytic bimolecular halogen-for-halogen substitution reactions (S_H2) at thermal energies. They suggested that highly exothermic substitution reactions might be more probable. Kinetic studies by Iyer and Rowland[12,13] demonstrated this point with thermal fluorine atom substitution for Cl, Br, and I in methyl halides (exothermicity of 105 kJ mol^{-1} with F/Cl, 159 kJ mol^{-1} with F/Br, and 218 kJ mol^{-1} with F/I). Firouzbakht et al.,[14] in their study of the effects of neon moderators on the ^{18}F-for-Cl substitution at the chiral center in (*S*)-(+)-2-chloropropionyl chloride demonstrated that nonthermal (energetic) F-for-Cl substitutions yielded a slight preference for stereochemical retention and thermal F-for-Cl substitutions yielded exclusive stereochemical inversion.

The present study investigated the stereochemical consequences of exothermic ^{38}Cl-for-Br substitution at asymmetric carbon atoms in moderated and unmoderated systems of (3*RS*,4*SR*)- and (3*RS*,4*RS*)-3-bromo-4-fluorohexane (BFH). This allowed the effect of ^{38}Cl recoil energy moderation on the exothermic Cl-for-Br substitution reaction to be observed in an attempt to provide evidence for a dual approach channel for substitution with diastereomers.

Experimental

(3*RS*,4*SR*)- and (3*RS*,4*RS*)-3-bromo-4-fluorohexane were prepared through the addition of bromide ions to *trans*- and *cis*-3-hexene respectively in the presence of a fluoride ion source.[15,16] Samples for irradiation were prepared for neutron irradiation by introducing the desired amount of substrate molecule and neon moderator into quartz ampoules. The neutron irradiations were carried out at the Omaha VA Medical Center TRIGA Reactor in a thermal neutron flux of 1.1×10^{11} n cm^{-2} sec^{-1} for 10 minutes. After irradiation ^{38}Cl-labelled substitution products were separated by radio-gas chromatography using a 34 ft. ×1/4 inch o.d. copper column packed with 10% tritolyl phosphate on Chromosorb F (80—100) mesh size (1 ft=0.3048 m, 1 inch=0.0254 m). The labelled products were trapped on charcoal plugs along with authentic samples and assayed for their radioactivity using a well type NaI(Tl) scintillation detector.

Results and Dicussion

Shown in Fig. 1 are the percent retention of configuration and total absolute yield for ^{38}Cl-for-Br substitution (ΔH=—57.0 kJ mol^{-1})[17] in 3-bromo-4-fluorohexanes as a function of neon moderator. Because of decreasing activity of labelled products with increasing neon moderator concentration, it was difficult to conduct experiments at greater than 0.98 mole fraction of moderator. A trend of decreasing retention of configuration with decreasing ^{38}Cl recoil energy in both diastereomers was observed. These findings clearly indicate that the stereochemical course of halogen-for-halogen substitution for exothermic reactions lead to results considerably different from those observed with

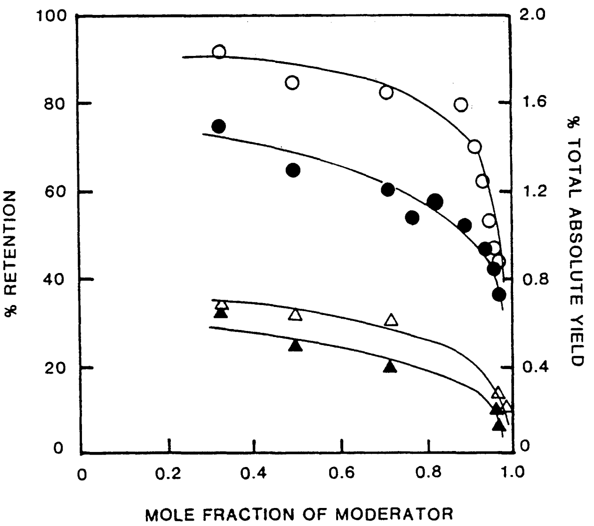

Fig. 1. Percent retention of stereochemical configuration and total absolute yield following ^{38}Cl-for-Br substitution in diastereomeric 3-bromo-4-fluorohexane (BFH) as a function of moderator concentration. For (3*RS*,4*SR*)-BFH: ○, retention; △, absolute yield. For (3*RS*,4*RS*)-BFH: ●, retention; ▲, absolute yield.

the substrates when the substitution reaction of the halogen species is either thermoneutral or endothermic. With the exothermic reaction, there is a significant drop in substitution yield as excess kinetic energy of ^{38}Cl atom is removed with increasing moderator concentration. From Fig. 1 it can be seen that the extrapolation to 100% mole fraction of moderator would result in almost 100% inversion of configuration, which is in close agreement with earlier work of Wolf et al.[14)] and Iyer and Rowland.[12,13)] Wolf et al.[14)] concluded from their studies that the front-side attack, leading to retention of configuration was the higher energy process.

When the mole fraction of moderator is much greater than that of the substrate, excess translational energy of chlorine atoms is removed predominantly by collisions with moderator and not with the substrate. The average number of collisions by energetic chlorine atoms in each energy range is thus controlled by Cl/moderator interactions; and the number of potentially reactive collisions with the substrate molecule is proportional to the substrate mole fraction. As the mole fraction of moderator is increased, the fraction of chlorine atoms which are thermalized before reaction increases. A racemic mixture of enantiomers would have been expected if the thermal substitution occurred in a stepwise process, due to the enhanced lifetime of the intermediates at the lower energy. Clearly this is not the case; it is assumed, that the substitution reaction takes place via a synchronous mechanism. Previously it has been stated that the stereochemical consequences of energetic halogen-for-halogen atom substitution are dependent on the mass of the recoil atom, steric hindrance and bond energy but not on the free energy of reaction.[10)] In the present study, thermal chlorine-for-bromine substitution yields almost 100% stereochemical inversion.

In an effort to evaluate conformational effects on the substitution reactions molecular mechanics calculations were performed and rotational populations and structure determined for the substrate molecules.[18,19)] The synclinal conformation of the (3*RS*, 4*RS*)-3-bromo-4-fluorohexane and the antiperiplanar conformation of the (3*RS*,4*SR*)-3-bromo-4-fluorohexane were found to be dominant (72.9% and 84.9% respectively) in the gas phase. Relative steric hindrance at each chiral carbon atom was calculated. The results indicate that the (3*RS*,4*SR*)-BFH has less steric hindrance than (3*RS*,4*RS*)-BFH (i.e. 6.35% versus 6.70% total relative steric hindrance), which is consistent with the absolute substitution yields. In addition, calculations indicate that the inversion pathway has approximately 2.5 times more steric hindrance than retention pathway in both (3*SR*,4*SR*)- and (3*RS*,4*RS*)-BFH, which is consistent with the observed percent retention of configuration yields in unmoderated systems.

The decrease in percent retention of configuration with increasing concentration of moderator suggests a higher energy barrier for substitution with retention than for inversion, as previously discussed. This energy barrier can be due to the large partial negative charge on the attached bromine or fluorine. The partially charged bromine will shield the chiral carbon because an incoming halogen would need to pass by the attached halogen to cause a substitution with retention of configuration. However, the inversion channel would not be affected in such a manner and will have a lower activation barrier. Finally it can be concluded that the principal factor controlling the stereochemistry of the reported substitution reactions is the kinetic energy of the displacing agent.

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