Kinetic resolution of (±)-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine in the reaction with (*S*)-naproxen chloride: a theoretical study

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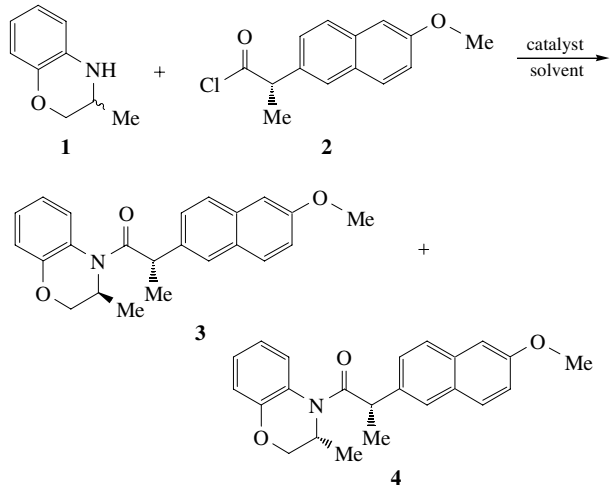
The kinetic resolution of (±)-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine by the action of (*S*)-naproxen chloride was theoretically studied based on various computation methods.

The kinetic resolution of racemates of chiral compounds is an effective method for preparing individual enantiomers.[1–3] Recently, we found that (*S*)-2-(6-methoxynaphthyl-2)propionyl chloride [(*S*)-naproxen chloride] is an appropriate reagent for the kinetic resolution of the racemic mixtures of heterocyclic amines.[4,5] The reaction of (±)-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine **1** with (*S*)-naproxen chloride **2** in the presence of tertiary amines results in the formation of (*S*,*S*)-diastereomeric amide **3** of high optical purity (*de* about 80%) (Scheme 1).

Here we report the results of theoretical studies on a reaction between (±)-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine **1** and (*S*)-naproxen chloride **2**, which were undertaken to get insight into the nature of this phenomenon and to understand the reasons of the kinetic resolution.

The yields of major (*S*,*S*)-diastereoisomer **3**, which is a rapidly formed product of the reaction of **1** with (*S*)-naproxen chloride **2**, depend on the solvents and catalysts used. Aliphatic tertiary amines, such as triethylamine, *N*-methylmorpholine and *N*-ethyl-*N*,*N*-di(isopropyl)amine, increase the yields of (*S*,*S*)-diastereoisomer **3** relative to those without a basic catalysis, while in the presence of pyridine or 4-(dimethylamino)pyridine the yields of **3** dramatically decreased. The solvent (acetonitrile, dichloromethane or benzene) has a strong influence on the ratio of products **3** and **4**. Indeed, the use of non-polar benzene enables one to enhance the optical purity of the (*S*,*S*)-diastereoisomer. It is clear that the kinetic resolution reaction depends on reagent–substrate complex formation; it can also be determined by differences in the thermodynamic characteristics of diastereoisomeric products.

Diastereoisomeric products were theoretically studied using *ab initio* DFT B3LYP/6-31G* computations[6] within the Gaussian-98 software.[7] The quantum-chemical study demonstrated that the aromatic systems of benzoxazine and (*S*)-naproxen chloride are parallel to each other in (*S*,*S*)-diastereoisomer **3**. A similar conformation is impossible in the case of (*R*,*S*)-diastereoisomer **4** due to the repulsion of methyl groups. The total energy of (*R*,*S*)-diastereoisomer **4** is only 0.3 kJ mol^{-1} lower than that of (*S*,*S*)-diastereoisomer **3**. It is obvious that this negligible difference between energies cannot be responsible for the higher yield of (*S*,*S*)-diastereoisomer completely, neither the difference in energies can explain the observed susceptibility of the reaction to the nature of solvents and catalysts used. Therefore, the reasons for the stereoselectivity of the process are supposed to be associated with the preliminary stage of substrate–reactant complex formation.



Scheme 1 Reaction between (±)-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine and (*S*)-naproxen chloride.

The substrate–reactant complexes were modelled within the Mech[8] genetic algorithm using the MM3 force field combined with MERA force field.[9,10] This approach allowed us to take into account the probability of complex interaction with neighbouring species in the reaction mixture. The conformational search was fulfilled along all Hessian modes in the Cartesian coordinates by modified algorithms[11,12] within the MultiGen[13] approach using combined MM3/MERA force field. The energy threshold for conformational search is 41.8 kJ mol^{-1}. As a result, 56 substrate and reactant conformers were found. The energies of conformers obtained in this approach are in good correlation with *ab initio* results. To explain the kinetic resolution, it is possible to use a pair of the lowest energy complexes because another pairs of complexes show an analogous result.

The modelling shows that the structures of (*S*)-naproxen chloride complexes with (*R*)- and (*S*)-stereoisomers of amine **1** are not equal (Figure 1). In the complex of 2,3-dihydro-(3*S*)-methyl-4*H*-1,4-benzoxazine with (*S*)-naproxen chloride a hydrogen atom of the amino group of benzoxazine and the carbonyl group of naproxen are arranged in the way one opposite the other and are linked through an intermolecular hydrogen bond. The distance between the carbonyl oxygen of naproxen and the amine hydrogen is 2.35 Å. Moreover, the aromatic fragments of these molecules are in parallel planes; this provides a good

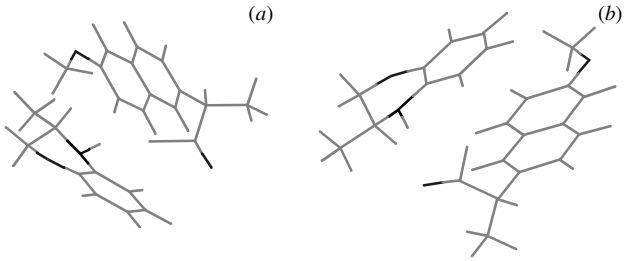


Figure 1 Results of the Mech analysis. Calculated structures for the substrate–reagent complexes: (*a*) 2,3-dihydro-(3*S*)-methyl-4*H*-1,4-benzoxazine–(*S*)-naproxen chloride; (*b*) 2,3-dihydro-(3*R*)-methyl-4*H*-1,4-benzoxazine–(*S*)-naproxen chloride.

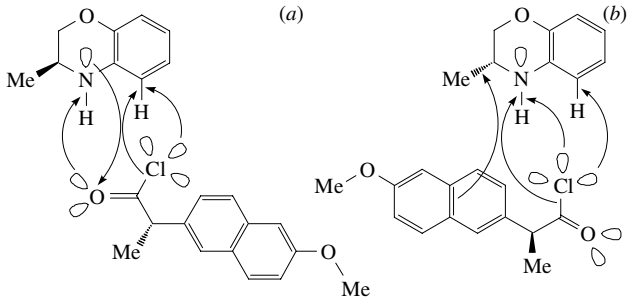


Figure 2 Redistribution of electronic density in the complexes of (*S*)-naproxen chloride with (*a*) 2,3-dihydro-(3*S*)-methyl-4*H*-1,4-benzoxazine; (*b*) 2,3-dihydro-(3*R*)-methyl-4*H*-1,4-benzoxazine. Results of Natural Bond Orbital Analysis within *ab initio* DFT B3LYP/6-31G*.

opportunity for the π–π interaction of aromatic systems. The Natural Bond Orbital Analysis (NBO)[14] carried out within *ab initio* DFT B3LYP/6-31G* revealed the following types of interactions for the (*S*)-isomer [Figure 2(a)]: (1) Hydrogen bond between the NH hydrogen of benzoxazine and the carbonyl oxygen of (*S*)-naproxen chloride. It results in electron transfer from oxygen of (*S*)-naproxen chloride to the N–H bond and to the Ridberg zone of benzoxazine. The electronic density of benzoxazine nitrogen redistributes to the C=O bond of (*S*)-naproxen chloride. (2) Lone pairs of the chlorine atom of (*S*)-naproxen chloride are distributed partially through the C–H bond of the benzene ring of benzoxazine. (3) π–π Interaction between the aromatic systems of 2,3-dihydro-(3*S*)-methyl-4*H*-1,4-benzoxazine and (*S*)-naproxen chloride.

The lowest energy complex of 2,3-dihydro-(3*R*)-methyl-4*H*-1,4-benzoxazine with (*S*)-naproxen chloride is formed through the interaction of benzoxazine NH with the chlorine atom of (*S*)-naproxen chloride. The internuclear distance is 3.30 Å. This electrostatic interaction is weaker than the hydrogen bond, which occurs in the complex with 2,3-dihydro-(3*S*)-methyl-4*H*-1,4-benzoxazine. NBO shows the following characteristics for the complex of the (*R*)-isomer: (1) interaction of the NH of benzoxazine with lone pairs of the chlorine atom of (*S*)-naproxen chloride (the electronic density is transferred from Cl orbitals to N–H); (2) lone pairs of the chlorine atom of (*S*)-naproxen chloride are distributed partially at the C–H bond of benzoxazine aromatic part; (3) the redistribution of electronic density from the C–C bond of the aromatic system of (*S*)-naproxen chloride to the methyl group attached to the asymmetric carbon of benzoxazine.

Obviously, the complex of the (*R*)-isomer formed due to the π–π electronic interaction of aromatic systems and Cl···H interaction is less stable than that of the (*S*)-isomer, which includes the C=O···H–N hydrogen bond. Actually, the *ab initio* DFT B3LYP/6-31G* computation shows that the charge of the (*R*)-isomer in a complex with (*S*)-naproxen chloride is –0.0052 a.u. At the same time, for a molecule of the (*S*)-isomer, the charge is significantly lower and equal to –0.0138 a.u. The total energy of the complex of the (*S*)-isomer with (*S*)-naproxen chloride is 6.1 kJ mol^{-1} lower than that of the complex of the (*R*)-isomer with (*S*)-naproxen chloride. Therefore, the intermolecular interactions of (*S*)-naproxen chloride with 2,3-dihydro-(3*S*)-methyl-4*H*-1,4-benzoxazine lead to the formation of a complex that is more stable than (*R*,*S*)-product **4**.

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