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COMPUTATIONAL CHEMICAL STUDIES OF CHIRAL STATIONARY PHASE MODELS

COMPLEXES OF METHYL N-(2-NAPHTHYL)ALANINATE WITH N-(3,5-DINITROBENZOYL)LEUCINE *n*-PROPYLAMIDE

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SUMMARY

Recent computational chemical studies on (*S*)-methyl N-(2-naphthyl)alaninate with (*S*)- and (*R*)-N-(3,5-dinitrobenzoyl)leucine *n*-propylamide were further refined by using semi-empirical quantum-chemical methods for determining structural and energetic parameters. These results confirm the earlier prediction that the same three primary interactions ("contact points") that others have proposed for the *SS* complex can also be achieved by the less stable *SR* complex without significant additional energy. Thus, a classical three-point mechanism for chiral recognition is not expected to be operative in this interaction model. We have verified earlier predictions that the computationally determined repulsive nature of the π interaction could become attractive through the use of more refined calculations, while still maintaining the equality between the *SS* and *SR* complexes.

INTRODUCTION

It is becoming increasingly evident, in areas such as drug design, that it is often critically important to separate enantiomers[1]. One approach, which is being widely developed, is stereoselective synthesis. Alternatively, methods are being developed for chiral separations after synthesis, typically by means of some resolving agent[2–7]. One of the most widely used approaches to the separation of enantiomers is chromatography on the chiral stationary phases developed by Pirkle and co-workers[7–10]. A model for the molecular interactions responsible for chiral separation has been suggested for some of these systems[7–10]. In order to aid in their analysis, computational chemical studies have been undertaken on models of these systems. For instance, Lipkowitz and co-workers[11–15] have used molecular mechanical and semi-empirical quantum-chemical methods to optimize the conformations of models for the isolated analytes and stationary phases. These workers have also studied intermolecular interactions of these models by using a rigid monomer approximation. Similar studies, based on molecular mechanical methods, have been reported by Norinder and Sundholm[16].

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Recently, we have also reported studies[17] on the model complex of (*S*)-methyl N-(2-naphthyl)alaninate (NAP) with (*S*)- and (*R*)-N-(3,5-dinitrobenzoyl)leucine *n*-propylamide (DNB; *SS* and *SR* complexes), where the former was used as a model for the stationary phase and the latter as the analyte. In these studies, all the geometric parameters of the complexes were fully optimized by molecular mechanical methods. Interaction energies for the complexes and model fragments were then evaluated by semi-empirical and *ab initio* quantum-chemical methods. In this way, the interaction model proposed by Pirkle and co-workers for the complex of the *S* enantiomers of NAP and DNB (*i.e.*, the *SS* complex; see Fig. 1) was examined.

In this model, three primary interactions are responsible for stabilization of the complex: a π–π interaction and two hydrogen bonds (see Fig. 1). Loss of one of these interactions has been suggested as responsible for the lesser stability of the (*S*)-NAP–(*R*)-DNB complex[7–10]. We therefore also investigated the interaction of (*S*)-NAP with (*R*)-DNB. Analysis of the results showed that the *SS* complex is stable in the form suggested by Pirkle and co-workers, but that the *SR* complex is able to maintain the same three interactions without any significant conformational strain. This led to the conclusion that the proposed model is not responsible for chiral recognition through a classical three-point interaction mechanism (we shall hereafter refer to such primary interactions as "contact points"). A classical three-point interaction required the participation of atoms or groups along three different bonds at the chiral center. The model proposed by Pirkle and co-workers, which involves three primary interactions between (*S*)-NAP and (*S*)- or (*R*)-DNB, can be considered a pseudo-two-point interaction scheme because the three contact points lie along only two of the bonds of the chiral center (see the Results and Discussion).

In a previous study[17], we found that the total interaction energies for the *SS* and *SR* complexes were similar to each other when assessed by the molecular mechanics-derived structures in semi-empirical quantum-chemical AM1 calculations[18],

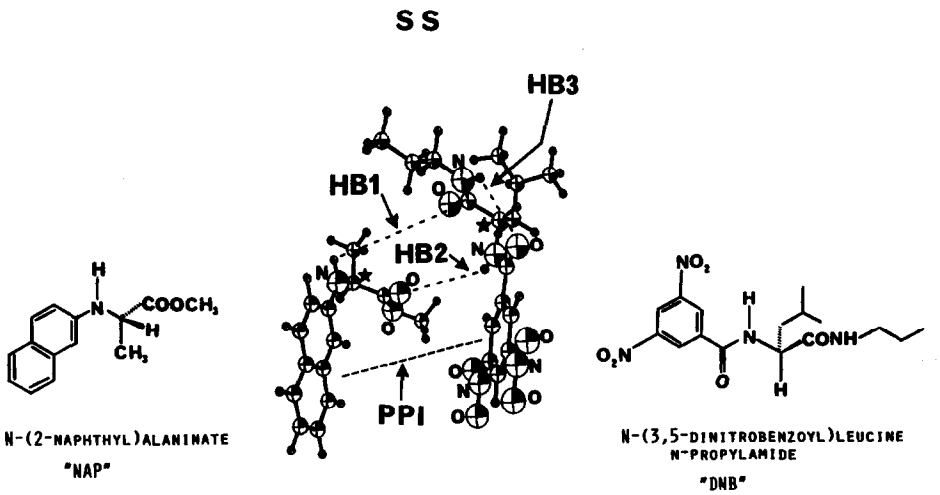


Fig. 1. Schematic representation of the interaction model for (*S*)-NAP with (*S*)-DNB. HB1 and HB2 represent the two intermolecular hydrogen bonds, and HB3 represents the intramolecular hydrogen bond in DNB. PPI denotes the interaction of the π systems of NAP and DNB.

i.e., AM1//MMFF (see ref. 17 for details of the calculations and see the Experimental section for an explanation of this notation). In addition, when these three interactions were modeled separately as small fragments, the interaction energies for the *SS* and *SR* models were also similar and, when added to each other, they approximately reproduced the total interaction energy of the respective complex. This suggested that these three interactions are indeed the dominant interactions of these complexes. It was also found that both hydrogen bonds were predicted to be stabilizing, HB2 (see Fig. 1) being more stable. This result was consistent with the NOE data of Pirkle and Pochapsky[8–10]. On the other hand, while the two (*SS* and *SR*) π interactions were found to be nearly equal to each other and therefore not expected to be responsible for chiral recognition, they were found to be slightly repulsive. Similar conclusions from experimental data for related systems have been reported by Wainer and Alembik[19]. Although chiral recognition could only be a function of the inequality of *SS* and *SR* interactions and does not depend on whether they are stabilizing or destabilizing, it was speculated that these destabilizing interactions could become stabilizing on further refinement of the calculations. Therefore, it seemed worthwhile to explore this aspect further. We report below more sophisticated quantum-chemical calculations on these systems, aimed at refining the question of the stability of the π interactions.

EXPERIMENTAL

Completely relaxed geometries of the complexes of (*S*)-NAP with the *R* and *S* enantiomers of DNB were obtained by using the semi-empirical quantum-chemical AM1[18] method, as implemented in AMPAC (Version 1.00)[20]. Substructures derived from the fully optimized complexes were generated in CHEM-X[21] in order to model the important interactions of the complexes. AM1 energies of interaction were calculated for the AM1 completely relaxed geometries of the complexes and frozen fragments thereof. In this paper, energy calculations using method "X" for structures derived from method "Y" are denoted X//Y. For example, AM1//MMFF signifies that an AM1 energy calculation was performed for a structure optimized by the MMFF method.

RESULTS AND DISCUSSION

In a previous study[17] the structures of the model complexes were fully optimized with the MMFF molecular-mechanics method. The local minimum investigated for the *SS* complex was that based on the model proposed by Pirkle and coworkers[7–10]. As described[17], a similar minimum was found for the SR complex. These structures are shown in Fig. 2 (upper structures). Full reoptimization of all the structural parameters for both complexes by means of the semi-empirical quantum-chemical AM1 method has now also been performed. These structures are also shown in Fig. 2 (lower structures). Some of their interesting features are evident. Once again, both the *SS* and the *SR* complexes maintain all three primary interactions. Also, the two structures are again strikingly similar to each other. The primary difference is in the reversal of the hydrogen atom and *sec.*-butyl group on the chiral center of (*R*)- *vs.* (*S*)-DNB. As pointed out previously[17], these groups sit outside the region of

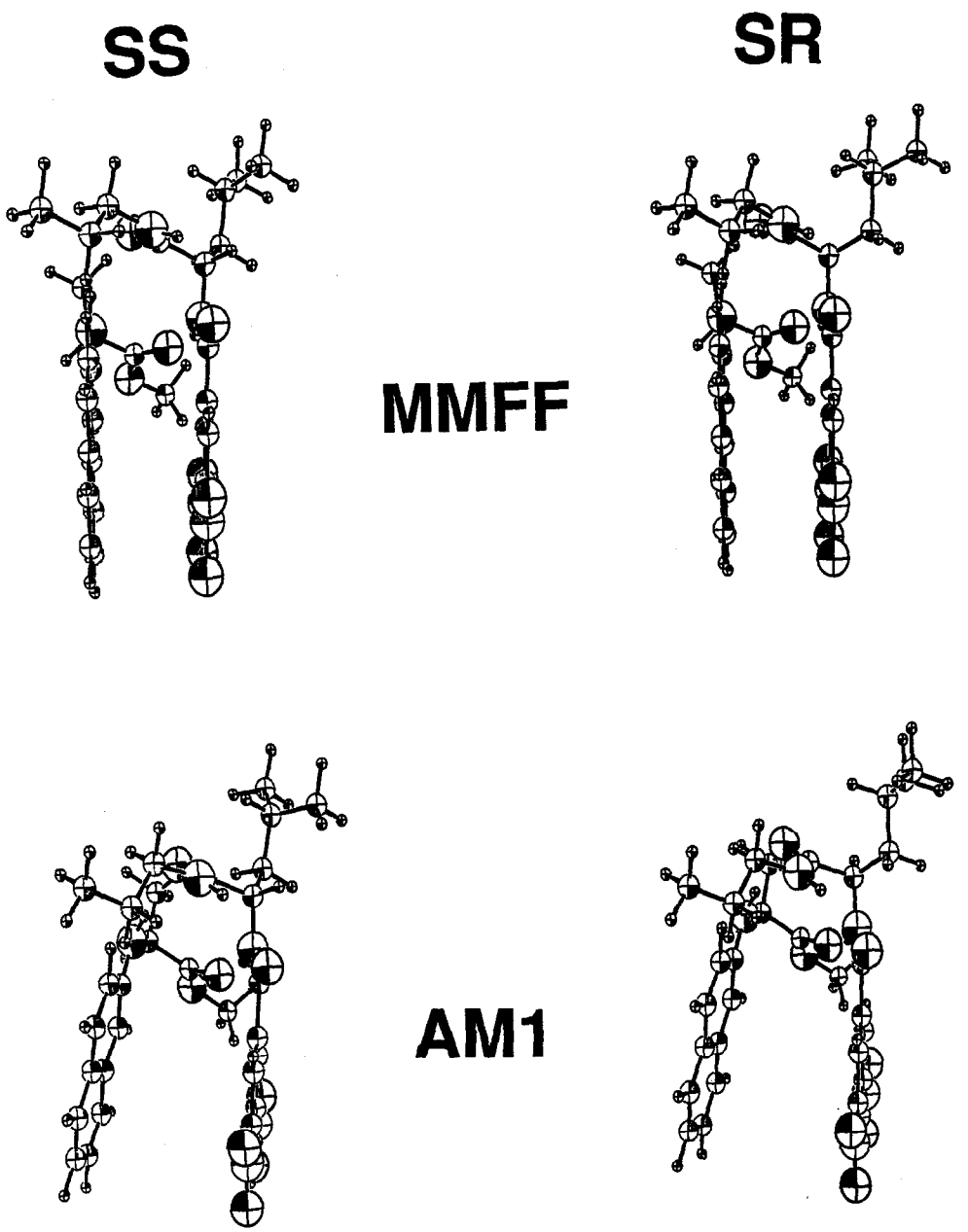
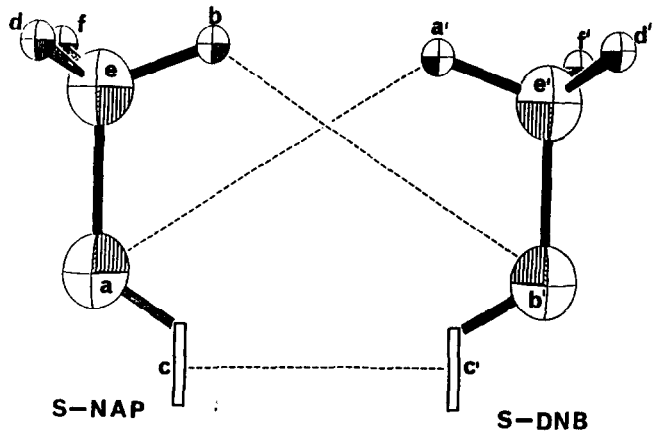


Fig. 2. Structures of the *SS* and *SR* complexes fully optimized with the MMFF molecular mechanics (see ref. 17) and the semi-empirical AM1 methods. See Fig. 1. for details.

the primary interactions and could only exert a differential effect in the form of through-space field interactions. Of course, it is possible that these differences could lead to chiral recognition. This could be illustrated with the recently proposed dis-



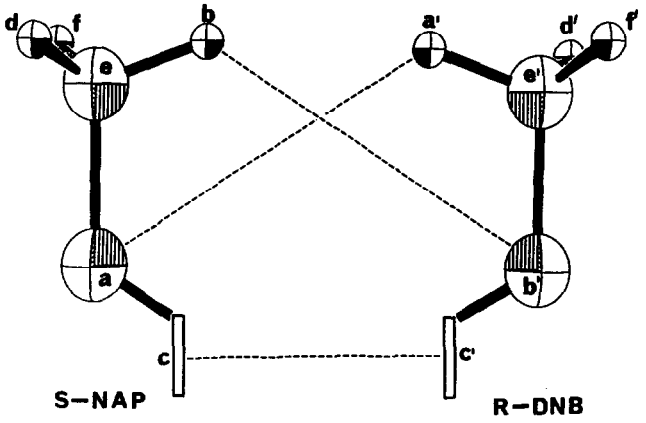


Fig. 3. Schematic representation of the primary interactions in the *SS* and *SR* complexes of NAP and DNB. a---a' and b---b' represent the two hydrogen bonds and c---c' represent the π–π interaction (see Fig. 1).

tance-matrix analysis[22]. Nevertheless, it is clear that a classical three-contact-point mechanism is not responsible for chiral recognition here. This is because the three contact points lie along only two of the bonds of the chiral centers. Thus, in terms of classical point-of-interaction schemes, these may be thought of as pseudo-two-point interactions (see Fig. 3).

It is also evident from the structures shown in Fig. 2 that the aromatic systems of the π interactions are not as close in space when optimized with the AM1 method. Hence the repulsive nature of the π interactions when the MMFF structures are used for AM1 calculations are likely to be a result of having too small a separation between the dinitrobenzoyl and naphthyl groups.

TABLE I

GEOMETRY OF COMPLEXES OF (*S*)-METHYL N-(2-NAPHTHYL)ALANINATE (NAP) WITH N-(3,5-DINITROBENZOYL)LEUCINE *n*-PROPYLAMIDE (DNB)

Parameter	*Geometry*			
	S(NAP)–S(DNB) complex		*S(NAP)–R(DNB) complex*	
	MMFF*	AM1*	MMFF*	AM1*
Geometric parameter**:				
HB1 (Å)	2.217	2.153	2.225	2.152
HB2 (Å)	2.341	2.081	2.302	2.073
HB3 (Å)	2.365	2.276	2.226	2.187
Naphthyl (NAP) and phenyl (DNB) rings:				
Distance between centroids (Å)	3.384	4.959	3.388	5.069
Measure of angle between normals (degrees)	2.4	11.5	2.1	14.0

* Method of geometry optimization. See the Experimental sections here and in ref. 17 for details.
** See Fig. 1.

Quantitatively, Tables I and II show that the structures and energies of the *SS* and *SR* complexes are indeed very close to each other for the AM1 optimized structures. Based on a comparison of the AM1 total energies of the AM1-derived (or molecular mechanics-derived) geometries of the complexes, the *SS* complex is 0.83 (or 0.89) kcal/mol more stable than the *SR* complex (see the bottom of Table II); this difference represents a combination of both the differential through-space field effects (see above) and conformational strain energy. As described more fully in ref. 17, while total energies may not be very reliable, energy differences, which are used as indicators of separability, may be more reliable. We note that energy differences of *ca.*

TABLE II

ENERGETICS OF COMPLEXES OF (*S*)-METHYL N-(2-NAPHTHYL)ALANINATE [NAP] WITH N-(3,5-DINITROBENZYL)LEUCINE *n*-PROPYLAMIDE [DNB]

*Structure***	*Parameter*	*S(NAP)–S(DNB) complex*		*S (NAP)–R(DNB) complex*	
		AM1//MMFF*	AM1//AM1*	AM1//MMFF*	AM1//AM1*
PHB1	Interaction energy	−2.94	−2.85	−2.91	−2.81
PHB2	(kcal/mol)***	−5.20	−6.70	−4.97	−6.64
PPI-SM		3.70	−0.84	3.66	−0.82
PPI		3.61	−1.04	3.69	−1.01
Complex		−5.19	−11.22	−4.96	−11.37
Complex	Difference in total energy (kcal/mol)	−0.89	−0.83		

* Method of energy calculation. See the Experimental section for a definition of the notation and see ref. 17 of the details of the AM1//MMFF calculations.
** See Fig. 4 and the Experimental section.
*** See the Results and Discussion section for a note about the accuracy of the interaction energies.

0.5 kcal/mol correspond to separability factors in the range of 1.0–1.5, whereas differences of 2–4 kcal/mol correspond to factors of 100–200.

The interaction energies of the complexes, and those based on the model fragments for the three primary interactions shown in Fig. 4, are very similar for the AM1 structures (see Table II). The substructures of the complexes were taken from the fully relaxed geometries of the complexes. The geometries of the isolated substructures were not subsequently relaxed. Hence the interaction energies of the complexes and the various substructures in Table II are calculated less accurately than the total energy of either complex. For example, with full relaxation permitted for all geomet-

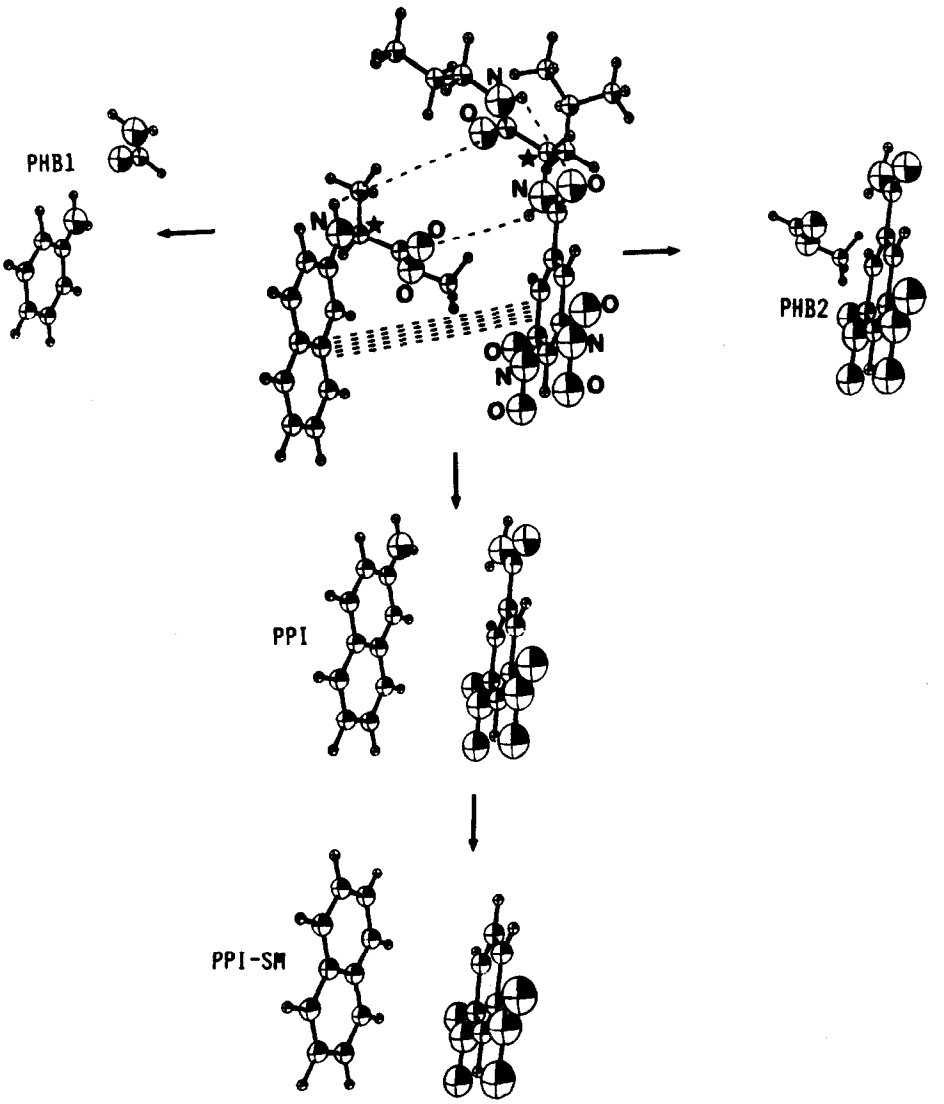


Fig. 4. Schematic representation of the model fragments of the NAP–DNB complex.

ric parameters of NAP and DNB (or analogously for the substructures), each as an isolated entity, the differences in the interaction energy of the *SS* and *SR* complexes would be equivalent in magnitude and direction to the difference in the total energies of the complexes due to the energetic equivalence of the two enantiomers of DNB.

The qualitative nature of the two hydrogen bonds remains the same for the AM1 structures, although the hydrogen bond HB2 is *ca.* 1.5 kcal/mol more stable here than with the MMFF structure. On the other hand, the π interactions for the *SS* and *SR* complexes remain similar to each other but are lowered in energy by *ca.* 4.5 kcal/mol so that they now contribute slightly to the stabilization of the complexes. It is apparent that a separation of the dinitrobenzoyl and naphthyl groups which is greater than that of the molecular mechanics-derived structures is required for the π interaction to become stabilizing (see above).

CONCLUSIONS

Further investigations of the proposed model for the interaction of the *SS* complexes of NAP and DNB based on the semi-empirical AM1 optimized results are in basic qualitative agreement with earlier findings that the same three contact points may be achieved by the *SR* complex also. This is because the three contact points, in classical terms, form a pseudo-two-point interaction mechanism. Hence this interaction scheme cannot be reponsible for chiral recognition through a classical three-point-interaction mechanism, requiring either the loss of one of these contact points for the less stable *SR* complex or inaccessible strain energy. If this interaction model is the energetically dominant one for both the *SS* and *SR* complexes, chiral recognition could be achieved via through-space field effects. These effects could be understood through the use of the distance-matrix analysis scheme recently proposed for chiral recognition[22] Alternatively, other mechanisms must be responsible for chiral recognition. For example, it may be that chiral recognition is achieved through the composite of many low-energy conformations of the complexes. Approaches for treating such mechanisms have recently been proposed[23,24]. Another possible factor is the dimerization of the analytes. Recent experimental findings by Pirkle and Pochapsky[8] support such a possibility.

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