Rationalization of Product Selectivities in Asymmetric Horner−Wadsworth−Emmons Reactions by Use of a New Method for Transition-State Modeling

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Received February 19, 1999

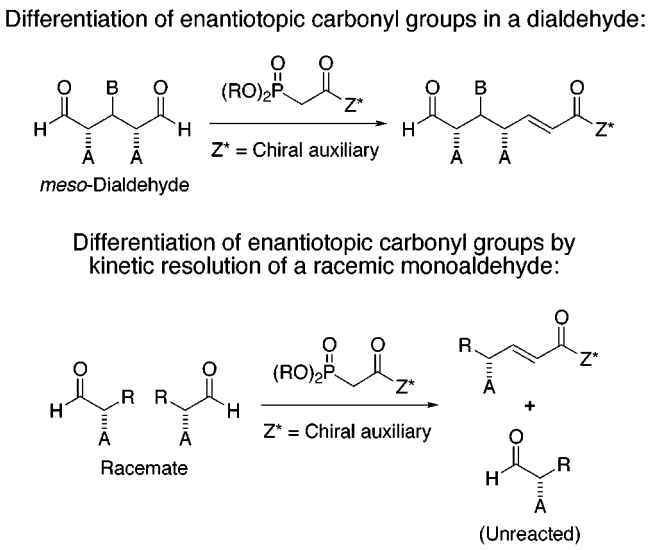
A new method for creating a transition-state force field, based on quantum chemical normal-mode analysis, is described. Except for distortions along the reaction coordinate, the potential energy surface around the TS is closely reproduced. The force field was used to rationalize the experimentally observed product selectivities in asymmetric Horner−Wadsworth−Emmons reactions between chiral phosphonates **1** and aldehydes **2**−**4**. It was shown that if the transition states for the addition step (TS1) and for the subsequent ring closure to an oxaphosphetane (TS2) are both considered in the modeling, the product selectivity can be rationalized with good accuracy. The calculations supported the previously reported hypothesis that the overall product selectivities result from the combined influence of the chiral auxiliary, the α-stereocenter(s) in the aldehyde, and the phosphonate alkoxy groups. Somewhat unexpectedly, the modeling showed that in several cases the influence of the aldehyde α-stereocenter is even more pronounced in TS2 than in TS1. The combined influence of the chiral auxiliary and the aldehyde α-stereocenter(s) explains the general observation that (*E*)- and (*Z*)-alkenes are formed with opposite enantiotopic group preference from the same substrate.

Introduction

The field of asymmetric organic synthesis has seen an explosive growth in recent years. On the basis of the concept of differentiation of enantiotopic functional groups, reaction types in which no additional sp^3 stereocenter is created at any of the bond-forming sites can also be used for asymmetric synthesis. One such class of reactions is asymmetric Wittig-type reactions, an area that has been studied by a number of research groups.[1] Opportunities for achieving asymmetric induction in reactions of this type include differentiation of enantiotopic groups either in a single bifunctional molecule, i.e., desymmetrization, or in separate substrate molecules, i.e., kinetic resolution (Scheme 1).

As part of a long-term project aimed at the development and application of asymmetric Wittig-type reactions,[1j,l,p,2] we have previously studied the mechanism of the general Horner−Wadsworth−Emmons (HWE) reaction by high-level quantum chemical (QC) methods[3] (Scheme 2). The reaction proceeds via initial formation of an oxyanion and subsequent ring closure to give an oxaphosphetane,[4] followed by rapid elimination to the

Scheme 1



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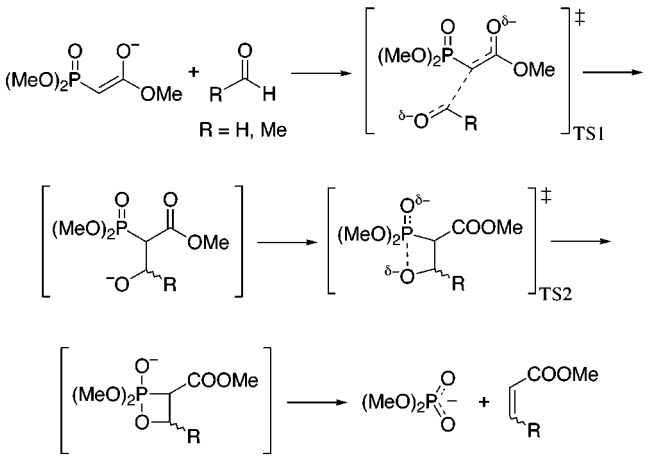
10.1021/jo990318d CCC: $18.00
Published on Web 07/14/1999

Scheme 2



final products. The two initial transition states (TS1 and TS2, Scheme 2) were found to be close in energy. Thus, both of these transition states could have an influence on the overall product selectivity.

Our initial QC study[3] has assisted in interpretation of experimental observations in a qualitative way.[1p] However, to gain a more quantitative understanding of the various interactions responsible for selectivity, it is necessary to submit larger model systems to computational analysis. In particular, the interactions in the two transition states depicted in Scheme 2 must be analyzed for synthetically interesting systems, incorporating the chiral auxiliary and enantiotopic aldehyde moieties. In previous experimental work, we have studied reactions between chiral phosphonates of type **1**, incorporating 8-phenylmenthol as the chiral auxiliary, and aldehyde substrates such as **2**−**4** (Figure 1).

In these reactions, the transition states can exist in eight different diastereomeric forms, each of which must be separately evaluated in the modeling (Figure 2). The flexibility of the substrates also necessitates extensive conformational searching in order to find the preferred path. At present, such an analysis cannot be performed at the level used in our initial study. An attractive alternative would be to model the reaction center by quantum chemical methods and add the influence of substituents at a molecular mechanics level (QM/MM method).[5] However, the requirement that several thousand conformations of the different configurations be investigated for each reaction puts any accurate QC investigation of the system beyond our computational resources. We therefore settled for an investigation by pure force field methods.

In this paper, we show that by use of a new method, high-level computational results can be used as a basis for creating a force field model for the title reaction. Furthermore, we demonstrate how this model can be used to rationalize the experimentally observed product selectivities in some selected systems. A long-term goal, in addition to understanding in detail the factors responsible for the reaction selectivity, is to produce a tool for rapid virtual screening of potential reagent-substrate combinations.

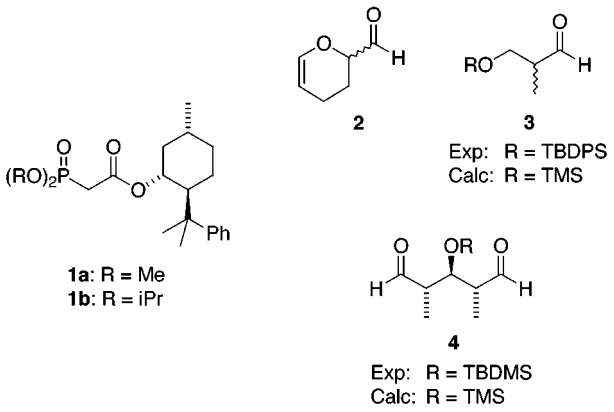


Figure 1. Reagents and substrates modeled in the current study. In **3** and **4**, a simplified protecting group was used in the conformational search.

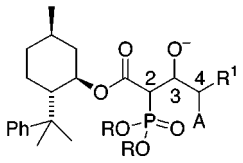


Figure 2. Numbering in the intermediate oxyanion, also used in the flanking transition states (TS1 and TS2, Scheme 2). Including all possible combinations of the stereocenters at C2, C3, and C4, eight diastereomeric forms are possible.

Computational Methods

Transition-State Model Parametrization. The HWE reaction can be run under many different conditions. As in our QC investigation,[3] our goal here is to model reactions run under conditions using dissociated counterions (e.g., potassium/18-crown-6) in low-polarity solvents.[6] Thus, we have based our force field models on high level investigations of the anionic systems in the gas phase, without any counterion. Inclusion of coordinating counterions is expected to influence the transition states drastically.[1l] Application of the current methods to systems including, for example, lithium or sodium ions might well require a redetermination of force field, and at the very least a thorough revalidation. The choice of solvent also has an effect on the reaction. In our preceding study, it was demonstrated that a solvent change could alter the rate-determining step of the reaction.[3] For this reason, we do not attempt to determine the relative energy of the two sequential transition states from the force field model but rather obtain this quantity from a fit to experimental data (vide infra). The effect of solvation on the relative energies of diastereomeric transition states of the same type is expected to be minor and has been ignored in the current study. The same is true for the possibility of nonequal activation entropies.

Traditional force fields are not well suited for investigations of transition states involving bond breaking or formation. In general, the functional forms are chosen to reproduce the energy of a bond close to the equilibrium value only. Transition states have therefore been investigated by specially designed force fields.[7] In these, the reaction center is either frozen in an appropriate geometry or the force field is redefined to reproduce the transition-state structure as if it was a minimum

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(6) For specific examples, see refs 1p and 2.

on the potential energy surface (PES). We have chosen to utilize the latter strategy, employing a new method[8] for creating transition-state force fields.

Force field parametrization is initialized by selection of a training set of data, whereupon the agreement between force field results and the training set is optimized by variation of the parameters.[9] It has been shown that the local PES around stationary points can be reproduced well if accurate quantum chemical Hessian data (Cartesian second derivatives of the calculated energy) are included in the training set.[9−11] However, inclusion of such data poses a special problem for transition-state models. The vibrational normal modes of a molecule are uniquely defined by the mass-weighted Hessian, and vice versa. Transition states have, by definition, exactly one normal mode with a negative eigenvalue, whereas the force field, treating the TS as a minimum, should only display positive eigenvalues. This has previously precluded the use of calculated Hessian information in the parametrization of transition-state force fields. Dasgupta and Goddard[10] have previously shown how a ground-state Hessian can be improved before being used as reference data in force field parametrization. The mass-weighted Hessian is diagonalized and the eigenvalues are replaced by the corresponding experimental values, whereupon the modified Hessian is obtained by matrix multiplication. In a similar but more profound change, we adjust the single calculated negative eigenvalue for a mass-weighted TS Hessian to a large positive value, without modifying the other eigenvalues or any eigenvector.[8] Subsequent matrix multiplication will yield a modified mass-weighted Hessian, now corresponding to a minimum. Use of these modified Hessians in the parametrization training set yields a force field that will keep the complex at one fixed point along the reaction coordinate but will respond to small distortions perpendicular to the reaction coordinate in the same way the high-level calculations would. Thus, relative energies of diastereomeric transition states, and nonbonded interactions between substituents, should be well represented by the force field.

Quantum Mechanical Calculations. All calculations were performed using the Gaussian 94 program.[12] Geometry optimizations of transition-state structures were performed using the B3LYP hybrid functional[13] together with the 6-31+G* basis set with subsequent calculations of Hessians. In total, nine TS isomers were evaluated yielding a total of 29250 unique mass-weighted Hessian elements, which were used as reference data in the parametrization. The Hessians were used without scaling[14] in the following molecular mechanics parametrization. CHelpG charges[15] were calculated at the same level of theory and used as reference data in the training set.

Molecular Mechanics Calculations. All force field calculations were performed on Silicon Graphics workstations utilizing MM3* in MacroModel V6.0,[16,17] using default settings consistently. Transition-state parameters were added as described herein; the new parameters are available as Supporting Information. The MM3* force field is based upon, but not identical to, the 1989 version of the Allinger MM3 force field.[18] The parameters are usually interchangeable, but some differences in paradigm should be noted. The treatment of electrostatics in MM3 is based mainly upon dipole interactions (but also includes charge−charge and charge-dipole interactions), whereas MM3* utilizes point charges determined by using the MM3 dipoles as charge flux parameters. MM3* also uses a nondirectional 10−12 Lennard-Jones-type potential for hydrogen bonds in lieu of the directional Buckingham potential in MM3. For conjugated systems, MM3 uses a VESCF scheme to determine π-bond orders and scales bond and torsional parameters according to the calculated bond order. MM3* instead relies on user identification of single or double bonds and uses a substructure matching scheme to identify and replace the parameters for specific conjugated systems.

Calculation of Product Selectivities. Asymmetric HWE reactions can proceed through eight different diastereomeric pathways, depending on the reacting face of both the phosphonate anion and the aldehyde and the configuration at the stereocenter α to the reacting aldehyde unit. Several assumptions about the reaction paths were made on the basis of our QC study.[3] We considered the possibility that the first step might be reversible, and it was assumed that no crossover takes place between diastereomeric paths. The entropic differences between transition states of the same type were neglected. The free energy difference between TS1 and TS2 (Scheme 2) is small, but not known accurately, and was therefore treated as a variable to be determined by fitting to experimental data. The phosphonate anion was assumed to exist mainly as the (*E*)-enolate,[4,19,20] but the expected product distribution from the *Z* form was also investigated. An overall postulated (*Z*)-enolate content of 8% of the total phosphonate was found to give a substantial improvement in the correlation with experimental data. Note that this number also includes any (*Z*)-enolate that is formed during the reaction. In cases where TS1 is rate limiting, the (*Z*)-enolate content is not expected to vary under the reaction, and 8% may therefore be too high. On the other hand, when TS1 is lower in energy, some equilibration may be expected, leading to a possible change in the (*Z*)-enolate content. We could have corrected for this by fitting the (*Z*)-enolate content for each reaction, but only at a serious risk of overfitting our data.

In the reactions investigated, the conformational space was searched exhaustively for all isomeric transition states, using the pseudo-systematic Monte Carlo search followed by a low-mode conformational search.[21] Overall, at least 45 000 con-

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(14) The recommended scaling factors for determination of ZPE and thermodynamic vibrational contributions at the B3LYP/6-31G* level are very close to unity: Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502.

(15) Breneman, C. M.; Wiberg, K. B. *J. Comput. Chem.* **1990**, *11*, 361.

(16) MacroModel V6.0: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caulfield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

(17) MM3* is among the best force fields available today, giving an average error around 2 kJ/mol for conformational energies of small organic molecules: Gundertofte, K.; Liljefors, T.; Norrby, P.-O.; Pettersson, I. *J. Comput. Chem.* **1996**, *17*, 429.

(18) (a) Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551. (b) Lii, J.-H.; Allinger, N. L. *J. Am. Chem. Soc.* **1989**, *111*, 8556. (c) Lii, J.-H.; Allinger, N. L. *J. Am. Chem. Soc.* **1989**, *111*, 8576.

(19) (a) Bottin-Strzalko, T.; Corset, J.; Froment, F.; Pouet, M.-J.; Seyden-Penne, J.; Simmonin, M.-P. *J. Org. Chem.* **1980**, *45*, 1270. The geometry of the lithium enolate derived from **1a** has been determined as *E* on the basis of NMR: (b) Gais, H.-J.; Schmiedl, G.; Ossenkamp, R. K. L. *Liebigs Ann./Recueil* **1997**, 2419. See also ref 1a.

(20) In the formal *E*/*Z* nomenclature, the priorities of the oxygen substituents may vary with the metal cation. For consistency, in the current work the anionic enolate oxygen is always considered to have a lower priority than the alkoxy group.

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formations were minimized for each reaction studied. The relative reaction rate for one complete diastereomeric path, r, was calculated from eq 1 (see the Supporting Information for a derivation). The parameter δ is the fitted energy difference between TS1 and TS2, and x_Z is the postulated average fraction of phosphonate enolate in the Z form (kept fixed to enable us to derive an analytic expression; when the first step is reversible, x_Z should be seen as an average over the course of the reaction). All summations are over one diastereomer only.

$$r \propto \frac{(1-x_Z)\sum_i^{(E)\text{-TS1}} e^{-\Delta E_i/RT} + x_Z \sum_i^{(Z)\text{-TS1}} e^{-\Delta E_i/RT}}{1+\sum_i^{\text{TS1}} e^{-\Delta E_i/RT} \Big/ \sum_i^{\text{TS2}} e^{(\delta-\Delta E_i)/RT}} \quad (1)$$

The effects of the accumulation of the slower reacting enantiomer in the kinetic resolutions were not considered significant, as more than 2 equiv of the substrates were present in the corresponding experimental reactions. The further reaction of the second aldehyde moiety in the desymmetrization example (i.e., **1a** + **4**) was also ignored. Experimentally, the effect of the bis-addition is to increase the isomeric purity of the monoaddition product.[22]

Results

Molecular Mechanics Parameters. The optimized parameters for both transition states are reported separately in the Supporting Information. The internal predictivity for TS structures is illustrated in Figure 3, by overlays between QC and MM structures. As can be seen, the correspondence is good in the central part of the structure, where parameters have been refined. Some small deviations in the position of the phosphonate alkoxy groups can be traced to two sources: the torsional parameters around the P−O bonds and the nonbonded interactions between the alkoxy groups and the aldehyde oxygen.[3]

The correspondence between QC and MM Hessian elements is depicted in Figure 4. A few features are worth noting. First of all, the plot contains several thousand data points, and the majority of these are on the diagonal. However, one group of deviations can be found along the x axis. These are elements for which the force field has no interaction; therefore, no parameter modification could improve the fit. An illustrative case is the largest deviation, which comes from TS1 when the P═O bond is anti to the forming C−C bond. If both of these bonds are considered to be approximately parallel to the z axis, the largest Hessian error is for the element connecting the z coordinates of the aldehyde carbonyl carbon and the phosphonate oxo. A large value is found for this element in the QC calculations. Chemically, this is very reasonable, as there should be a strong conjugation between the P═O bond and the forming C−C bond in the TS. In the force field, a stretch−stretch function could be used to model this interaction, but such functions are not implemented in MacroModel. In practice, the effect on optimized TS structures will be that if the forming TS bond is distorted by steric interactions the P═O bond length will be wrong by a few hundredths of an angstrom. The effect on the desired observables, energy differences between diastereomeric transition states, should be completely negligible. Several of the larger Hessian deviations were scrutinized, and in no case did we find errors that would be expected to interfere with the

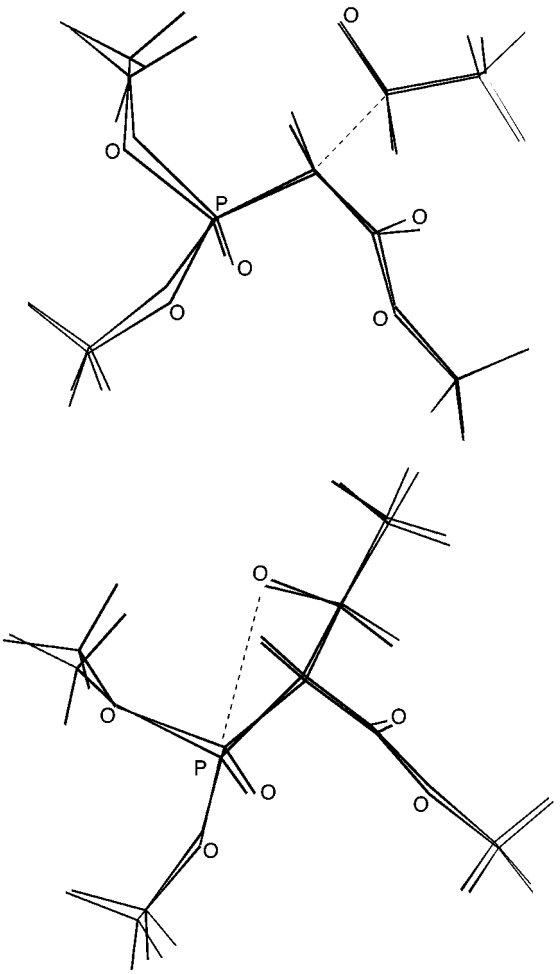

Figure 3. Overlay between QC and MM structures of TS1 (above) and TS2 (below) for addition of trimethyl phosphonoacetate anion to acetaldehyde. The rms deviation was minimized for the P−C−C−O moiety (the atoms that will form the oxaphosphetane).

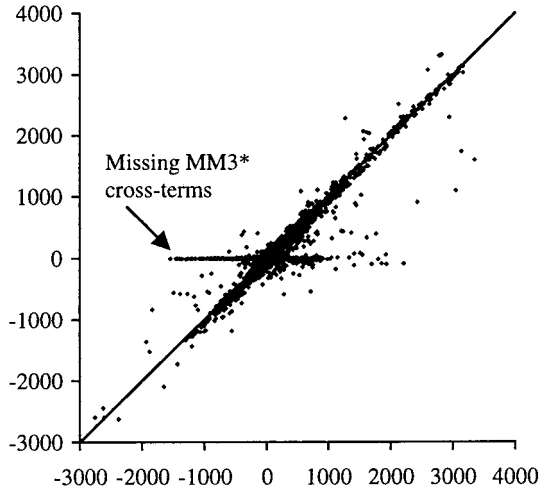

Figure 4. Comparison between QC and MM mass-weighted Hessian elements (in kJ mol^{-1} Å^{-2} au^{-1}). Note that a few QC elements are due to interactions that cannot be reproduced by the functional form of the force field.

(22) Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525.

Table 1. Experimental and Calculated Product Selectivities

entry	reaction	product ratio[a]	expt[b]	8% (*Z*)-enolate[c,d]	no (*Z*)-enolate[d]	no (*Z*)-enolate, TS1 only[e]
1	**1a** + **2**	*E*/*Z*	39:61	46:54	47:53	20:80
2		*E*,*R*/*E*,*S*	95:5	97:3	99:1	99:1
3		*Z*,*R*/*Z*,*S*	9:91	9:91	0:100	40:60
4	**1b** + **2**	*E*/*Z*	95:5	98:2	98:2	77:23
5		*E*,*R*/*E*,*S*	84:16	91:9	99:1	100:0
6		*Z*,*R*/*Z*,*S*	28:72	4:96	2:98	56:44
7	**1a** + **3**	*E*/*Z*	28:72	56:44	55:45	55:45
8		*E*,*R*/*E*,*S*	5:95	10:90	1:99	1:99
9		*Z*,*R*/*Z*,*S*	91:9	88:12	92:8	92:8
10	**1b** + **3**	*E*/*Z*	94:6	93:7	96:4	68:32
11		*E*,*R*/*E*,*S*	6:94	5:95	2:98	0:100
12		*Z*,*R*/*Z*,*S*	54:46	52:48	99:1	96:4
13	**1a** + **4**	*E*/*Z*	99:1	98:2	98:2	43:57
14		*E*,*R*/*E*,*S*	5:95	2:98	0:100	0:100

[a] *R* and *S* denote the configuration at the allylic stereocenter (the former aldehyde α-carbon). [b] Entries 1−6: ref 2b. Entries 7−12: Anvelt, J.; Soone, A.; Rein, T. Unpublished results. Entries 13−14: ref 1p. [c] The postulated (*Z*)-enolate content of the phosphonate anion was set to 8%. [d] The energy difference between TS1 and TS2 was fit for each reaction (*not* for each entry). [e] Predictions based solely on TS1, with 100% isomerically pure (*E*)-phosphonate enolate.

performance of the force field in selectivity predictions. As in the example given, strong deviations generally can be traced to conjugation with the forming C−C bond. This bond is constrained by a very high force constant in the model. Therefore, deviations from the reference value are very small, leading to a negligible influence of any cross-terms involving this bond.

Calculated Product Selectivities. The experimental and calculated selectivities in the reactions of chiral phosphonates **1** with the aldehyde substrates **2**−**4** (Figure 1) are shown in Table 1.

The correlation between experimental and calculated energies for some of the diastereoselectivities in Table 1 is illustrated in Figure 5.

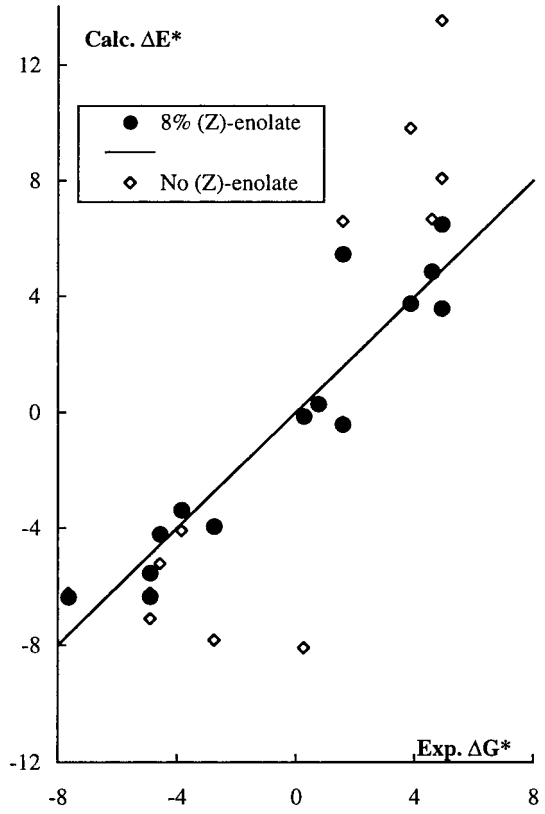

Figure 5. Correlation between experimental and calculated energies for the diastereoselectivities shown in Table 1: ΔG^* or $\Delta E^* = -RT \ln K$.

Discussion

Our quantum chemical study[3] has shown that in reactions with phosphonates containing simple alkyl groups (e.g., methyl) TS1 and TS2 are expected to be close in energy, and their relative energy levels will depend on several parameters (e.g., the solvent polarity, the nature of the counterion, and steric factors in both reactants). The particular diastereomeric intermediate from which the major end product is formed must be able to follow a low-energy path through both TS1 and TS2, and it will therefore be necessary to include appropriate models of both transition states when analyzing reaction stereoselectivities. As can be seen in Table 1, our molecular mechanics modeling gives good agreement between calculated and experimental data. In our full model, the largest errors in relative activation energies are below 4 kJ/mol (Figure 5). This can be compared to the performance of molecular mechanics for estimation of conformational energy differences in small neutral molecules, where the *average* error is ca. 2 kJ/mol for the best force fields available today.[17] In only one case, in which the experimentally observed selectivity is low, do we predict the wrong major product isomer (entry 7). Our previous "working model"[1a] rationalized the product selectivity in the reaction qualitatively by estimating effects in the initial addition, TS1. It is now clear that selectivities previously assumed to arise in TS1 in some cases are due to interactions in TS2 (vide infra). It can be seen in Table 1 that basing a computational model solely on TS1 leads to inferior predictions.

Origin of the Diastereoselection. The molecular mechanics modeling results confirm our previous hypothesis that the overall product selectivity in the asymmetric HWE reactions results from the combined influence of three main factors: the chiral auxiliary, the α-stereocenter(s) in the aldehyde substrate, and the alkoxy groups in the phosphonate ester. Only for one of the eight possible diastereomeric forms of the intermediates will all these three controlling elements act in synergy.

Role of the Chiral Auxiliary. The chiral auxiliary has previously been postulated to determine the face selectivity of the enolate. This hypothesis is strongly supported by the modeling. The effect is found to be large, and formation of intermediates with 2*S* configuration is favored by 9−14 kJ/mol in TS1.

Role of the α-Stereocenter in the Aldehyde. The face selectivity at the aldehyde will mainly be influenced by the existing α-stereocenter (i.e., C4 in the intermediate). It is clear from an analysis of all asymmetric HWE reactions performed by us to date that a common pattern is followed for all substrates containing α-heteroatom substituents (this applies to reactions with racemic monoaldehydes,[1l,2b−d] e.g., **2**, as well as dialdehydes[1p,2a]). In all these reactions, the major products observed experimentally are the ones that would arise if TS1 follows the Felkin−Anh−Eisenstein[23] (FAE) model. On the other hand, the products observed experimentally

from reactions with **3** and **4** would, according to a similar analysis, be disfavored by the FAE model.[24] Inspection of the favored transition states indicates that the nucleophilic attack at the aldehyde follows the approach vector postulated in the FAE model but also that the conformation of the aldehyde can differ from that predicted by the empirical rules. Thus, the conformations of the α-alkoxy aldehyde **2** obey the FAE model, but aldehydes with a *β*-alkoxy moiety (**3** and **4**) prefer conformations in which the Cα−C*β* bond is eclipsed with the carbonyl (due mainly to a favorable electrostatic interaction between the positive *β*-carbon and the aldehyde oxygen).[25] A somewhat surprising observation is that TS2 also gives a similar selectivity pattern for the relative stereochemistry at C3 and C4; in several cases, the diastereomeric path chosen is more influenced by TS2 than by TS1.

Role of Sterically Demanding Groups in Either Reactant. Structural changes in the phosphonate alkoxy groups will influence the relative face selectivity of the enolate and the aldehyde in TS1 and, thus, the relative stereochemistry at C2 and C3 in the intermediates.[3] Furthermore, the relative energy levels of TS1 and TS2 are affected. Overall, both of these factors will influence the *E*/*Z* selectivity of the reaction. Our QC study[3] indicated that a rate-determining TS2 will always favor *E*-selective pathways, a conclusion substantiated in this MM study. The selective disfavoring of *Z*-selective routes in TS2 is caused by steric interactions between the carboxylic ester functionality and the aldehyde residue, an effect that is even more pronounced when the steric bulk of the aldehyde is increased (e.g., by branching at the α-carbon). In contrast, increasing the steric demand of the phosphonate alkoxy groups will not have any large influence on the *E*/*Z* selectivity in TS2 but will increase the energy of TS2 relative to TS1, thereby allowing the inherent *E* selectivity of TS2 to dominate the product pattern.

Geometric Selectivity and Enantiotopic Group Preference. The formation of (*E*)- and (*Z*)-alkenes with opposite absolute configuration at the allylic stereocenter from the same substrate (and thus from reaction at opposite enantiotopic aldehyde groups) is a general trend that we have observed in all asymmetric HWE reactions studied by us to date. The current model readily explains this outcome. Since the favored *absolute* configuration at C2 is always the same, and the *relative* stereochemistry between C3 and C4 is controlled by the configuration at C4, it automatically follows that reactions at opposite enantiotopic aldehyde groups will lead to intermediates with opposite relative configuration at C2/C3 and therefore to products with opposite alkene geometry. Whether the (*E*)- or the (*Z*)-alkene is the major product of the reaction will, in turn, also depend on the specific structure of the phosphonate alkoxy groups (vide infra).

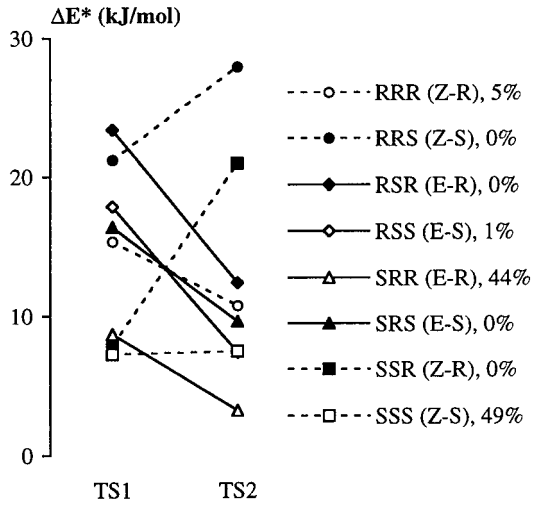

Figure 6. Plot of the Boltzmann-averaged energies for the eight different diastereomeric pathways in the reaction between **1a** and **2**. Only relative energies are considered; the zero-point is chosen arbitrarily. Open symbols correspond to FAE and filled to anti-FAE pathways. Squares and triangles indicate *2S* configuration in the intermediate. Paths with solid lines (triangles and diamonds) lead to *E* products; dashed lines lead to *Z* products. Shown in the legend text are (i) the configurations at C2, C3, and C4 in the intermediates, (ii) the product configuration, and (iii) the fraction of product formed via each path.

Rationalizations of Specific Reactions. Reaction between 1a and 2. Our calculations show that for this reaction TS1 and TS2 are very close in energy. Thus, both transition states contribute to the diastereoselection and the major products must necessarily follow low energy pathways through both of them. As seen in Figure 6, the selectivity in TS1 is dominated by the effect of the chiral auxiliary (vide supra). For the path leading to *E* product, the α-stereocenter in the aldehyde (C4 in the intermediate) gives an FAE-type influence in TS1; this effect has a similar magnitude also in TS2. For paths leading to *Z* product, the effect of the α-stereocenter is negligible in TS1 but very strong in TS2, leading to high calculated diastereomeric excess for the *Z* product, in perfect agreement with the experimental results. Thus, consideration of only TS1 would in this case lead to acceptable predictions for the *E* product, but not for the *Z* product.

Reaction between 1b and 2. Exchanging the methyl groups in the phosphoryl unit for isopropyl groups has a dramatic influence on the product distribution and turns the reaction toward pronounced *E* selectivity. The disfavoring of *Z* isomers is totally dominated by steric interactions in TS2 (Figure 7). In addition, the aldehyde α-stereocenter influences TS2 in a way similar to its effect in the reaction between **1a** and **2** discussed above.

Reaction between 1a and 3. For this reaction, the calculations show that TS1 is rate limiting and the influence of TS2 on the selectivity is completely negligible (Figure 8). The most favorable path (calculated to account for 50% of the product) is through the 2*S*,3*R*,4*S* diaste-

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(24) Evans has introduced[23h] a stereochemical model that rationalizes the merged influence of α and *β* substituents in aldol-type additions to substituted aldehydes, including α-methyl-*β*-alkoxy aldehydes. However, from substrates containing α and *β* substituents in an anti relationship (as in dialdehyde **4**) the Evans model also predicts formation of FAE-type products.

(25) The conformations of α-substituted aldehydes, and nucleophilic attack on these aldehydes by LiH, have been studied by ab initio methods: (a) Frenking, G.; Köhler, K. F.; Reetz, M. T. *Tetrahedron* **1993**, *49*, 3971. (b) Frenking, G.; Köhler, K. F.; Reetz, M. T. *Tetrahedron* **1993**, *49*, 3983.

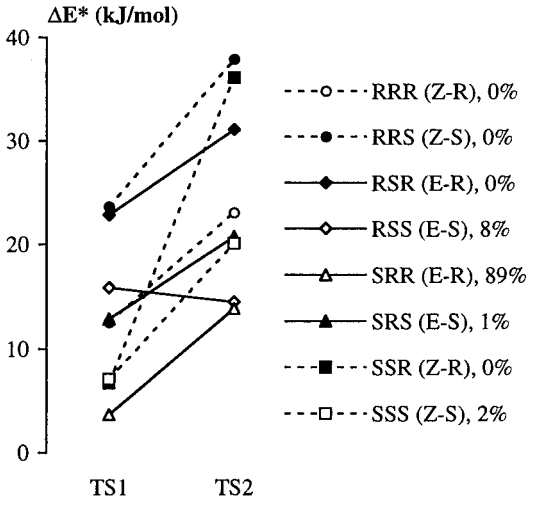

Figure 7. Reaction between **1b** and **2** (see Figure 6 caption for details).

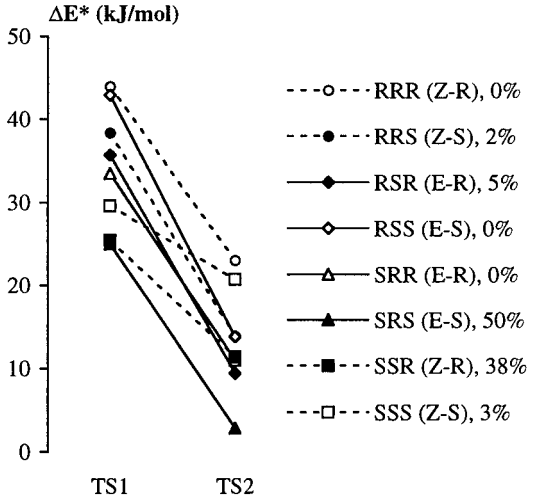

Figure 8. Reaction between **1a** and **3** (see Figure 6 caption for details).

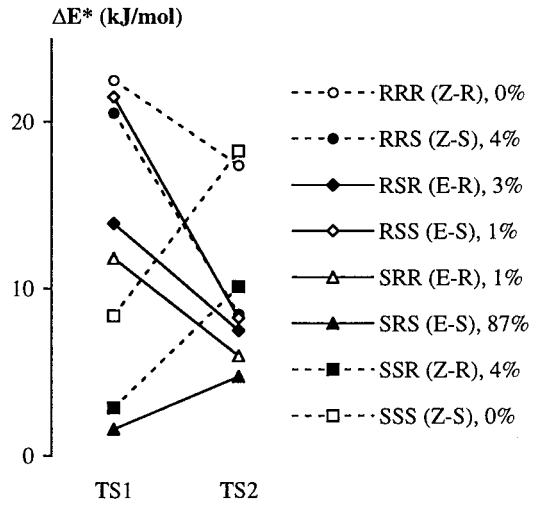

Figure 9. Reaction between **1b** and **3** (see Figure 6 caption for details).

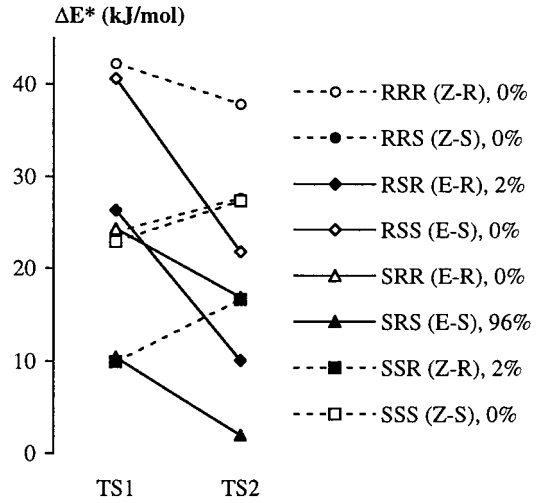

Figure 10. Reaction between **1a** and **4** (see Figure 6 caption for details).

reomer of the intermediate, leading to the *E,S* product. The second most important path, accounting for 38% of the product, is through the 2*S*,3*S*,4*R* intermediate to the *Z,R* product. The overall effect is that the geometric selectivity is low, but the enantiotopic group preference is high for both product geometries, in accord with experimental results (Table 1). In this case, the aldehyde α-stereocenter influences the diastereoselectivity in TS1 by favoring unlike relative configurations (i.e., *R,S* or *S,R*) at C3 and C4. This result disagrees with what would be predicted from the FAE model but is readily explained by the preferred eclipsed conformation of the aldehyde (vide supra).

Reaction between 1b and 3. As has been seen in the reactions with aldehyde **2**, increasing the steric demand of the phosphonate will increase the influence of TS2. In the reaction of **3** with the dimethyl phosphonate **1a**, the influence of TS2 is negligible; in contrast, TS1 and TS2 are of almost equal importance for the selectivity in the reaction between **1b** and **3**. The pattern of selectivity in TS1 is similar to the one in the reaction between **1a** and **3** (pure 2*S* configuration, high anti-FAE selectivity), whereas TS2 is responsible for the high *E* selectivity (Figure 9). Again, it can be seen that when both transition states influence the reaction there is a high preference for one out of the eight possible diastereomeric pathways, in this case leading to preferential formation of the *E,S* product.

Reaction between 1a and 4. The sense of enantiotopic group preference in the reaction with dialdehyde **4** is the same as in the reactions with **3**, as a result of the similarity in structure between the substrates. However, the dialdehyde **4** differs from the smaller monoaldehyde **3** with respect to the *E*/*Z* selectivity: whereas reaction of **3** with **1a** is slightly *Z*-selective, **4** gives almost exclusively (*E*)-alkene. This effect is caused by a largely increased influence of TS2 due to the more sterically demanding substrate (Figure 10), blocking the path through the 2*S*,3*S*,4*R* intermediate, which was the main source of *Z* product in the reaction with **3**.

Modeling of Reactions involving Bis(trifluoroethyl) Phosphonates. Bis(trifluoroethyl) phosphonate reagents are known to yield *Z* products with good to excellent selectivity. Recent quantum chemical studies[26] indicate that this *Z* selectivity (and to a lesser extent the

(26) Brandt, P. Presentation at the ACS National meeting in Dallas, Spring 1998; paper COMP197. See also ref 3.

Z selectivity of certain aryl phosphonates[27]) arises from specific nonbonded interactions with the reaction center. These interactions have not yet been integrated into our molecular mechanics model of the reaction, and consequently, all attempts to use the current force field to model this class of reactions have yielded poor results. This finding is consistent with our previous finding of a C−H hydrogen-bonded oxyanion intermediate in the reaction.

Conclusions

In summary, we have described a method for creating a TS force field based on QC normal-mode analyses for the transition state. Except for distortions along the reaction coordinate, the PES around the TS is closely reproduced. The force field has been used to rationalize selectivities in some asymmetric HWE reactions. It was shown that if the transition states for the addition step and for the subsequent ring closure to an oxaphosphetane are both considered in the modeling, good correlation between calculated and experimental product selectivities can be obtained. In all cases in which high selectivities have been observed experimentally, the modeling predicted the correct major product isomer and also gave a good estimate of the level of selectivity.

The calculations allowed identification of some important factors influencing the product selectivities. The chiral auxiliary employed in this study (8-phenylmenthol) strongly favors intermediates with a specific configuration at C2 in the intermediates. The stereocenter α to the reacting aldehyde exerts an influence on either TS1 or TS2 (or both), depending on the particular structures of the reactants, and controls the relative stereochemistry at C3/C4 in the intermediates. In some cases, the influence of the aldehyde α-stereocenter was even more pronounced in TS2 than in TS1. The general observation that (*E*)- and (*Z*)-alkenes are formed with opposite enantiotopic group preference from the same substrate is nicely explained as resulting from the combined influence of the chiral auxiliary and the aldehyde stereocenter(s). Furthermore, structural changes in the phosphonate alkoxy groups influence both the relative stereochemistry at C2 and C3 in the intermediates and the relative energy levels of TS1 and TS2, factors that control the overall *E*/*Z* selectivity. In general, TS2 is *E*-selective; increasing the size of the phosphoryl group does not enhance the inherent *E* selectivity of TS2 but does increase the influence of TS2 relative to TS1.

One of the long-term goals of our work is to produce a tool for rapid virtual screening of potential reagent-substrate combinations, to evaluate new reactants before actually synthesizing them. We envision that the modeling tool presented in this paper will be a very useful adjunct for improving the synthetic utility of the title reaction even further.

Acknowledgment. Financial support from the Danish Medical Research Council, the Danish Technical Research Council, and the STINT Foundation (postdoctoral fellowship for P.B.) is gratefully acknowledged. The National Supercomputer Centre in Linköping, Sweden, provided access to supercomputer time, and this work was also supported with computing resources by the Swedish Council for High Performance Computing (HPDR) and Parallelldatorcentrum (PDC), Royal Institute of Technology.

Note Added in Proof. Very recently, a review discussing the Felkin−Anh−Eisenstein model and other related models has been published: Mengel, A.; Reiser, O. *Chem. Rev. (Washington, DC)* **1999**, *99*, 1191.

Supporting Information Available: Force field parameters in MacroModel format and Cartesian coordinates for nine transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

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