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The *ortho*-Hydroxy-*ortho'*-Formyl Biaryl / Lactol Equilibrium: Quantumchemical Studies on Structure and Dynamics[1]

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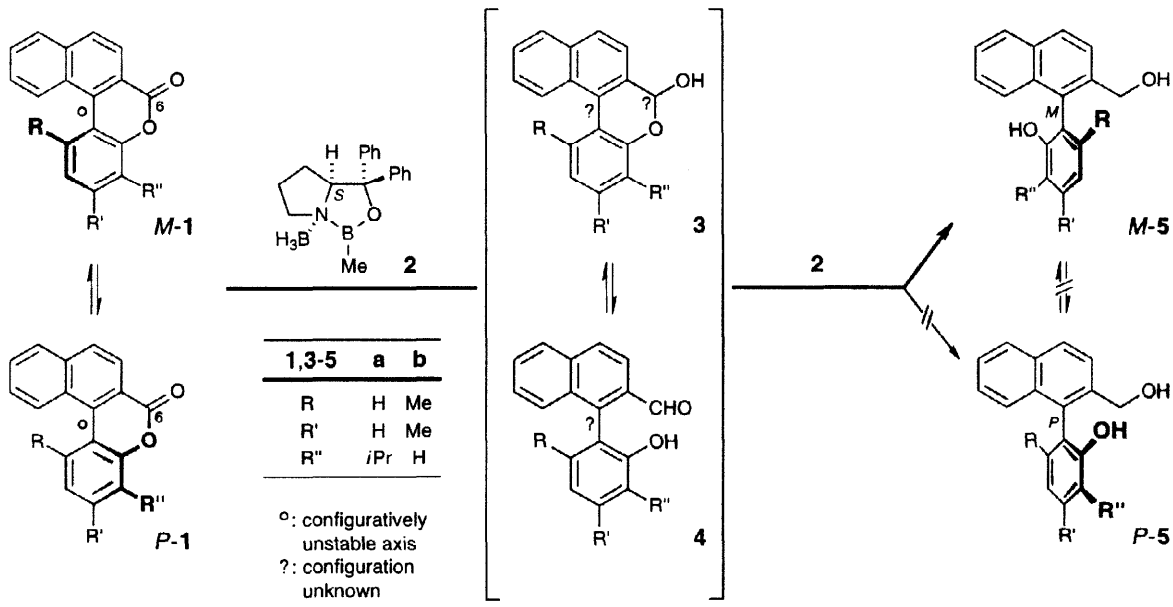
Abstract: The equilibrium between the lactol-bridged biaryls **3** and the ring opened hydroxy aldehyde isomers **4** as well as their atropisomerization are investigated by quantumchemical calculations. The suitability of semiempirical and different modern *ab initio* methods is validated by comparison with experimentally observed equilibria and crystallographic data. It is shown that for the description of the equilibrium between **3** and **4** Hartree-Fock *ab initio* methods lead to a significant improvement compared with semiempirical methods. Furthermore, the consideration of solvent effects by using AM1-SM4, PM3-SM4 and PM3-SM3 gives satisfying results in the description of the equilibrium investigated.

INTRODUCTION

Lactol-bridged biaryls of type **3** and the corresponding open-chain hydroxy aldehydes **4**[2,3] (or, rather, their metallated analogs) are key intermediates in the atropo-enantioselective reduction of rapidly enantiomerizing biaryl lactones of type **1** to give configuratively stable biaryl alcohols **5**, *e.g.* using oxazaborolidine-activated borane (Scheme 1).[4–6] This preparatively useful and mechanistically interesting novel principle of stereoselective biaryl synthesis has shown its efficiency in the directed preparation of stereochemically pure biaryl natural products[7–9] (and their bioactive analogs[10]), and of efficient reagents for stereoselective synthesis.[11]



Scheme 1. Stereoselective formation of biaryls **5**.

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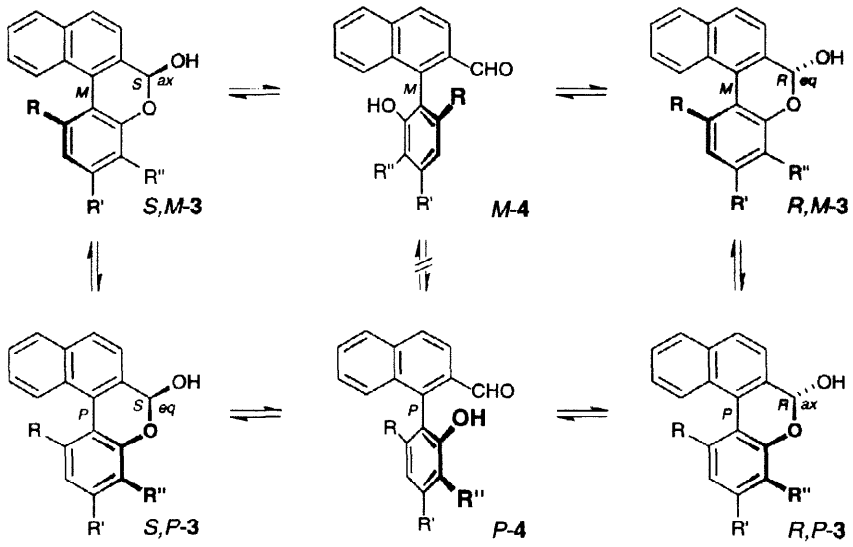
For the likewise highly selective cleavage of lactones **1** with chiral metallated *N*-nucleophiles,[4,6] experimental and quantumchemical investigations hint at a dynamic kinetic racemate resolution at the level of the starting lactones **1**,[4,12] *i.e.* with the *N*-nucleophiles irreversibly cleaving only one of the two rapidly interconverting atropenantiomeric forms of **1**. For the atropo-enantioselective reaction with *H*-nucleophiles, by contrast, the selectivity-determining step of the now more complex reduction sequence is not known *a priori*, because the intermediate aldehyde **4** is configuratively unstable at the axis and might thus constitute a 'stereochemical leakage'.[5] Its enantiomerization should occur *chemically*, *via* the corresponding lactols,[5] *e.g.* by cyclization of *M*-**4** to *S,M*-**3**, its helimerization to *S,P*-**3** and cleavage to give *P*-**4** – or *via* *R,M*-**3** and *R,P*-**3** (see Scheme 2).



Scheme 2. Mechanistic pathways for the 'chemical' atropisomerization of **4**, *via* lactols **3**.[5]

AM1 calculations on the complete mechanistic course of the enantioselective reduction of **1b** underline the importance and relevance of the aldehyde/lactol intermediates and suggest their dynamic kinetic resolution to be the selectivity-determining step of the reaction sequence **1** → **5**.[13] As described in the preceding paper,[2] we have therefore prepared a series of such presumed synthetic intermediates and have investigated their structures, among them **3a/4a** and **3b/4b**, which, because of the sterically demanding methyl group next to the axis, presents itself in its aldehyde form, exclusively. In this paper, we report on the quantumchemical calculation of structures, relative stabilities (and thus equilibria), and atropisomerization barriers of such biaryl lactols and aldehydes.

RESULTS AND DISCUSSION

Structures and relative energies of lactols 3

Experimental work showed a significant dependence of the equilibrium between lactols **3** and their ring opened hydroxy aldehyde isomers **4**, on the solvent and on the size of the substituent R (see Scheme 2) next to the biaryl axis.[2] Thus, the equilibrium between **3b** and **4b** (R = Me) is quantitatively shifted to the hydroxy aldehyde form, whereas in **3a** and **4a** (R = H) the lactol form prevails. For a profound understanding of these sensitive equilibria, quantumchemical investigations with different state-of-the-art semiempirical (with and without solvent), Hartree-Fock, and density functional *ab initio* methods (Tables 1 and 2) were performed.

Semiempirical AM1 calculations (Tables 1 and 2, entry 1) reveal a general preference of the lactol form **3** in both cases by 7.75 kcal/mol (**3a** ⇌ **4a**) and 4.37 kcal/mol (**3b** ⇌ **4b**), respectively, which is inconsistent with the experimental results.[2] Two reasons for this failure are imaginable: the neglect of the influence of the solvent on the equilibrium, or, secondly, the AM1 parameterization giving wrong results for the comparison of these isomers. The PM3 parameterization, by contrast, leads to a qualitatively correct description of the observed equilibria. The PM3 results show a decreased preference of the lactol isomer in the case of low sterical hindrance at the axis (**4a**, $\Delta\Delta H_f$ = 2.87 kcal/mol; Table 1, entry 2), but correctly favor the hydroxy aldehyde form in the case of more bulky substituents in the *ortho* position (**4b**, $\Delta\Delta H_f$ = -1.80 kcal/mol; Table 1, entry 2).

For a closer view at solvent effects we performed semiempirical AM1 and PM3 calculations using the SM3 and SM4 solvation models (solvents: H_2O[15,16] and *n*-hexane,[17] respectively; Tables 1 and 2, entries 3-5) as implemented in AMSOL5.4.[18] As the calculated solvation energies (ΔE_S) with AM1-SM4 or PM3-SM4 are quite similar, it seems that the reason for the failure of AM1 is not the neglect of the influence of the solvent on

Table 1. Relative heats of formation $\Delta\Delta H_f$ (kcal/mol) of the minimum structures for the isomerization of lactols **3a** and hydroxy aldehydes **4a**; all *ab initio* calculated ΔH_f values are ZVPE corrected with RHF/3-21G* energies

Entry	Method	*S,P*-**3a** (OH_{eq})	*S,M*-**3a** (OH_{ax})	**4a**
1	AM1	0.82	0.00	7.75
2	PM3	0.43	0.00	2.87
3	AM1-SM4	0.70	0.00	7.15
4	PM3-SM4	0.62	0.00	2.02
5	PM3-SM3	1.22	0.00	1.70
6	RHF/3-21G*//RHF/3-21G*	-0.02	0.00	4.17
7	RHF/6-31G*	0.23	0.00	-0.21
8	MP2/6-31G*//RHF/6-31G*	1.67	0.00	2.78
9	B3LYP/6-31G*//RHF/6-31G*	0.95	0.00	1.61
10	B3LYP/6-31G*	1.12	0.00	1.59

Table 2. Relative heats of formation $\Delta\Delta H_f$ (kcal/mol) for the isomerization of lactols **3b** and hydroxy aldehydes **4b**; all *ab initio* calculated ΔH_f values are ZVPE corrected with RHF/3-21G* energies

Entry	Method	*S,P*-**3b** (OH_{eq})	*S,M*-**3b** (OH_{ax})	**4b**
1	AM1	0.76	0.00	4.37
2	PM3	0.36	0.00	-1.80
3	AM1-SM4	0.74	0.00	3.90
4	PM3-SM4	0.64	0.00	-2.67
5	PM3-SM3	1.28	0.00	-3.44
6	RHF/3-21G*	-1.81	0.00	-2.67
7	RHF/6-31G*	-0.39	0.00	-4.80
8	MP2/6-31G*//RHF/6-31G*	0.41	0.00	-0.39
9	B3LYP/6-31G*//RHF/6-31G*	0.17	0.00	-0.88

the equilibrium, but probably rather a consequence of the insufficient AM1 parameterization in this case. Due to the higher ΔE_S values of the aldehyde forms **4** compared with the lactol type isomers **3**, the consideration of solvent effects in combination with the PM3 Hamiltonian leads to an improved description of the equilibrium.

If solvent effects are not responsible for the failure of AM1, the use of Hartree-Fock (HF) *ab initio* methods should result in an improved theoretical description of the experimentally observed equilibria. Indeed, all *ab initio* methods used in this investigation agree qualitatively correctly with the experiments shown in Tables 1 and 2. Two main trends are observed in varying the size of the basis sets and considering electron correlation. Expansion of the basis set leads to a lowering of the relative energies of formation of the hydroxy aldehyde isomers **4** (Tables 1 and 2, entries 6 and 7), whereas the consideration of electron correlation (MP2 and B3LYP; Table 1, entries 8-10 and Table 2, entries 8 and 9) leads to an increase of the relative heats of formation of the hydroxy aldehydes **4**. These qualitively best methods used in this investigation are in good agreement with the experimental values.

All correlation methods correctly show a slight preference of the lactol isomer with the hydroxy substituent in an axial position, whereas HF calculations without correlation prefer the isomer with the hydroxy group equatorial. In comparison with the crystal structure of **3a**,[2] which also has an axial hydroxy substituent, and in agreement with NOE-measurements, the correlation methods (as expected) show the qualitatively right geometry.

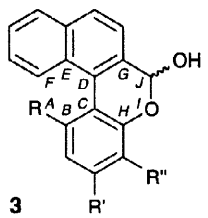
In contrast to the energetic variation, the computed molecular geometries vary only little in dependence on the theoretical method applied. Some selected geometry parameters are presented in Table 3. The calculated molecular geometry of lactol **3a** (RHF/6-31G*) agrees well with the experimental one obtained through an X-ray structure analysis.[2] As for other, related bridged biaryls,[14,19] *S,M*-**3a** shows a helically distorted geometry. The overall distortion of the biaryls is measured by the sum of dihedral angles at the 'inner spiral loop'[19] (Table 3). As expected, this value is much higher for the (experimentally not observable) lactol **3b** (61.2°) than for **3a** (calculated: 42.9°; experimental: 44.8°), as a consequence of the increased steric hindrance at the biaryl axis.

Atropisomerization of the lactols 3

One of the most important aspects of the mechanistic course of the atroposelective lactone reduction is the kinetics of the atropisomerization process of the lactols, especially with respect to their proposed[13] use as direct substrates for atropo-enantioselective reductions and thus stereoselective biaryl synthesis. Due to the chemical and configurative instability of these rapidly opening intermediates and thus lack of experimental values, only theoretical methods are able to provide this important information. In earlier work we have shown that quantumchemical methods are in good agreement with experimental atropisomerization barriers for helically twisted biaryl lactones **1**.[14] We have therefore chosen a similar strategy for the analysis of the lactols **3**. For a complete evaluation of the configurational space, a potential energy surface was calculated with AM1 by varying two particular dihedral angles, ABDE and FECB (Table 3). The 3D plot and the isocontour plot (Fig. 1) show the two atropisomeric minima *S,M*-**3b** and *S,P*-**3b** of lactol **3b** and, at the saddle points of the surface, the two expected diastereomorphous transition structures TS[*S,M*-**3b**⇌*S,P*-**3b**]$_{eq}$ and TS[*S,M*-**3b**⇌*S,P*-**3b**]$_{ax}$ (see Figs. 1 and 2). The maximum in the middle of the plot corresponds to the area where van der Waals clashes of the methyl group (R = Me, see Scheme 1) and the naphthyl half lead to geometries with distinctly higher energies.

Refinement of the molecular energies with theoretical methods of higher quality (Table 4, entries 3-6) than AM1 (Table 4, entry 1) essentially lead to similar results. Only PM3 (Table 4, entry 2) gives generally

Table 3. Dihedral angles α (ABCD), β (BCDE), γ (CDEF), δ (HCDG), ϵ (HIJG) [deg.], overall distortion of the 'inner spiral loop' ($\Sigma_{\alpha\beta\gamma}$) and endocyclic C-O bondlengths IJ [Å] of the ground and transition structures for the isomerization of lactols **3b** and **3a**



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Compound	Method	α	β	γ	$\Sigma_{\alpha\beta\gamma}$	δ	ϵ	IJ
S,P-**3a**	AM1	4.0	27.6	13.0	**44.6**	23.5	46.5	1.44
(OH_{eq})	RHF/6-31G*	1.9	30.7	11.5	**44.1**	26.19	57.9	1.41
S,M-**3a**	AM1	3.6	27.1	14.1	**44.8**	23.1	41.8	1.43
(OH_{ax})	RHF/6-31G*	1.4	29.4	12.1	**42.9**	24.3	53.7	1.40
	Experimental (X-ray)	2.3	31.0	11.5	**44.8**	24.3	54.6	1.38
TS[*S,M*-**3a**⇌*S,P*-**3a**]$_{eq}$	AM1	6.2	14.9	-19.0	**2.1**	12.4	42.4	1.42
(OH_{eq})	RHF/6-31G*	0.6	5.3	-15.4	**-9.5**	7.2	45.6	1.39
TS[*S,M*-**3a**⇌*S,P*-**3a**]$_{ax}$	AM1	-6.1	-14.8	18.8	**2.1**	-12.3	-45.2	1.43
(OH_{ax})	RHF/6-31G*	-0.9	-4.5	17.2	**11.8**	-7.6	-48.1	1.39
S,P-**3b**	AM1	12.5	36.4	11.9	**60.8**	29.4	49.5	1.44
(OH_{eq})	RHF/6-31G*	10.1	40.9	10.7	**61.7**	31.7	59.9	1.41
S,M-**3b**	AM1	12.4	36.1	12.6	**61.1**	25.2	45.0	1.43
(OH_{ax})	RHF/6-31G*	9.7	40.1	11.4	**61.2**	30.2	56.6	1.40
TS[*S,M*-**3b**⇌*S,P*-**3b**]$_{eq}$	AM1	-28.6	-17.5	41.6	**-4.5**	-14.2	-39.5	1.48
(OH_{eq})	RHF/6-31G*	-9.39	-12.0	32.4	**11.0**	-12.9	-55.9	1.39
TS[*S,M*-**3b**⇌*S,P*-**3b**]$_{ax}$	AM1	27.8	17.9	-42.1	**3.6**	14.5	39.4	1.42
(OH_{ax})	RHF/6-31G*	10.3	12.4	-31.2	**-8.5**	12.0	51.6	1.38

lower atropisomerization barriers, which might be a systematic error of the PM3 parameterization. The calculated energies of the transition structures are presented in Table 4. The quintessence of the comparison of the theoretical methods used in this investigation is that they all give a good impression of the atropisomerization barrier. The differences between the methods are much smaller than for the comparison of the relative energies of lactols **3** and hydroxy aldehydes **4**. For lactol **3a**, the activation barriers vary between 4.44 kcal/mol (PM3; Table 4, entry 2) and 9.42 kcal/mol (RHF/3-21G*; Table 4, entry 3), **3a** is thus stereochemically unstable. The activation enthalpies for the more hindered lactol **3b** are between 15.22 kcal/mol (PM3; Table 4, entry 2) and 23.74 kcal/mol (RHF/6-31G*; Table 4, entry 3), and thus generally much higher. For the *total* atropisomerization barrier of the hydroxy aldehyde **4**, the energetic difference between **4** and helimerizing lactol forms **3** must additionally be taken into account.

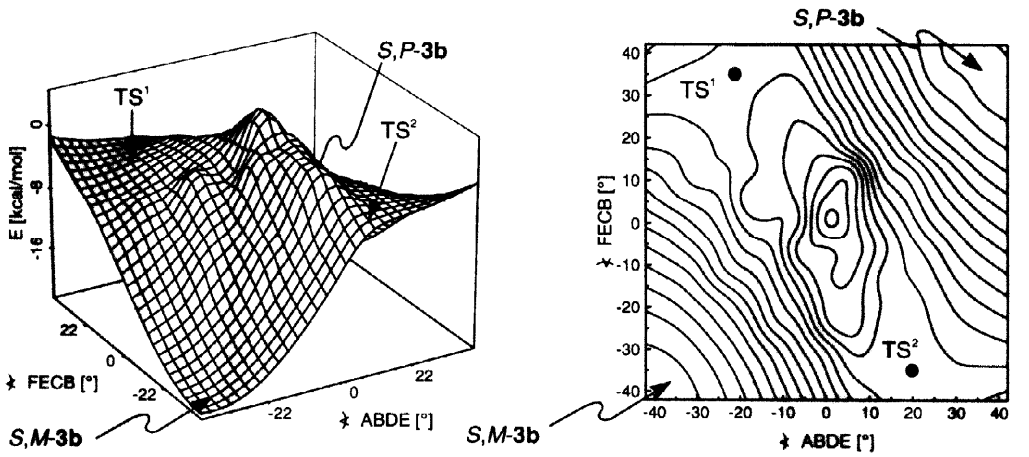

Fig. 1. AM1 potential enery surface for the atropisomerization process of lactol **3b**; TS^1 = TS[*S,M*-**3b** ⇌ *S,P*-**3b**]$_{eq}$ and TS^2 = TS[*S,M*-**3b** ⇌ *S,P*-**3b**]$_{ax}$.

Table 4. Activation enthalpies $\Delta H^{\neq}$ (kcal/mol) of the transition structures for the atropisomerization of lactols **3b** and **3a**; all *ab initio* calculated ΔH_f values are ZVPE corrected with RHF/3-21G* energies

		TS[*S,M*-**3a**⇌*S,P*-**3a**]		TS[*S,M*-**3b**⇌*S,P*-**3b**]	
Entry	Method	with OH_{eq}	OH_{ax}	OH_{eq}	OH_{ax}
1	AM1	7.47	8.07	19.66	18.96
2	PM3	4.44	5.17	16.32	15.22
3	RHF/3-21G*	8.48	9.42	24.96	23.17
4	RHF/6-31G*	7.53	8.66	22.49	22.84
5	MP2/6-31G*//RHF/6-31G*	8.06	9.91	21.21	22.17
6	B3LYP/6-31G*//RHF/6-31G*	6.15	7.69	18.71	19.53

CONCLUSIONS AND FURTHER PERSPECTIVES

The presented calculations reveal that *ab initio* methods can give valuable insight into the molecular behavior of synthetically interesting biaryl hydroxy aldehydes and their lactol-bridged cyclic forms. For the analysis of the isomerization process between hydroxy aldehydes and their isomeric lactols, the use of *ab initio* methods and the consideration of solvent effects lead to significant improvements of the calculated equilibria over AM1 results, which are in contrast to experimental observations. *Ab initio* methods as well as semiempirical techniques give a good impression of the atropisomerization behavior of helically twisted lactols. As a practical consequence, stereoselective reactions by dynamic kinetic resolution of hydroxy aldehydes like **4** as predicted by the calculations, are most promising and might even be fine-tuned by the computationally assisted variation of the atropisomerization barrier.

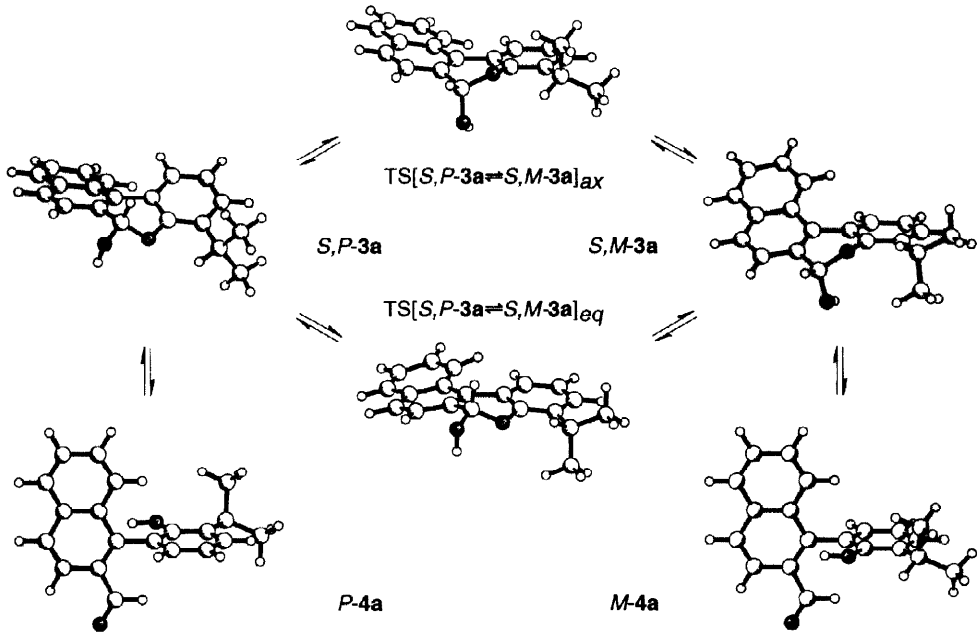

Fig. 2. Calculated ground and transition state geometries (RHF/6-31G*) for lactol **3a** and hydroxy aldehyde **4a**.

COMPUTATIONAL METHODS

The input geometries for the AM1 calculations were obtained by using the MM2 force field[20] within the SYBYL program package.[21] Conformational analyses on all minimum geometries were done starting with the SYBYL RANDOMSEARCH algorithm, followed by a further refinement of the obtained minima by semiempirical calculations. Semiempirical AM1 and PM3 as well as SM3 and SM4 calculations were performed on Silicon Graphics IRIS Indy (R4400) and SNI PPro LinuX workstations using the VAMP 5.0, VAMP 6.1,[22] and AMSOL 5.4[18] programs. Semiempirical ground structures were minimized by applying the EF algorithm[23] with a gradient norm specification of 0.01 mdyn/Å, whereas semiempirical transition structures were optimized by the NS01A algorithm.[24] *Ab initio* calculations were carried out on a LinuX PPro cluster as well as on CRAY YMP, CRAY T90 and VPP700 Supercomputers using the GAUSSIAN 94 program.[25] Minima were obtained with the Berny algorithm,[26] and transition states were optimized by initial calculation of the molecular forces followed by a transition state search. Force calculations were applied to characterize minima and transition structures by calculation of their normal vibrations. In all cases, the correspondence of transition structures to their local minima was determined by semiempirical IRC calculations.

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