Tetrahedron Vol. 46, No. 20, pp. 7003-7010, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

DIRECT DERIVATIZATION OF GLYOXAL INTO CHIRAL TEMPLATES PROVIDING COMPLETE DISCRIMINATION BETWEEN THE ALDEHYDE GROUPS

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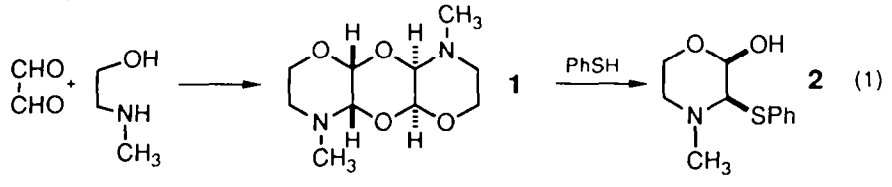
(*Received in Belgium* 19 *July* 1990)

ABSTRACT - Condensation between glyoxal, thiophenol and N-substituted (*R*)-phenylglycinol led to morpholine derivatives. The totally stereoselective formation of heterocycle **6** gives access to a chiral masked form of glyoxal in which the symmetry features of the dialdehyde have disappeared. The cyclisation is consistent with Baldwin rules for ring closures when applied to different competing pathways. AM1 conformational calculations were used in order to rationalize the stereochemical outcome of the reported transformation.

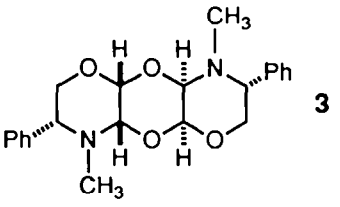
Highly functionalized small molecules are valuable materials for total synthesis. In this respect, glyoxal looks like a very gifted candidate. Many useful derivatives can be designed from this simplest member of the α-dicarbonyl family provided that a suitable masked form be available, that is a form not exhibiting the symmetric character of glyoxal. For this end, two requirements are needed: (i) such a synthon should provide discrimination between the two aldehydic functions, and (ii) it should allow differentiation of the enantiofaces of the carbonyl groups. Such conditions have already been fulfilled for α-ketoaldehydes by using α-oxathianyl[1] and α-aminal[2] derivatives. However, in the case of glyoxal, there is no report, to the best of our knowledge, of synthetic applications of directly derivatized synthons;[3] the only published method[4] describes the synthetic use of a chiral monoacetal of glyoxal resulting from ozonolysis of the corresponding 2-hexenal derivative.

Some years ago, Le Rouzic *et al.*[5] reported that compound (±)-**2** was the result of the condensation between thiophenol and the dioxazinodioxane **1** which had been previously obtained[6] from a condensation between glyoxal and N-methyl ethanolamine (eq. 1).[8] It was thus of interest to know whether this interesting regioselective differentiation between the two identical carbonyl functions of glyoxal is also amenable to chiral differentiation. We present below a detailed study of the condensation between glyoxal and N-methyl-(*R*)-phenylglycinol which affords a chiral glyoxal-equivalent ; transformations of this synthon to optically pure α-amino acids and β-amino alcohols will give rise to a full account in due course.[9]



(1)

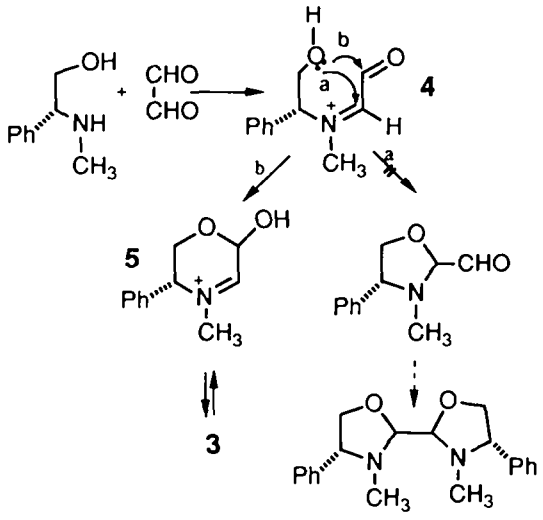
The synthesis of the tricyclic compound **3** was effected by treatment of N-methyl-(*R*)-phenylglycinol with an aqueous solution of glyoxal.This chiral derivative of glyoxal was obtained in a diastereoisomerically pure form as evidenced by (^{1}H) NMR and (^{13}C) NMR. The relative stereochemistry of the rings was assigned from the following sets of observations. First, the small vicinal coupling constant (1Hz) exhibited by the hydrogens at ring junction indicates a *cis* stereochemistry. On the other hand, all analogous atoms in the two morpholine moieties are anisochronous : for instance, the two N-CH-O groups present two resonances for the carbon atom (81.1 and 81.7 ppm) and two resonances for the hydrogens (4.65 and 4.95 ppm). The latter feature indicates a *cis-anti-cis* tricyclic structure since in the isomeric *cis-syn-cis* the paired atoms would be magnetically equivalent owing to a C_2 symmetry.



3

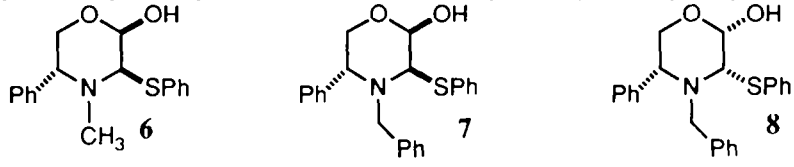
It is worth noting that no bis-oxazolidine product was obtained during the preceeding condensation.[10] This is consistent with Baldwin's rules for ring closure in trigonal systems[12] which are specially enlightening when unequally favoured processes are competing within the same molecule.[13] In the case at hand, the iminium ion **4**, resulting from the condensation of the amino group of the β-amino alcohol with the first carbonyl function of glyoxal, may follow two pathways of ring closure (cf. Scheme 1). Pathway *a* would lead to an oxazolidine via a 5-*endo-trig* mode of attack which is stereoelectronically disfavored ; yet this process is operative with monoaldehydes and affords oxazolidine derivatives,[14] since in this case there is no other practicable evolution.[15] However such an alternative pathway exists when starting from glyoxal : actually intermediate **4** leads to the cyclized iminium ion **5** via the favoured 6-*exo-trig* ring closure process *b*. A head-to-tail condensation between two molecules of intermediate **5** accounts for the production of tricyclic product **3**.

Morpholine derivative **6** was quantitatively obtained by two different procedures: (i) treatment of compound **3** with thiophenol (2 equiv) in aqueous medium, (ii) direct condensation between glyoxal, N-methyl-(*R*)-phenylglycinol and thiophenol in aqueous solution (one-pot procedure). Structure of morpholine **6** was secured by an X-ray analysis[9] which, in particular, establishes the axial position of the phenylthio substituent; this point will be adressed below. This relative stereochemistry of OH and SPh groups is consistent with an intramolecular hydrogen bond. In fact, in the corresponding (^{1}H) NMR spectrum (dilute $CDCl_3$ solution : 5mg/1ml) the hydroxy hydrogen appears as a doublet (δ 4.5 , J : 13.5 Hz) which is shifted to lower field (δ 6.67) in DMSO solution.[16]

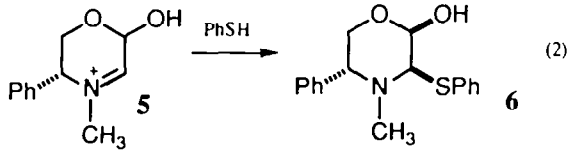


Scheme 1

An analogous reaction was observed when starting from N-benzyl-(*R*)-phenylglycinol, but, in this case, the stereoselectivity was poorer. Actually a mixture of compounds **7** (83%) and **8** (17%) was obtained as evidenced by NMR. The *cis* relationship between OH and SPh in both isomers was deduced from (i) the coupling constant (J : 1.8 Hz) shown by the vicinal ring hydrogens and (ii) the existence of the intramolecular hydrogen bond (see above). Stereochemistry of the major isomer **7** was assigned by comparison with the corresponding spectra displayed by the analogous morpholine **6** whose structure was previously unambiguously determined.

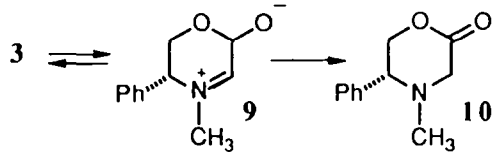


Is tricyclic compound **3** an intermediate in the condensation between glyoxal, N-methyl-(*R*)-phenylglycinol and thiophenol leading to **6** ? Actually the real intermediate is likely to be the iminium ion **5** (cf. Scheme I) : product **6** would thus arise from a stereoselective addition of thiophenol onto the C=N bond leading to an *anti* adduct (with respect to the phenyl group) (eq. 2).



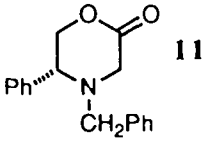
(2)

Treated by magnesium bromide in THF, compound **3** yielded N-methyl-2,3,5,6-tetrahydro-4*H*-oxazin-2-one **10**. The intermediacy of iminium ion **9** could possibly account for this transformation via 1,2 hydride shift (eq.3). This result is consistent with the above assumption of tricyclic compound **3** being in equilibrium with the corresponding iminium ion **5** which is the actual reactive species.[17]



(3)

On the other hand, it was observed that the tetrahydro oxazinone **10** also resulted from treatment of the morpholine derivative **6** with $MgBr_2$. In the same way, the mixture of N-benzyl morpholinols **7** and **8** afforded tetrahydro oxazinone **11** which was recently described by Dellaria and Santarsiero.[18]



11

Addition of thiophenol to the iminium moiety of intermediate **5** led to morpholine derivative **6** in a single diastereoisomeric form (eq. 2). Rationalization of this stereoselectivity can hardly be straightforward since the substrate may exhibit four stereoisomeric structures : two diastereoisomers interconvertible via ring-chain tautomerism, each of which showing two half-chair conformers owing to ring inversion. AM1 calculations however gave clear-cut indication that the favored structure is **5A** (Fig. 1) in which the phenyl and the hydroxy groups are respectively pseudo-equatorial and pseudo-axial.

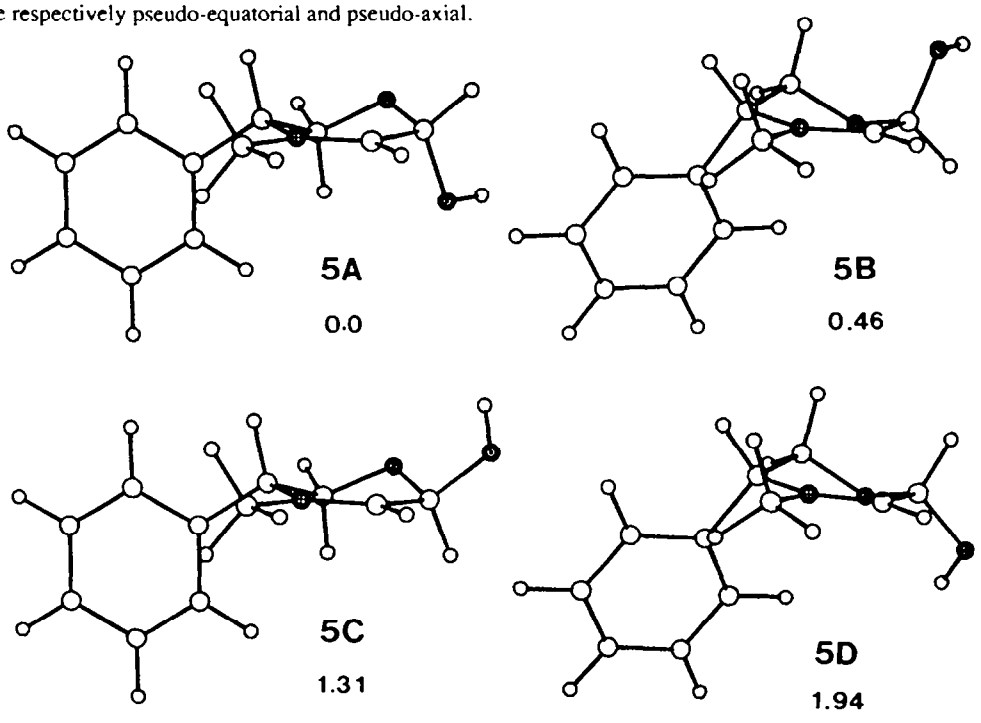


Figure 1

Relative energies (kcal/mol) of the stable stereoisomers of the hydroxy iminium intermediate

Enthalpy differences between **5A** *vs* **5C** (1.31 kcal) and between **5B** vs **5D** (1.48 kcal) point out the importance of the anomeric effect leading to a pseudo-axial geometry of the hydroxy group; actually this stabilizing effect should be reduced in the aqueous solution in which the condensation (eq. 2) took place.[19] On the other hand, that allylic 1,2-strain here is negligible can be deduced from energy differences between **5A** *vs* **5B** and between **5C** *vs* **5D** (Fig. 1) which both show that a pseudo-equatorial position of the phenyl group is favored.

Though the most populated structure **5A** may not be the reactive one (Curtin-Hammett principle) and thermodynamic control may interfere,we feel it likely that addition of thiophenol occurs on that stereoisomer as depicted in Figure 2.

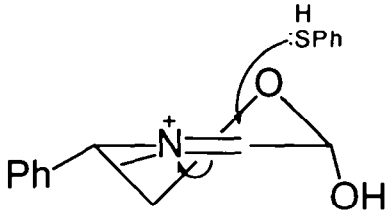


Figure 2

Nucleophilic attack of thiophenol onto the C=N$^+$ bond of intermediate 5A

The remarkable diastereoselectivity of this process would thus be governed by three factors : (i) axial atttack leading to a chair-like transition state, [20] (ii) *anti* selectivity in relation to the phenyl substituent which hinders the lower side of the C=N bond,[20] (iii) *anti* selectivity in relation to the hydroxy group in agreement with the observations of Hehre *et al.*[21] who stated that for nucleophiles which are devoid of an associated metal "addition should occur preferentially onto the olefin face that is the more removed from electron-rich functionality". Ring-chain tautomerism would ultimately lead to **6** .

Findings reported in this article show that glyoxal can easily be transformed into a chiral derivative in which the masked aldehydic groups are totally differentiated. Asymmetric synthesis which make use of synthon **6** are currently in progress.[9]

EXPERIMENTAL PART

General comments. ^{1}H and ^{13}C NMR spectra were determined on a Bruker AC 200 spectrometer at 200 and 50 MHz respectively. The proton and the carbon shifts are reported in ppm downfield from TMS. Infrared spectra were measured with a Perkin-Elmer 1420 instrument. Optical rotations were determined with a Perkin Elmer 141 polarimeter. Melting points were obtained with a Reichert apparatus (hot stage provided with a microscope). Microanalysis were performed by the Laboratory of Microanalysis of the Université P. et M. Curie. N-Methyl-(*R*)-phenylglycinol was prepared by following a published procedure.[22]

N-Benzyl-(*R*)-phenylglycinol

To a solution of (*R*)-phenylglycinol (5 g, 36.5 mmol)[23] and 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) (5.54g, 36.6 mmol) in toluene (100 ml), benzyl bromide (6.25 g, 36.5 mmol) was added dropwise over 0.5 h at room temperature. The resulting suspension was stirred an additional hour. Then water (100 ml) was added. The toluene layer was decantated, washed with water (50 ml) and brine (50 ml). The aqueous layer was extracted with CH_2Cl_2 (2 x 50 ml) and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent followed by flash chromatography (80% Et_2O/petroleum ether) gave N-benzyl-(*R*)-phenylglycinol as a white solid (5.86 g, 71%) : mp 84°C (lit.[24] : 86°C); $[\alpha]_D^{20}$ -81° (*c* 0.85, EtOH) (lit.[24] +80° for the *S* enantiomer).

(3*R*, 7*R*)-Perhydro-4,8-dimethyl-3,7-diphenyl-4,8-diaza-1,5,9,10-tetraoxaanthracene (3)

A suspension of N-methyl-(*R*)-phenylglycinol (750 mg, 5 mmol) in an aqueous solution of glyoxal (1.13ml, 4.4M M solution) was stirred in the presence of diethyl ether (10 ml) at room temperature for 60 h. The reaction mixture was filtered and the residue was washed with ether and dried under vacuum (0.1 mm Hg) to give **3** as a white solid (0.6 g, 63%) : mp 190°C (sublimation); $[\alpha]_D^{20}$ -21.1° (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) : 2.31 and 2.41 (s, 3H, N-CH_3), 3.5-4.2 (m, 6H, H2,H3,H6,H7), 4.65 (d, 1H, J = 2 Hz , N-CH-O), 4.95 (d, 1H, J = 1 Hz, N-CH-O); ^{13}C NMR : 36.5 and 39.0 (N-CH_3), 59.1 and 61.8 (C-3, C-7), 66.6 and 71.3 (C-2, C-6), 81.1 and 81.7 (O-CH-N),93.1 and 93.6 (O-CH-O). Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.85; H, 6.78; N, 7.16.

(2*R*,3*R*,5*R*)-4-Methyl-5-phenyl-3-(phenylthio)-2-morpholinol (6)

N-Methyl-(*R*)-phenylglycinol (7.7 g, 0.05 mol) was added into an aqueous solution of glyoxal (29 ml, 1.6 M solution). After 3 h stirring at room temperature, water (150 ml) and thiophenol (5.6 g, 0.05 mol) were successively added. After the reaction mixture was sitirred for 4 h, the resulting precipitate was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, the solvent was evaporated and the solid residue was washed with Et_2O affording **6** (13 g, 85%) : mp 119°C ; $[\alpha]_D^{20}$ +322° (*c* 1.2, $CHCl_3$) ; 1H NMR : 2.14 (s, 3H, N-CH_3), 3.47-3.73 (m, 2H, CH_2), 3.82 (dd, 1H, J = 1.7 and 9.5 Hz, N-C*H*-Ph), 4.5 (d, 1H, J = 13.5 Hz, OH), 4.65 (d, 1H, J = 1.5 Hz, N-CH-S), 5.09 (dd, 1H, J = 1.5 and 13.5 Hz, O-CH-O), 7.2-7.6 (m, 5H, Ph) ; ^{13}C NMR ($CDCl_3$) : 40.4 (N-CH_3), 61.4 (C-5), 71.4 (C-6), 88.5 (C-3), 93.1 (C-2), 127-137 (Ph) ; IR ($CHCl_3$): 3420 cm^{-1}. Anal. Calcd for $C_{17}H_{19}NO_2S$: C, 67.74; H, 6.35; N, 4.64. Found: C, 67.45; H, 6.45; N, 4.26.

Morpholinol **6** was also prepared from compound **3** as follows. A mixture of compound **3** (200 mg, 0.05 mmol) and thiophenol (130 mg, 0.11 mmol) was suspended in water (8 ml) for 4 days. The reaction mixture was extracted with Et_2O, Washed with water, dried over $MgSO_4$ and evaporated in vacuo. Flash chromatography of the residue (40% Et_2O/petroleum ether) gave compound **6** (244 mg, 78%) identical in all respects with the above described product.

(2*R*,3*R*,5*R*)-4-Benzyl-5-phenyl-3-(phenylthio)-2-morpholinol (7) and (2S,3S,5R)-4-benzyl-5-phenyl-3-(phenylthio)-2-morpholinol (8)

A suspension of N-benzyl-(*R*)-phenylglycinol (0.6 g, 2.6 mmol) in an aqueous solution of glyoxal (0.42 M, 6.5 ml) was stirred for 48 h at room temperature. Water (10 ml) and thiophenol (0.29 g, 2.6 mmol) were then added and stirring was continued for 3 h. The resulting mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporation of the solvent afforded amixture of compounds **7** and **8** as anoil (0.90 g, 90%); ^1H NMR ($CDCl_3$): 4.32 (d, J = 14 Hz, OH of **7**), 4.57 (d, J = 1.8 Hz,N-CH-S of **7**), 5.01(dd,J = 1.8 and 14 Hz, O-CH-O of **7**), 5.33 (dd, J = 1.5 and 12 Hz, O-CH-O of **8**), other proton resonances appear as complex multiplets at 3.5-4.3 and 6.7-7.5 ppm; ^{13}C NMR ($CDCl_3$): 53.1 (N-*C*H_2Ph of **8**), 53.6 (N-*C*H_2Ph of **7**), 60.8 (C-5 of **7**), 61.6 (C-5 of **8**), 71.6 (C-6), 82.9 (C-3), 93.3 (C-2 of **8**), 93.6 (C-2 of **7**), 126-138 (Ph). Pure compound **7** isolated from the above mixture of isomers **7** (83%) and **8** (17%) by flash chromatography (20% Et_2O/petroleum ether) as a viscous oil: $[\alpha]_D^{20}$ +215° (*c* 0.5 , $CHCl_3$). Anal. Calcd for $C_{23}H_{23}NO_2S$: C, 73.18; H, 6.14; N, 3.71. Found: C, 73.18; H, 6.34; N, 3.57.

(5*R*)-2,3,5,6-Tetrahydro-5-phenyl-N-methyl-4*H*-1,4-oxazin-2-one (10)

(i) Preparation from tetraoxaanthracene **3** :

Compound **3** (0.91 g, 2.4 mmol) was added into a suspension of $MgBr_2$ (made *in situ* from 0.9 g of 1,2-dibromoethane and 115 mg of magnesium) in THF (25 ml). The resulting mixture was stirred for 0.5 h at room temperature. The reaction mixture was poured into water (20 ml) and the product was extracted with ether. The organic layer was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave **10** as a white solid (0.85 g, 93%) which was purified as described hereafter.

(ii) Preparation from morpholinol **6** :

A THF solution (20 ml) of compound **6** (3g, 10 mmol) was added into a suspension of $MgBr_2$ (made *in situ* from 1.9 g of 1,2-dibromoethane and 0,24 g of magnesium) in THF (30ml). The resulting mixture was refluxed for 2h. the above work-up procedure yielded crude **6**. Flash chromatography of this residue (10% Et_2O/petroleum ether in order to eluate thiophenol, then 80% Et_2O/petroleum ether) afforded **10** as a white solid (1.5g, 79%): mp 40°C; $[\alpha]_D^{20}$ -137° (c 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) : 2.07 (s, 3H, N-CH_3), 3.14 (AB, J_{AB} =18Hz, N-C*H*H), 3.42 (dd, 1H, J=9 and 5 Hz, N-C*H*-Ph), 3.84 (AB, J_{AB} =18 Hz, N-CH*H*),4.25-4.30 (m, 2H, CH_2-O), 7.33-7.38 (m, 5H, Ph);13C NMR ($CDCl_3$):42.4 (N-CH_3),56.8 (C-3), 64.6(C-5),73.3 (C-6), 128.2, 128.7, 128.9, 136.1 (Ph),167.4 (C=O) . IR ($CHCl_3$) : 1740 cm^{-1}. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.08; H, 6.85; N, 7.32. Found: C, 68.81; H, 6.86; N, 7.07.

(5*R*)-2,3,5,6-Tetrahydro-5-phenyl-N-benzyl-4*H*-1,4-oxazin-2-one (11)

The above mixture of **7** and **8** (1.5 g, 4 mmol) in THF solution (10 ml) was added in a suspension of $MgBr_2$ (made *in situ* from 0.76 g of 1,2-dibromoethane and 95 mg of magnesium) in THF (5 ml). The resulting mixture was refluxed for 1 h. The preceding work-up procedure followed by flash chromatography of the residue (10% Et_2O/petroleum ether in order to eluate thiophenol, then 50% Et_2O/petroleum ether) afforded **11** as a white solid (0.75 g, 71%): mp 92°C (lit.[18] : 92.5-93.5°C); $[\alpha]_D^{20}$ -57.7°(c 0.8, CH_2Cl_2)(lit.[18]: -59.1°).

Conformational calculations

The energies and geometries of the stable stereoisomers were obtained by AM1 calculations.[25] Standard geometries (bond lengths, angles and dihedral angles) were used as input and optimized by Bartel's method (gradient minimization by the NLLSQ procedure in AMPAC). The calculations were performed in the the Centre de Calcul Recherches de l'Université P. et M. Curie on Gould UTX 2.1 (PN 9050 processor) and Gould UTX 3.1 (NP1 processor) computers

Acknowledgments

Roussel Uclaf and CNRS are thanked for financial support.

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