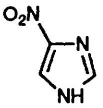
Geometry Optimisation at the Semiempirical Self-consistent-reaction-field Level using the AMPAC and MOPAC Programs

Henry S. Rzepa,[a],* ManYin Yi,[a] Mati M. Karelson[b] and Michael C. Zerner[c]
[a] *Department of Chemistry, Imperial College of Science and Medicine, London SW7 2AY, UK*†
[b] *Department of Chemistry, Tartu State University, Tartu, Estonia*
[c] *Department of Chemistry, University of Florida, Gainesville, Florida, 32611-2046, USA*

The self-consistent-reaction-field (SCRF) solvation model as recently implemented in the AMPAC and MOPAC semiempirical SCF-MO programs can result in significant errors in the calculated energies of some polar molecules. This is due to geometry optimisation using approximate gradients evaluated assuming first-order invariance of the density matrix with respect to geometry. For highly polar molecules in particular, we suggest that SCRF geometry optimisations are carried out with full re-evaluation of the density matrix for each gradient, a procedure that results in an increase in the computing time, but increased accuracy.

The self-consistent-reaction-field (SCRF) model has been applied to the calculation of condensed-phase properties of molecules such as solvation energies at both *ab initio*[1] and, more recently, at semiempirical SCF-MO levels.[2] The results reported at the semiempirical AM1 and PM3 SCF-MO levels indicate that the SCRF method can provide a valuable indication of, *e.g.*, the relative energies of related polar molecules in a condensed-phase environment such as water.[2] Recently, the SCRF method has been published as an addition[3] to the standard AMPAC[4] or MOPAC programs.[5,6] In implementing this code in both MOPAC and AMPAC (V2.1), we discovered certain anomalies for highly polar molecules which can result in calculated energies and geometries which might have significant errors. In this paper, we analyse the cause of this error and propose a solution.



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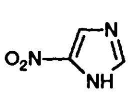

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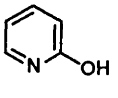

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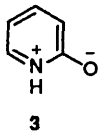

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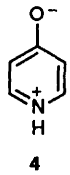

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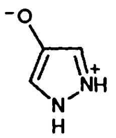

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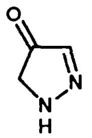

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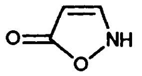

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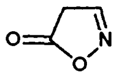

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Results and Discussion

Inspection of the published[3] AM1 output for compound **1a** indicated that default SCRF geometry optimisation using the Broyden–Fletcher–Goldfarb–Shanno (BFGS) algorithm[6] proceeded with abnormally large gradient norms, the final value being 88 kcal per Å or radian.‡ A normal value would be <1. Our implementation of the SCRF subroutines gave similar large final gradient norms for the published input data corresponding[3] to **1a**. Where the SCRF result is less than 5 kcal mol^{-1} lower than the gas-phase SCF energy, the default geometry optimisation *does* complete with relatively small final gradient norms (1–12), as for example **2** and **3**. However, if the SCRF energy lowering is >5 kcal mol^{-1} as with isomer **4** (Table 1), the final gradient norms are unacceptably large.

We initially noted that optimisation based on eigenvector-following (EF) techniques[7] invariably resulted in rapid geometry optimisation to much smaller final gradient norms (<0.03) but to *higher* final energies. This is because the EF procedure allows the energy to increase as well as decrease, whereas the default BFGS algorithm in MOPAC or AMPAC allows only the latter.[6] We also noted that the algorithm used to refine transition states in the MOPAC or AMPAC programs (NLLSQ)[6] also results in small gradient norms for SCRF optimisation, since, here too, the energy is allowed to increase as well as decrease. The origin of this effect is due to the approximation[6] used to calculate the gradients in the standard AMPAC or MOPAC programs. The following analysis makes this clear. The SCRF Fock operator f is given by eqn. (1) with

$$f = f_0 - 0.5g(\varepsilon)\langle\bar{\mu}\rangle\,\bar{\mu} \qquad (1)$$

f_0 the usual coulomb Fock operator, and $g(\varepsilon)$ is given by eqn. (2). μ is the dipole operator, and ε, the bulk relative

$$g(\varepsilon) = 2(\varepsilon - 1)/[(2\varepsilon + 1)\,a^{**}3] \qquad (2)$$

permittivity. The resulting molecular orbital problem is solved

$$f\psi_i = \varepsilon_i\psi_i \qquad (3)$$

iteratively for orbitals $\{\psi_i\}$, orbital energies $\{\varepsilon_i\}$, and energy.

$$\langle\Psi|H|\Psi\rangle = E(\mathrm{QM}) = \langle\Psi|H_0|\Psi\rangle - g(\varepsilon)\langle\Psi|\bar{\mu}|\Psi\rangle|^2 \qquad (4)$$

The first-order dependence of this energy on density (p) vanishes: i.e.,

$$\mathrm{d}E(\mathrm{QM})/\mathrm{d}p_{ia} = 0 \qquad (5)$$

since it is this condition with the orthnormality constraint of $\{\psi_i\}$, *viz*.

$$\langle\psi_i|\psi_j\rangle = 0, \text{ if } i \neq j, \ \langle\psi_i|\psi_j\rangle = 1 \text{ if } i = j \qquad (6)$$

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† E-mail: RZEPA@UK.AC.IC.CH.VAXA
‡ 1 cal = 4.184 J.

that leads to the Fock eqn. (3). The reason that small geometric changes do not require a full SCF calculation for the gradient can be seen from inspection of eqn (7).

$$E(q') - E(q_0) = (\mathrm{d}E/\mathrm{d}q)_{p0}\Delta q + \Sigma_{i,a}(\mathrm{d}E/\mathrm{d}p_{ia})_{q0}(\mathrm{d}p_{ia}/\mathrm{d}q)\Delta q + \text{second-order terms} \quad (7)$$

In eqn. (7), q represents a nuclear coordinate and $(\ )_{p0}$ implies the derivative at fixed density, and this may be taken numerically or analytically. The term $(\mathrm{d}E/\mathrm{d}p)_{q0}$ refers to derivatives with energy (and if this were an *ab-initio* method, with overlap) integrals determined at $q0$. It is this term that vanishes, making the evaluation of $\mathrm{d}p/\mathrm{d}q$ unnecessary. The finite difference methods used in MOPAC and AMPAC are thus correct only at first order, but errors have proved to be inconsequential if small geometry changes are utilized in these finite differences.

The system energy of the SCRF model, however, is not given by eqn. (4); a term representing the solvent energy 'cost' must be added.

$$E(\text{Total}) = E(\text{QM}) + 0.5g(\varepsilon)|\langle\Psi|\bar{\mu}|\Psi\rangle|^2 \quad (8)$$

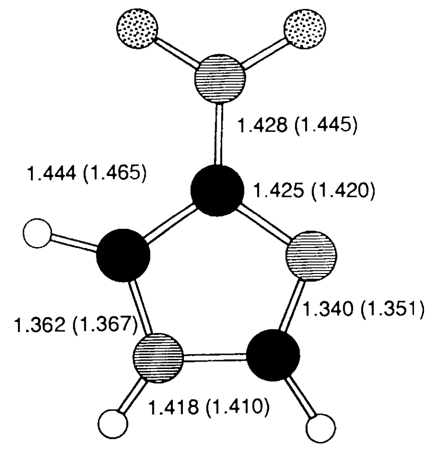
The derivative of the total energy with respect to p does not vanish, an inconsistency that arises through the variation principle when mixing one part of the system treated microscopically and the other macroscopically.[2,3] The derivative of the solvent cost term requires $\mathrm{d}p/\mathrm{d}q$, eqn. (9).

$$E(\text{surroundings}) = 0.5g(\varepsilon)|\langle\Psi|\bar{\mu}|\Psi\rangle|^2 \quad (9a)$$

$$\mathrm{dE(surroundings)}/\mathrm{d}q = g(\varepsilon)\langle\Psi|\bar{\mu}|\Psi\rangle\{\langle\Psi|\mathrm{d}\bar{\mu}/\mathrm{d}q|\Psi\rangle + \Sigma_{s,r}\langle X_s|\bar{\mu}|X_r\rangle(\mathrm{d}p_{sr}/\mathrm{d}q)\} \quad (9b)$$

In the above, $\{X_s\}$ are the atomic orbitals used in the calculation. In zero-differential overlap theories, such as AM1 or PM3, $\mathrm{d}\bar{\mu}/\mathrm{d}q$ is zero, but the second term does *not* vanish. Its evaluation either requires a coupled, perturbed Hartree Fock treatment, or a full SCF at each geometry if finite differences are to be used for gradients. Either procedure is time consuming.

We have found that finite difference optimisation works best using the AMPAC program[4] (V2.1) together with the selection of numerical derivatives (keyword DERINU) and increased SCF tolerances (keyword PRECISE), when final gradient norms of <0.4 can be obtained. The AMPAC or MOPAC subroutine DERIV was not supplied with the original modifications[3] and hence has to be modified by addition of the array COORD as the second argument in the call to subroutine ITER. This makes this call consistent with the published modifications to ITER.[3] Our results show that geometry optimisation using this technique results in lower final energies compared with those obtained using approximate gradients. Although, typically, this lowering can be quite small (≈ 2 kcal mol^{-1}; Table 1), the value for highly dipolar systems such as the glycine zwitterion[8] can be as high as 12 kcal mol^{-1}. The final energy obtained will, of course, depend on the initial starting geometry for the optimisation, taken in our examples[8] as the SCF-level gas-phase structure.



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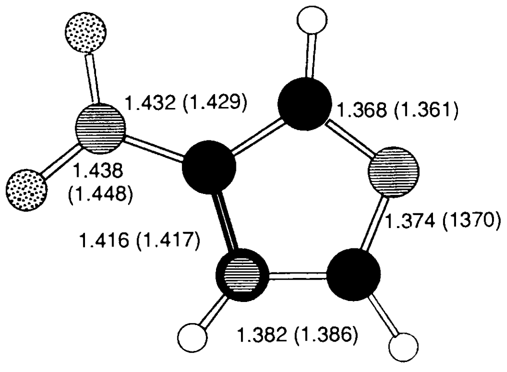

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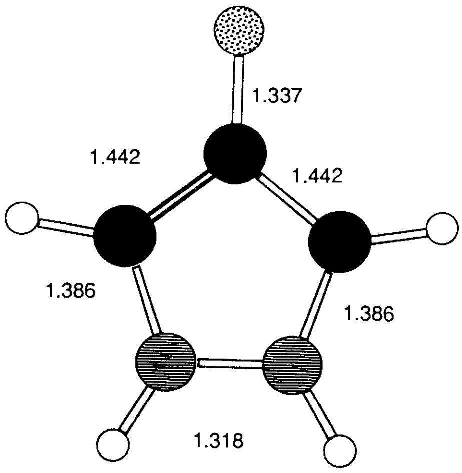

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Fig. 1 Calculated AM1 geometries for **1a**, **1b** and **5**. Bond lengths in Å, together with the published values obtained using the approximate gradient in parentheses (see the text).

We have also re-investigated several systems reported in earlier papers by Karelson *et al.* for which SCRF energies were reported to be lower than the SCF values,[2,3] using the quoted values for the reaction cavity size. We noted firstly that our *gas phase* SCF results for systems **5**–**7** (Table 1) were up to 5 kcal mol^{-1} lower in energy than the published values. However, we are able to reproduce exactly the published gas-phase results for **5**–**7** by enforcing planar geometries for the heterocycles. These planar stationary points had one negative root in the calculated Hessian matrix, and hence are not true minima. This result emphasizes the importance of optimising all $3N - 6$ degrees of freedom, and of not starting with exactly planar geometries. At the SCRF level, the difference between our results and the published values was 5.3 kcal mol^{-1} for, *e.g.*, **5** but only 0.2 kcal mol^{-1} for **7**. Some significant differences in the geometries (Fig. 1) and properties such as the dipole moment are also obtained (11.95 D * published, 11.04 D calculated in the present

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* 1 D $\approx 3.335 \times 10^{-30}$ C m.

Table 1 Calculated AM1 energies (kcal mol^{-1}) at the SCF gas-phase and SCRF condensed-phase level for polar systems

	Gas phase		SCRF Model	
Compd.	ΔH this work	ΔH published[2,3]	ΔH this work	ΔH published[2,3]
1a	56.88	56.88	31.61	33.89 (88)[a]
1b	55.50	55.50	48.37	49.20 (41)[a]
2	−11.77	−11.79	−12.36	−12.30
3	−11.31	−11.24	−16.33	−16.09
4	−4.53	−4.20	−18.39	−17.68
5	59.10	65.47	2.84	8.15
6	21.47	24.14	15.59	17.18
7	−4.83	0.98	−25.46	−25.23[b]
8	−14.62	−14.44	−28.83	−25.83

[a] Final gradient norms in parentheses, from the output published in ref. 3. [b] The value reported in ref. 2(*b*) of −26.76 appears to be a typographical error.

work for compound **1a**). Most notably, the gas-phase geometry of **5** is calculated to be significantly non-planar, but the SCRF geometry is indeed planar, clearly as a consequence of stabilisation of the dipolar resonance form. In other work[8] on dipolar species such as glycine zwitterion, we note that the use of approximate gradients in the SCRF optimisation procedure starting from a gas-phase structure results in geometries in which the intramolecular hydrogen bond is retained, but that the use of accurate SCRF gradients results in qualitatively correct solution geometries in which the hydrogen bond is cleaved.

The errors due to the use of approximate gradients need not necessarily affect any chemical conclusions drawn. For example, structure **1b** is more stable than **1a** in the gase phase by 1.4 kcal mol^{-1}, but **1a** is more stable in water by 16.8 kcal mol^{-1}. Structure **5** is stabilised in solution by *ca.* 56 kcal mol^{-1}, in spite of the *ca.* 6 kcal mol^{-1} errors in the calculation of each species separately. We emphasize again that only highly polar molecules are significantly affected by the gradient error, and that the errors in energy and geometry for less polar systems are quite small. Nevertheless, the approximate procedure cannot be considered correct, should be confined only to relatively non-polar systems, and the results viewed with some care.

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