Some applications of the direct reaction field approach

Piet Th. van Duijnen*, Ferdinand Grozema, Marcel Swart

Department of Chemistry (OMAC), University of Groningen, Nijenborgh 4, 9747 AG Groningen, Netherlands

Abstract

The Direct Reaction Field approach is briefly reviewed. Preliminary reports of the calculations on solvent induced shifts in the $\pi^* \rightarrow n$ transition of acetone in various solvents, and the dissociation of tert-butyl chloride in water are given. © 1999 Elsevier Science B.V. All rights reserved.

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1. Introduction

Most state-of-the-art calculations in quantum chemistry are restricted to atoms and molecules in vacuum. As most of chemistry occurs in solution, there is increasing need for applications to aggregates of molecules to obtain insight into the effects of the environment on e.g. molecular properties, spectra, chemical reactions, etc., on the electronic level. However, complete quantum mechanical calculations on systems consisting of thousands of molecules are out of reach, let alone the averaging over millions of configurations necessary to obtain results which can be compared with experiments.

Fortunately, most of the interactions can be described by a mixed quantum chemical/classical approach. To this end we have been developing, over more than 15 years [1–3], the Direct Reaction Field (DRF) method for describing condensed phase problems, in which a quantum part (QM) of a system is embedded in a classical environment (MM).

In the following sections we review our DRF approach to the description of condensed phase systems, and give preliminary reports of two applications: the $\pi^* \rightarrow n$ transition of acetone in various solvents, and the hydrolysis of tert-butyl chloride.

2. The DRF approach

The DRF [1–4] approach is summarized in Fig. 1. Here we have one or more “quantum systems” (QM) with explicit electrons, and a classical system (MM) consisting of a set of discrete classical sub-systems: A, B, ... characterized by sets of point charges $\{q^A\}, \{q^B\}$ and polarizabilities $\{\alpha^A\}, \{\alpha^B\}$. The complete discrete part may be embedded in a continuum with dielectric constants $\epsilon$ and $\epsilon_\infty$, and a finite ion-strength leading to a Debye screening radius of $\kappa^{-1}$. The point charges are usually obtained from appropriate ab initio calculations [5]. The polarizabilities come from (ab initio) calculations or from experiment [6], in either case using Thole’s model [7]. If required, the discrete classical parts are subject to Monte Carlo sampling using the same parameterization in the force field as outlined later [8].

The total energy of the discrete system can be written as:

$$\Delta U^{\text{discr}} = \Delta U^{\text{QM}} + \Delta U^{\text{MM}} + \Delta U^{\text{QM/MM}} \quad (1)$$
with $\Delta U^{QM}$ the expectation value of the vacuum Hamiltonian of QM over the non-vacuum wave function.

With $\nu_{sp} = 1/|r_p - r_s|$ the operator for the coulomb potential at $p$ from a source at $s$, and $f_{sp} = \nabla_p \nu_{sp}$ the corresponding electric field we get:

$$
\Delta U^{MM} = \frac{1}{2} \sum_{i,j=A,B} q_i^A v_{ij} q_j^B + \frac{1}{2} \sum_{i,j,A,B,rs} q_i^A f_{ir} A_{rs} f_{jr} q_j^B
$$

$$
+ \Delta U^{disp} + \Delta U^{rep}
$$

where $\Delta U^{disp}$ and $\Delta U^{rep}$ are the induction energy, the dispersion energy (the classical polarizability contribution), the dispersion and short range repulsion energy (also often called “screening of the coulomb interaction”), the dielectric constants and the Debye screening length $\kappa^{-1}$ for finite ionic strength of the solution. The boundary is usually the solvent accessible surface. The geometry of the system should be such that (practically) no electronic charged density of the quantum system is here included, although we keep it in practice separated in order to make it also possible to deal with non-equilibrium situations.

For the classical dispersion energy we use the Slater–Kirkwood expression with $t(i,j)$ the (modified [7]) interaction tensor for induced dipoles in $i$ and $j$.

$$
\Delta U^{disp} = \sum_{i<j} \frac{1}{4} \frac{\text{Tr}(\alpha_i t(i;j) \alpha_j)}{\sqrt{\alpha_i/\alpha_j + \sqrt{\alpha_j/\alpha_i}}}
$$

For the short range repulsion we use the CHARMM expression:

$$
\Delta U^{rep} = \sum_{i<j} \frac{3}{4} \frac{\alpha_i \alpha_j (r_i + r_j)^6}{\sqrt{\alpha_i/\alpha_j + \sqrt{\alpha_j/\alpha_i}} r_{ij}^{-12}}
$$

in which $\alpha_i$, $n_i$, and $r_i$ are the isotropic polarizability, number of valence electrons, and radius of atomic center $i$, respectively, and $r_{ij}$ is the distance between centers $i$ and $j$. We use the integral number of valence electrons of an atom, and the same atomic polarizabilities that go into the electrostatic, response, and dispersion terms, leaving only the atomic radii as independent parameters. The latter are obtained from wave functions as local (atomic) contributions to the second moment of the electronic charge distribution.

For the QM/MM interaction we have:

$$
\Delta U^{QM/MM} = \sum_{A,i,j} q_i^A v_{ij} z_j + e \sum_{A,j} q_i^A \langle \psi_j \rangle
$$

$$
+ \sum_{A,i,j,r,s} q_i^A f_{ir} A_{rs} f_{jr} z_j
$$

$$
+ e \sum_{A,k,r,s} q_i^A f_{kr} A_{rs} \langle f(s; k) \rangle
$$

$$
+ \frac{1}{2} \sum_{i,j,r,s} Z_{fr} A_{rs} f_{jr} Z_j
$$

$$
+ e \sum_{i,k,r,s} Z_{fr} A_{rs} \langle f(s; k) \rangle
$$

$$
+ \frac{1}{2} e^2 \sum_{k,r,s} \langle f(k; r) A_{rs} f(s; k) \rangle
$$

$$
+ \frac{1}{2} e^2 \sum_{k,j,r,s} \langle f(k; r) A_{rs} \langle f(s; \ell) \rangle \rangle
$$

$$
+ \Delta U^{QM/MM}_{rep}
$$

where the $\{Z\}$ are the nuclear charges. In the field expectation values we have made explicit the

![Diagram](image-url)
electronic charge \((e)\) and the electron labels \((k, \ell)\). Also we have separated the screening of the self energy in the electron/electron screening term – which is a one-electron operator – from the screening of the two-electron term, which in practice leads to screened coulomb and exchange contributions. The repulsion term in Eq. (5) is the same as in Eq. (4), although we may optionally get the radii of the QM atoms “‘on the fly’”, and depending on the classical environment, instead of fixing them on their vacuum values.

All operators are added directly to the vacuum hamiltonian \(H^0\) of QM:

\[
H = H^0 + H^{\text{es}} + H^{\text{rf}}
\]

with \(H^{\text{es}}\) and \(H^{\text{rf}}\) the electrostatic and reaction potential operators, respectively.

The difference of expectation values

\[
\langle H^{\text{rf}} \rangle = -\frac{1}{2} \langle f^\dagger A f \rangle = -\frac{1}{2} \langle f^\dagger A(f) \rangle
\]

\[
= \Delta U_{\text{DRF}}^{\text{ind}} + \Delta U_{\text{DRF}}^{\text{disp}}
\]

contains, in addition to the induction term – which will also be obtained from a supermolecule SCF calculation – a fluctuation term, which was shown to be an upper limit to the dispersion interaction [4]. In fact, this term differs a constant factor from the screening two-electron exchange energy. Obviously, the last term is only available separately in the single determinant approximation to the wave function for QM. For these cases we take

\[
\gamma = \frac{I_{\text{MM}}}{I_{\text{QM}} + I_{\text{MM}}} 
\]

with \(I_{\text{QM}}\) and \(I_{\text{MM}}\) the ionization energies of QM and MM, respectively. If QM and MM are identical we have \(\gamma = 0.5\), while for \(\gamma = 0\) the method renders in fact the Average Reaction Field (ARF) rather than the DRF approach. ARF is usually obtained by coupling QM and MM by adding the expectation value of the reaction potential to \(H^0\) and reiterate e.g. the SCF procedure, instead of using the reaction potential operator “‘Directly’”.

The ARF approach is used by us for non-SCF wave functions, because in constructing CI or MCSCF wave functions the explicit control over the exchange interactions is lost. An estimate of the dispersion is then obtained by performing one-determinant DRF calculations for the leading components of the CI expansion and scale them with the corresponding expansion coefficients.

The matrix \(A\) – in Eqs. (2), (5), and (8) – is a \((\text{super})\text{matrix}\) representing the total linear response of the complete discrete classical part, in which all particles interact self consistently. Taking a set of points \(\{p\}\) with polarizabilities \(\{\alpha p\}\) in a uniform electric field \(F^0\) we have for the induced dipole moment in point \(p\):

\[
m_p = \alpha_p \left( F^0(p) - \sum_{q \neq p} t(p; q)m_q \right)
\]

A formal solution for \(\{m_p\}\) can be found by collecting the \(N^\text{pol}\) equations into a single super matrix equation of dimension \(N^\text{pol} \times N^\text{pol}\):

\[
M = \alpha (F^0 - TM)
\]

where \(F^0\) and \(M\) are \(N^\text{pol}\)-dimensional vectors, and \(\alpha T\) are square \(3N^\text{pol} \times 3N^\text{pol}\) matrices. The super vectors and matrices are blocked into \(3N^\text{pol}\) and \(3M^\text{pol}\) elements, respectively: \(M = m_{pq}\), \(\alpha_{pq} = \alpha_p \delta_{pq}\), \(T_{pq} = t(p; q)(1 - \delta_{pq})\), and \(\delta_{pq}\) is the Kronecker delta. Then

\[
\Lambda = \left( \alpha^{-1} + T \right)^{-1}
\]

may be considered as an ordinary polarizability.
matrix (but of an \(N^{pol}\) membered system):

\[
\mathbf{M} = \mathbf{F} \left( \alpha^{-1} + \mathbf{T}\mathbf{M} \right)^{-1}
\]

(14)

A is obtained either by an exact matrix inversion or by solving the associated linear equations by iteration. We note that Eq. (14) is a self consistent solution for any field, e.g. the electric field of QM during any stage of e.g. the Hartree–Fock procedure, and can expressed in terms of integrals over any basis set, which can be added to the vacuum hamiltonian.

The \(\{\mathbf{t}(p,q)\}\) are, when appropriate, screened according to the method described by Thole [7] in which (atomic) polarizabilities are taken as related to (model) charge distributions, the widths of which are related to the \(\{\alpha_p\}\). This leads also to a consistent screening of the potentials and fields of interaction for overlapping charge distributions. In general the polarizabilities are constructed following Thole’s original recipe and parameterization for obtaining (molecular) polarizabilities with experimental accuracy. This model has been re-parameterized, also for computed polarizabilities from specific basis sets [6].

The advantage of this way of treating the relay matrix is that only atomic polarizabilities are needed as input, while changes in geometry will be automatically reflected in \(A\). Optionally one may reduce parts of \(A\) first to group polarizabilities so as to reduce the dimensionality of the problem.

The extension with a dielectric continuum around the discrete part(s) is straightforward. For example, one might divide the continuum into an infinite set of finite volumes \(\{V_i\}\) and assign \(\alpha_i = \chi V_i\) to each of them with \(\chi = (e^{-1})/4\pi\) where \(\epsilon\) the electric susceptibility. These polarizabilities could be used directly in Eq. (13), were it not for the infinite dimensionality of the problem.

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The general picture remains the same: all information about the reaction potentials are contained in a single relay matrix. The electronic contributions to the source potentials and fields of course have first to be formalized in terms of integrals over basis functions. Such details are given elsewhere [3].

The wave functions for QM, which may be of any type, are made self consistent with the external (reaction) potentials, thus leading to an overall self consistent solution for the energy and other properties of the complete system. DRF has been implemented [3] in HONDO8.1 [11].

Obviously, any part of the system may be omitted: leaving out the discrete classical part we obtain something like Tomasi’s method[12] or leaving out QM we just have a polarizable classical force field [8].
In Table 1 we give a preliminary report of the results for water, acetonitrile, tetrachloromethane, and two new solvents. A complete report, covering more solvents was published recently [15]. As before, the computed shift in water (1493 cm⁻¹) is reasonable compared to the experimental data [16, 17] (1700 cm⁻¹). The shift in acetonitrile (+478 cm⁻¹) agrees much better with the experimental value (+400 cm⁻¹) than the value reported earlier, probably as a result of sampling over a larger number of conformations. The computed value for MeOH (+729 cm⁻¹) also agrees quite well with the experimental value (+850 cm⁻¹). For dioxane experiments [18] show no appreciable shift, while our value of +54 cm⁻¹ is reasonably close to zero. The red shift in CCl₄ (−278 cm⁻¹) is excellent compared to the experimental value of −250 cm⁻¹ reported by Hayes [17], but is too small in comparison to the shift observed by Bayliss (−450 cm⁻¹) [16].

The uncertainties given in Table 1 are root mean square deviations over the 100 conformations analyzed, and therefore probably larger than in our earlier work. The values do not indicate the error in the maximum position of the transition, but rather reflect the broadness of the maxima mentioned by Bayliss [16]. In polar solvents the r.m.s. deviation is much larger than in apolar ones. This indicates, that in polar solvents, the shift in the transition is very much dependent on the orientation of the solvent molecules directly surrounding the solute, a broad variety of orientations is present, causing broad absorption maxima. In apolar solvents the orientation is not that important and the deviation is much smaller.

An analysis of the contributions to the shifts is given in Table 2. ΔE-pol and ΔE-disp denote the contributions of the in electrostatic and dispersion interactions, respectively, to the shift. ΔE-ind is the contribution as a result of the induction, i.e. the

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### Table 1
Computed and experimental shifts in cm⁻¹; the uncertainties given are root mean square deviations over the 100 conformations selected

<table>
<thead>
<tr>
<th>Solvent</th>
<th>De Vries et al.</th>
<th>This work</th>
<th>Experimental*</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂O</td>
<td>1821 ± 330</td>
<td>+1493 ± 514</td>
<td>+1700 ± 200</td>
</tr>
<tr>
<td>MeOH</td>
<td>n.a.</td>
<td>+729 ± 862</td>
<td>+850 ± 200</td>
</tr>
<tr>
<td>MeCN</td>
<td>922 ± 310</td>
<td>+478 ± 390</td>
<td>+400 ± 200</td>
</tr>
<tr>
<td>CCl₄</td>
<td>−381 ± 75</td>
<td>−278 ± 36</td>
<td>−250 ± 200</td>
</tr>
<tr>
<td>Dioxane</td>
<td>n.a.</td>
<td>+54 ± 354</td>
<td>0 ± 200</td>
</tr>
</tbody>
</table>

* Experimental values from Refs. [17] and [16].

### Table 2
Analysis of the contribution to the shifts (cm⁻¹)

<table>
<thead>
<tr>
<th>Solvent</th>
<th>ΔE-pol</th>
<th>ΔE-ind</th>
<th>ΔE-el</th>
<th>ΔE-disp</th>
<th>ΔE-q</th>
<th>ΔE-tot</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂O</td>
<td>−311</td>
<td>+577</td>
<td>+2503</td>
<td>−1204</td>
<td>−72</td>
<td>+1493</td>
</tr>
<tr>
<td>MeOH</td>
<td>−469</td>
<td>+613</td>
<td>+2127</td>
<td>−14669</td>
<td>−73</td>
<td>+729</td>
</tr>
<tr>
<td>MeCN</td>
<td>−336</td>
<td>+519</td>
<td>+1588</td>
<td>−1267</td>
<td>−26</td>
<td>+478</td>
</tr>
<tr>
<td>CCl₄</td>
<td>−68</td>
<td>+134</td>
<td>−3</td>
<td>−342</td>
<td>+1</td>
<td>−278</td>
</tr>
<tr>
<td>Dioxane</td>
<td>−432</td>
<td>+5666</td>
<td>+1208</td>
<td>−1268</td>
<td>−20</td>
<td>+54</td>
</tr>
</tbody>
</table>
interaction between the quantum system and the moments induced by the quantum system. $\Delta E$-pol consists of three parts: the interaction of the quantum system and the moments induced by the classical system (1), the interaction between the classical system and the moments induced by the quantum system (2) and finally the cost of inducing all moments (3). $\Delta E$-$q$ is the change of the intrinsic excitation energy of the quantum system (solute) caused by solvation.

When analyzing the contributions to the shifts in polar solvents (H$_2$O, MeCN, and MeOH), it will be clear that the dispersion component of the shift is an essential one. Without it, the blue shifts would be overestimated by 1200 to 1500 cm$^{-1}$. In the case of CCl$_4$, there is very little electrostatic interaction, thus dispersion dominates in this case, leading to a red shift.

So, our main conclusion of Ref. [13] stands still, i.e. without accounting for dispersion the computed shifts are wrong, which is not compatible with recent results of Thompson [19].

### 3.2. Hydrolysis of tert-butyl-chloride

Here we report a completely classical treatment of the ‘solvation’ of the vacuum Minimal Energy Reaction Path (MERP) of the hydrolysis of tert-butyl-chloride. Our main goal here was testing our classical force field [8] in practice, in which we used the work of Jorgensen et al. [20] as a reference point, while we tried to see if we could improve on that of Hartsough et al. [21]. The latter authors report serious deviations from experiment for the hydration energies of the Cl$^-$ ion and of Tetramethylammonium$^+$ (TMA) – which is used as a bench mark, because the experimental hydration energy of the tert-butyl$^+$ ion (tBut) is unknown – of +14 and −9 kcal/mol, respectively. From the snapshots of their MD simulation it is clear that Cl$^-$ has a first solvation shell of about four waters. A simple calculation with a single point charge and the experimental polarizability of water gives a polarization energy of −3 kcal/mol per water molecule. As the main difference with the force fields of both Jorgensen and Hartsough and ours is the presence of explicit solvent polarizabilities in the latter, we expected to do better in this respect. Moreover, Hartsough et al. applied in their procedure a number of ad hoc and rather unphysical approximations in order to ‘enhance’ the electrostatic interactions. To estimate the long range interaction they used the Born correction [22], by putting a point charge in an empty spherical cavity, with a radius equal to their cutoff radius of 9 Å, in a dielectric continuum with $\epsilon = 80$, i.e. not accounting for the interaction of the water molecules with the continuum. So, enough differences to make a repetition worthwhile.

We performed MC calculations of the tBut, TMA and Cl$^-$ ions, each surrounded by 62 water molecules at $T = 298$ K, using $5 \times 10^5$ steps for equilibration, and $1 \times 10^6$ steps for sampling. This was repeated for the waters without solute, as reference. We just used the Metropolis scheme without any sophistication. The charges on water were taken from ab initio calculations, the polarizability was set at the experimental value. For the long range interactions we added – for a number of accepted MC configurations – a dielectric continuum with $\epsilon = 80$. As boundary we took the solvent accessible Connolly surface [23,24]. The free energy of cavitation was estimated from Pierotti’s expression [25].

Our results so far are summarized in Table 3.

![Table 3](image-url)

<table>
<thead>
<tr>
<th>Solvation energies</th>
<th>$\Delta U_{\text{int}}$</th>
<th>$\Delta G_{\text{adv}}$</th>
<th>$\Delta G_{\text{adv}}$</th>
<th>$\Delta G_{\text{tot}}$</th>
<th>$\Delta G_{\text{exp}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>tBut$^+$</td>
<td>−43</td>
<td>−30</td>
<td>−15</td>
<td>−45</td>
<td>n.a.</td>
</tr>
<tr>
<td>Cl$^-$</td>
<td>−74</td>
<td>−62</td>
<td>−19</td>
<td>−81</td>
<td>−76.0$^c$</td>
</tr>
<tr>
<td>TMA$^+$</td>
<td>−40</td>
<td>−34</td>
<td>−17</td>
<td>−51</td>
<td>−50.4</td>
</tr>
<tr>
<td>Water</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* From Monte Carlo calculation on discrete system.

* Continuum contribution: $\Delta G_{\text{adv}} = \Delta G_{\text{os}} + \Delta G_{\text{cov}}$.

* $\Delta S_{\text{adv}}(\text{Cl}^-) = −18.4 \text{ cal/(mol K)}$, leading to $\Delta U'_{\text{adv}}(\text{Cl}^-) = −81.4 \text{ kcal/mol in at 298.15 K}$, which should be compared with the −74 kcal/mol in $\Delta U_{\text{int}}$ and part of $\Delta G_{\text{adv}}$.

Apparently our parameterization for Cl$^-$ is not perfect yet, but the improvement over Hartsough et al. is evident. The difference between $\Delta U_{\text{int}}$ in Table 3 and the experimental value of −81.4 kcal/mol is most likely caused by the exchange repulsion ($\Delta U_{\text{QM/MM}}$ in Eqs. (1) and (4)), both in its form – as related to dispersion – and in the definition of the radius of the chloride ion. The calculated free energy of TMA is in good agreement with experiment, and therefore we have confidence in that for tBut as well.
Next, we solvated 15 points along the vacuum MERP of the dissociation of tButCl. We applied the MC sampling again, now with 124 water molecules, adding the solvation energies to the corresponding values of the MERP energies, to arrive at the potential of mean force in solution. Fig. 2 gives an impression of the results.

From Fig. 2, the four stages of the Winstein scheme [26] emerge clearly: the reactants (R), the Intimate Ion Pair (IIP) at a longer C–Cl distance without water yet inserted, the Solvent Separated IP with about a single water molecule between tBut and the chloride ions, the Solvent Separated IP (SSIP) and the Separated IP (SIP) where both ions are solvated, but still strongly interacting, and, finally the Dissociated IP at infinite dilution. The calculated energy of activation (~20 kcal/mol) for the rate determining step, R → IIP, is in good agreement with the experimental value of Winstein et al. [27] (19.5 kcal/mol). The depth at IIP relative to the barriers was estimated from experiment by Abraham as 14.5 ± 5 kcal/mol [28] above R, while Keirstead et al. [29] found from their simulation a well depth of 20 kcal/mol, putting IIP at a lower energy than R. However, these authors used a heavily parameterized expression for the quantum hamiltonian of the reactants and a Lennard–Jones-plus coulomb potential for the interaction with and in the solvent. The barriers between the various wells are very different from those found by the other authors. Owing to the relatively small number of solvent molecules (Jorgensen: 250, Hartsough:458) we get fairly large error margins in some of our runs, sometimes larger than ±10 kcal/mol. Hence we think of improving our procedure, or better, use MD instead, as we have now gradients for our DRF force fields ready [30], and leave this discussion for some time.

4. Conclusions

We have briefly reviewed our DRF computational approach to condensed phase problems. This is as ‘ab initio’ as one might wish, in the sense that no empirical information is used related directly to the quantities computed.

The solvent induced shifts in the $\pi^* \leftarrow \pi$ transition of acetone in various solvents are obtained almost within experimental accuracy. Also the Potential of Mean Force for the hydrolysis of tert-butyl-chloride with our relatively simple Monte Carlo procedure is globally in agreement with experiment and findings of other authors.

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References