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Commentationes

The *C*-Potential Surface for Predicting Conformations of Molecules in Solution*

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A new "*C*-potential" $C(R_M)$ for predictions of conformations, relative stabilities of isomers, transition states, of a molecule M in solution as a function of its geometry R_M is given. The potential includes all the solvent effects including the "solvophobic force" given earlier by the writer with parameters fully specified in terms of simple handbook properties of liquids. It is proved that $C(R_M)$ can be used in statistical mechanical equations for equilibria and for activated complex rates just as though it were an ordinary potential energy surface dependent on R_M only.

Key words: Conformation in solution – Sovent effects – Potential energy surface

1. The Potential Energy Surface in the Gas Phase

Quantum mechanically one calculates the adiabatic electronic potential energy surface $U(R_M)$ for a set of atoms $\{i\} = \{1, 2 \dots n\} \equiv \mathrm{M}$ at positions $R_M = \{\underset{\sim}{R}_1, \underset{\sim}{R}_2, \dots \underset{\sim}{R}_n\}$.

The "adiabatic chemistry" of this set of atoms *in vacuo* (in dilute gas phase) is contained in $U(R_M)$.

This *U-surface* may have *prominent features:* minima, valleys, barrier tops, etc. corresponding to a stable molecule, or to several molecules in interaction, to constitutional or configurational (conformational) isomers, activated complexes (‡), etc.

Depending on the depth (or height) $|U_0^a(R_M^{a;0})|$ and width ΔR_M^a of the a^{th} prominent feature but considering also the temperature T and the entropy effects [1] we may have a "significant structure" (a molecule, an isomer, a complex, etc.) as H. Eyring calls it, $\{P_M^a, R_M^a\}$ on the phase space $\{P_M, R_M\}$[1]. Then for each "*a*" only that portion of the phase space (and of *U*-space, $U(\{R_M^a\})$) need be considered leading to a partition function [2] (microcanonical),

$$(\text{p.f.})_a = \Lambda_M Q_M^a \tag{1}$$

with

$$Q_M^a = \int_{\{R_M^a\}} e^{-U(\{R_M^a\})}\, d\tau_M \tag{2}$$

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[1] A large $|U_0^a| \gg kT$ is *not* sufficient for applicability of the "significant structure" $(\text{p.f.})_a$ method. Entropy effects need be considered; e.g. though H_2, $|U_0|/k \sim 50000$ °K, the H_2 (gas) is nearly all dissociated to 2H already at 5000 °K.

($d\tau_{\mathrm{M}} = d\tau_1\, d\tau_2 \ldots d\tau_n$), and

$$\Lambda_{\mathrm{M}} = \lambda_1 \lambda_2 \ldots \lambda_n\,; \qquad \lambda_i = \left(\frac{2\pi m_i k T}{h^2}\right)^{3/2} \tag{3}$$

each atom i of M having mass m_i[2].

Prediction of conformation, most stable chemical species, etc. is then an equilibrium K, (or quasi-equilibrium for rates $\propto K^{\neq}$) problem; e.g.

$$a \rightleftharpoons a^{\neq} \rightleftharpoons a'\,; \qquad \Delta\mu = 0 \tag{4}$$

chemical potential

$$A_i = A_i^0 + kT \ln x_i \tag{5a}$$

$$K = \frac{x_i'}{x_i} = e^{-\Delta A^0/kT}\,. \tag{5b}$$

Portions of the U-surface have been mapped

$$U(\{R_{\mathrm{M}}^a\}) \rightarrow A_2^0(T, V) \tag{6}$$

via the configurational integral, Q, Eq. (2) into Helmholtz free energies per molecule,

$$\bar{A}_a^0 = -kT \ln(\mathrm{p.f.})_a\,. \tag{7}$$

What if no prominent features are discernable (relative to kT) on $U(R_{\mathrm{M}})$? Then, if M is a molecule, it is flopping around a good many conformations. If M is an assembly of atoms $\{i\} = \mathrm{M}$, or of molecules made of them, the constituents are reacting ("chemical forces") [3], interacting ("physical forces") [3] over the entire $U(R_{\mathrm{M}})$[3]. Then the (p.f.) and $K_{\mathrm{eq.}}$ method no longer applies. But one can still calculate the free energy of the entire atomic assembly [1] from the Q-integral [4] over all of $U(R_{\mathrm{M}})$

$$Q_{\mathrm{M}} = \int_{-\infty}^{\infty} e^{-U(R_{\mathrm{M}})/kT}\, d\tau_{\mathrm{M}}\,. \tag{8}$$

2. Potential Surface in Solution and Quantum Chemical Calculation

All of the above is for M by itself, *in vacuo*. What if the molecule is in solution? Predictions of conformation, stability of isomeric forms based on quantum chemical calculations of $U(R_{\mathrm{M}})$ will then no longer remain valid. There are large "solvophobic forces" [5] when solvent, driving isomerizations, reactions, foldings of biopolymers contrary to the tendencies the molecules had *in vacuo*.

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[2] This classical method, even for a stable molecule with some quantum effects is more convenient than the usual energy-levels method of $(\mathrm{p.f.})_a = (\mathrm{p.f.})_{\mathrm{trans}}\, (\mathrm{p.f.})_{\mathrm{rot}}\, (\mathrm{p.f.})_{\mathrm{vibr}}$. Only integrations [over portion of $U(R_{\mathrm{M}})$] are needed. Quantum corrections coming mainly from $\{h\nu_{\mathrm{vibr}}\}$ are easily introduced as multiplicative factors to $(\mathrm{p.f.})_a$, Eqs. (1), (2); see [2].

[3] In accustomed quantum chemistry, a P.E.-curve $U(R)$ is treated with separate theories for long range attractions (van der Waals forces) and for short range forces (non-bonded repulsions and "chemical" valence-bond forces) with the well-known difficulty of patching the region, important though it is, in between. A full theory of *a priori* electronic P.E.-surfaces covering all of $U(R)$ in the same way has been derived recently by the present writer. [It starts from $U(R) = \Delta E_C(R) + \Delta E_{\text{all-ext.}}(R)$ with E_C, the energy containing all the specifically non-closed shell type correlation effects ($E_C = E_{\mathrm{RHF}} + E_{\mathrm{INT}} + E_{\mathrm{F}}$) given rigorously by NCMET added to the MO-effects.] Hence $\Delta E_C(R)$ contains all of "chemical" and short range forces. The $\Delta E_{\text{all-ext.}}(R)$ contains the remaining (hence closed shell-like) "all-external" correlations which reduce rigorously to the R^{-6} attractions at large R. For this theory and its recent applications by various workers to P.E.-curves $U(R_{\mathrm{M}})$. See [3].

We present here a new potential surface, the *C-potential* which includes all of the solvent effects. It is easily derived from the theory of solvent effects on isomerization or molecular association equilibria and rates, we have given previously [5]. Solvents may be polar or non-polar. We also show that the $C(R_M)$ may be used in statistical mechanics just as if it were an ordinary P.E.-surface [in Eqs. (2), (8), etc.], i.e. over the coordinates $R_M = \{R_1, R_2, \ldots R_n\}$ of M only, even though the action of solvent is in it.

The C-potential, for the atomic assembly M at an isomeric-conformational point R_M, is

$$C(R_M) = U(R_M) + A^0_{\text{solv.eff}}(R_M) \tag{9}$$

where $A^0_{\text{solv.eff}}(R_M)$ is the "unitary" ($x^0_m \equiv 1$) Helmholtz free energy (per molecule M) for placing the "molecule" M frozen at its fixed R_M coordinates, into the solvent at T, V, i.e. of the process

$$\begin{gathered} M(R_M)\,(\textit{in vacuo}) + \text{solvent}\,(l.) \rightleftharpoons \mathrm{M}(R_M)\,(\text{in soln.}) \\ \Delta A^0 \equiv A^0_{\text{solv.eff}}(R_M)\,. \end{gathered} \tag{10}$$

As $P \Delta V^0_{\text{solv.eff}} \cong 0$ at $P \cong 1$ atm, we have also $A^0_{\text{solv.eff}} \cong F^0_{\text{solv.eff}}(T, P)$.

$$C(R_M) \cong U(R_M) + F^0_{\text{solv.eff}}(R_M)\,. \tag{11}$$

Then, [5]

$$F^0_{\text{solv.eff}}(R_M) = F_C(R_M) + F_{\text{int}}(R_M) + kT \ln \frac{kT/P_0}{v_1}\,. \tag{12}$$

$F_C(R_M)$ = free energy of making a cavity "prepared" [5] to accomodate $\mathrm{M}(R_M)$; $F_{\text{int}}(R_M)$ = free energy of interaction of $\mathrm{M}(R_M)$, then placed in the cavity, with the solvent around it; $P_0 \equiv 1$ atm., v_1 = molecular volume of solvent ① from its density $\varrho_1(T, P)$ and molecular weight.

$$F_C(R_M) = \kappa^e_1(\varphi^{-1/3}_{1\mathrm{RM}}) \times \sigma(R_M)\, \gamma_1 (1 - W_{1\mathrm{M}}) \tag{13a}$$

$$W_{1\mathrm{M}} = (1 - \eta_{1\mathrm{RM}}) \frac{\partial \ln \gamma_1}{\partial \ln T} + \frac{2}{3} \mathscr{A}_{\mathrm{M}} T \tag{13b}$$

where

$$\eta_{1\mathrm{RM}} = \frac{\kappa^s_1(\varphi^{-1/3}_{1\mathrm{RM}})}{\kappa^e_1(\varphi^{-1/3}_{1\mathrm{RM}})}\,. \tag{13c}$$

Equation (13) includes some geometric properties of $\mathrm{M}(R_M)$ and some properties of the pure solvent ①, the latter all obtained from simple macroscopic experimental quantities pertinent to the pure liquids. The

$\sigma(R_M)$ = geometric surface area of the molecule M at its fixed conformation R_M,
$v(R_M)$ = geometric volume of $\mathrm{M}(R_M)$

are easily obtained for example from space-filling models.

For the solvent:

γ_1 = pure solvent ordinary surface tension at T, P,
$\varphi_{1\mathrm{RM}}$ = volume ratio $v_1/v(R_M)$; v_1 obtained from density of pure solvent at T, P and its molecular weight.

Further, $\kappa^e_1(\varphi^{-1/3}_{1\mathrm{RM}})$ is a dimensionless function giving the deviation of the energy ($\approx$ enthalpy) part of the microscopic surface tension at the molecular dimensions

R_M from the macroscopic surface tension part [5]. The $\kappa_1^s(\varphi)$ is a similar function in Eq. (13c), for the entropy part of γ. This writer has evaluated $\kappa_1^e(\varphi)$ and $\kappa_1^s(\varphi)$ from theory he developed on pure liquids (where $\varphi = 1$) and dilute solutions which allows reliable curves to be obtained from thermodynamic data on pure liquids and simple solutions of varying φ. For each $\kappa(\varphi)$ a separate curve is obtained, one for non-polar solvents, one for polar solvents which include water.

The $\kappa_1^e(\varphi = 1)$ and $\kappa_1^s(\varphi = 1)$ values are tabulated for many common solvents in Ref. [7]. These can be used wherever $M(R_M)$ and solvent molecule sizes are roughly comparable. The full $\kappa(\varphi)$ curves will also be published. Note also that for all $\kappa(\varphi)$,

$$\kappa(\varphi) \to 1 \tag{14}$$

as

$$\varphi \to 0, \quad \text{i.e. if} \quad V(R_M) \gg V_1 .$$

In conformation studies, the $M(R_M)$ usually has some molecular side groups g like phenyl, alkyl, etc. which can orient in different ways.

We have for the interaction [5, 7] of a group g of M with the liquid,

$$F^g_{\mathrm{vdW}}(R^g_{\mathrm{M}}) = -f(\varphi_{1g}, \bar{l}_{1g})\, \Delta_{1g} D_1 D_g B_{1g} \tag{15a}$$

with

$$\Delta_{1g} = \mu \frac{I_g I_1}{I_g + I_1}; \qquad \mu \cong 1.35 \tag{15b}$$

I_g resp. I_1 = ionization potential of side group g resp. solvent molecule ①.

$$D_i = \frac{n_i^2 - 1}{n_i^2 + 2} = \frac{4\pi}{3v_i} N_0 \bar{\alpha}_i \tag{15c}$$

$n_i, v_i, \bar{\alpha}_i$ = refractive index, molecular volume (V_i/N_0), average polariability of $i \in$ {side group g or solvent ①}; properties derived from pure liquids (solvent and a liquid of models of g).

The $f(\varphi_{1g}, \bar{l}_{1g})$ is a dimensionless function of relative solvent-solute size and molecular "core sizes" given [5, 6] in terms of simple macroscopic handbook properties of the pure liquids involved. The $f(\varphi, \bar{l})$ results from integration of the (g-solvent molecule) interaction over the first discrete solvation layer, then over the rest of the solvent.

In Eq. (15a) we have

$$-f(\varphi_{1g}, \bar{l}_{1g})\, B_{1g} = \frac{27}{8\pi}(1 - x)(Q' + Q'') \tag{16a}$$

$x \approx 0.436$ for most solvents, polar, non-polar [7].

The Q' is obtained analytically,

$$Q' = \frac{\pi}{6y^3(1-t)^3}\left[\frac{1}{2}\left(\frac{\mu}{\tau}\right)^6\left(\frac{1}{9} + \frac{1}{5\tau} + \frac{1}{11\tau^2}\right) - \left(\frac{1}{3} + \frac{1}{2\tau} + \frac{1}{5\tau^2}\right)\right], \tag{16b}$$

where
$$\mu=\frac{3}{7\omega+0.24};$$
$$\tau=\frac{1}{t}-1;\quad t=\frac{\bar{l}}{R_s};\quad \bar{l}=\left(\frac{7\omega+0.24}{7\omega+3.24}\right)\frac{2}{\beta}\left(\frac{3v}{4\pi}\right)^{1/3};$$
$$R_s=\left(\frac{3}{4\pi}\right)^{1/3}(v_g^{1/3}+\chi v_1^{1/3});$$

with
$$\beta\cong 1.15;$$
$$y=\frac{1}{2}(1+\chi);\quad \chi\cong 0.85;$$

v_g, v_1 = average molecular volumes of liquid of g and of solvent ①,
ω = acentric factor (a macroscopic property of a pure liquid).
(The t is with $\bar{l}$ average between that of liquid of g and of solvent.)

All these quantities (β, χ, ω are used in Ref. [6].

The Q'' is an integral which is evaluated numerically. But it is a smaller part. For most liquids we have found $(Q''/Q')\cong 0.1$.

The above $F^g_{\mathrm{vdW}}(R^g_{\mathrm{M}})$ has resulted essentially from an integral of the type (the form of $U^e(r)$ "effective intermolecular pair potential" given in Ref. [6] and approximations for $g^{(2)}$ also used in Ref. [6] gave rise to Q' and Q'' above),

$$e^g_{\mathrm{vdW}}\equiv\varrho\int_0^\infty U^e_{1g}(r)\,g^{(2)}(r;R_{\mathrm{M}})\,4\pi r^2dr\,.$$

Here ϱ = number density of solvent ①.

We have now completely specified $A^0_{\mathrm{solv,eff}}(R_{\mathrm{M}})$. It has no adjustable parameters; all quantities in it are either geometric or from quantum calculations for $\mathrm{M}(R_{\mathrm{M}})$, and from simple macroscopic properties of pure liquids found in handbooks.

We now show that everything that was done with $U(R_{\mathrm{M}})$ for the gas phase, can be done with $C(R_{\mathrm{M}})$ in the solution phase.

Consider the total P.E.-surface U_t of a collection of solvent molecules $\{s\}$ together with the $\mathrm{M}(R_{\mathrm{M}})$ in their midst:

$$U_t=U(R_{\mathrm{M}})+U_{\mathrm{MS}}(R_{\mathrm{MS}})+U_{\mathrm{SS}}(R_{\mathrm{SS}})\tag{17}$$

R_{MS} = distances from $\mathrm{M}(R_{\mathrm{M}})$ to solvent molecules; R_{SS} = distances between solvent molecules.

The free energy of the entire collection (per M) is:

$$A=-kT\ln\Lambda_{\mathrm{M}}\Lambda_{\{s\}}Q\tag{18a}$$

with $\Lambda_{\{s\}}=\lambda_s^{N_s}/N_s!$ and $\lambda_s=(2\pi M_skT/h^2)^{3/2}$, and

$$Q=\int_{R_{\mathrm{M}}}d\tau_{\mathrm{M}}\int_{\{s\}}d\tau_{\{s\}}\,e^{-U_t(R_{\mathrm{M}},R_{\{s\}})/kT}\,.\tag{18b}$$

For $C(R_\mathrm{M})$ to act "as if it were a $U(R_\mathrm{M})$" all we need to show is that, A, Eq. (18) equals

$$A = -kT \ln \Lambda_\mathrm{M} Q_\mathrm{M}^C\,, \tag{18c}$$

$$Q_\mathrm{M}^C = \int_{R_\mathrm{M}} d\tau_\mathrm{M}\, e^{-C(R_\mathrm{M})/kT}\,. \tag{18d}$$

Comparing (18a, b) with (18c, d), we have

$$e^{-A^0_\mathrm{solv.eff}(R_\mathrm{M})/kT} = \Lambda_{\{s\}} \int_{\{s\}} d\tau_{\{s\}}\, e^{-[U_\mathrm{MS}(R_\mathrm{MS}) + U_\mathrm{SS}(R_\mathrm{SS})]/kT} \tag{19}$$

which follows from Eqs. (17), (9) and (18a, b). Q.E.D.

Remark: The integral in (19) is over all solvent positions, $R_{\{s\}}$. But as $\{s\}$ get close to $\mathrm{M}(R_\mathrm{M})$, the U_MS term becomes hard-core like repulsive making integrand zero. This is equivalent to integrating only outside of an $\mathrm{M}(R_\mathrm{M})$ cavity. The rest of $U_\mathrm{MS}(R_\mathrm{MS})$ in Eq. (19) leads to $A_\mathrm{int}(R_\mathrm{M})$ ($\cong F_\mathrm{int}$) in Eq. (12). The $U_\mathrm{SS}(R_\mathrm{SS})$ in Eqs. (17)–(19) we take relative to the $A_s(l.)$, free energy of pure solvent of same number of ⓢ-molecules. This affects $U_\mathrm{SS}(R_\mathrm{SS})$ within a constant. The U_SS term in the integral thus leads to $A_C(R_\mathrm{M})$ ($\cong F_C(R_\mathrm{M})$) of Eq. (12).

3. Use of the New Potential

The conformations and/or isomeric equilibria and ($\ddagger$)-rates of $\mathrm{M}(R_\mathrm{M})$ in solution is now studied by adding $F^0_\mathrm{solv.eff}(R_\mathrm{M})$ from Eqs. (12)–(16) to a quantum mechanical [3] (or semi-empirical [6]) gas phase P.E.-surface $U(R_\mathrm{M})$. More accurately, $U(R_\mathrm{M})$ is itself modified due to many-atom forces in the liquid, "effect of medium on van der Waals forces" into an "effective $U(R_\mathrm{M})$", $U^e(R_\mathrm{M})$ which is given in detail in separate work on that particular effect by this writer [6]. [In deriving Eqs. (13)–(16), U^e's were used in U_MS and U_SS.] The full $C(R_\mathrm{M})$ is

$$C(R_\mathrm{M}) \cong U^e(R_\mathrm{M}) + F^0_\mathrm{solv.eff}(R_\mathrm{M})\,. \tag{20}$$

A $C(R_\mathrm{M})$ "map" is easily obtained for molecules in solution, e.g. *cis*, ($\ddagger$), *trans*, etc. azobenzene [7]. One looks for new minima, etc. or calculates partition functions $(\mathrm{p.f.})_2$, or equilibria K, (or $K^{\neq} \propto$ rate) from it.

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