# Towards a Quantum Chemical Software Package Utilizing Transferable Fragments as Molecular Building Blocks

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Computer programs have been developed or are under development for the IBM personal computer that enable their users to get information on atomic charges, electrostatic potentials, conformational and other properties of molecular systems containing H, C, N, O, F, Si, P, S, or Cl atoms. The zero-order wavefunction is constructed of strictly localized molecular orbitals with fixed atomic orbital coefficients. The wave function can be refined by optimizing these coefficients, i.e., considering inductive effects via a coupled set of $2 \times 2$ secular equations within the CNDO/2 approximation. Delocalization and exchange effects are accounted for by expanding the wavefunction on a basis of the aforementioned strictly localized orbitals, instead of conventional atomic orbitals, and solving the corresponding SCF equations. Our method has been applied to the study of large systems. We calculated the electrostatic field of the complex of $\beta$-trypsin and basic pancreatic trypsin inhibitor and it has been found that strong field regions more or less coincide with hydration sites. A further potential application of protein electrostatic fields is in NMR spectroscopy. We found a linear correlation between $C^{\alpha}H$ or backbone NH proton chemical shifts and the protein field at the site of the corresponding proton. At last, we propose a simple method to mimic the bulk around atomic clusters modeling crystalline and amorphous silicon. Based on this method we found a linear correlation between atomic net charges and bond angle distortions in silicon clusters with 35 atoms.

## INTRODUCTION

The decreasing costs of computers facilitated propagation of theoretical chemistry software in industrial and academic laboratories all over the world. Several programs are available for mainframe,[1] mini-[2–4] and microcomputers[5–7] as well, that work more or less like a black box, similarly to IR or NMR spectrometers used for routine work in most organic chemistry laboratories. Since theoretical chemistry is becoming more and more popular among bench chemists, molecular biologists, and pharmacologists, there is a need for computer programs that yield rapid information on a given molecular property or process. Even if this information is only qualitative or semiquantitative, it may help very much in systematizing observations, understanding molecular phenomena, and designing molecules or novel experiments.

In this article we outline a quantum chemical program package that is under development for the IBM PC microcomputer and, more or less, complies with the above requirements. First, we discuss the methodology; afterwards some applications are described. We illustrate the adequacy of our methods on the location of hydration sites and on the prediction of trends in proton NMR chemical shifts in basic pancreatic trypsin inhibitor (BPTI) and on the calculation of the charge distribution in atomic clusters modeling amorphous silicon.

## METHODS

We restrict our studies to classical molecules containing H, C, N, O, F, Si, P, S, or Cl atoms, i.e., those that can be represented chemically by two-center, $\sigma$, two- or many-center $\pi$ bonds, and one-center lone pairs (lp).

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In this context methylfluoride or aniline are classical molecules, but the $CH_5^+$ cation, possessing a three-center bond, is not. The bonds can be represented by strictly localized molecular orbitals (SLMOs) expanded on the basis of conventional atomic orbitals[8–14]

$$\varphi_i^{lp} = h_{Ai} \tag{1}$$

$$\varphi_i^{\sigma} = c_{Ai}h_{Ai} + c_{Bi}h_{Bi}\,. \tag{2}$$

$$\varphi_i^{\pi} = \sum_a c_{ai}u_a^{npz} \tag{3}$$

$n = 2$ or 3, $h_{Ai}$ denotes a normalized hybrid orbital centered at atom $A$

$$h_{Ai} = \sum_{r=1}^{4} a_{Ai}^r u_A^r \tag{4}$$

$u_A^r$ is a normalized Slater-type orbital at atom $A$, $r = ns, np_x, np_y$, or $np_z$. If $A$ is hydrogen, $h_{Ai} = u_A^{1s}$. Hybrid coefficients (i.e., $s$-characters and orientations) in Eqs. (1) and (2) may be obtained either from the full SCF CNDO/2 wavefunctions by localization or from any hybridization procedure.[14] It is also possible to set up a library with fixed transferable hybrid coefficients.[15,16]

SLMOs of the form in eqs. (1)–(3) can be used to construct the total wavefunction at three different levels of approximation. In the simplest case the approximate wavefunction $\Psi^T$ is a single determinant of completely transferable SLMOs (bond increment method)

$$\Psi^T = \det|\varphi_i(j)| \tag{5}$$

The above approximation neglects inductive, exchange, and delocalization effects between different bonds. In spite of its relative crudeness, it works well for molecular electrostatic potentials (MEP). Using Eqs. (1)–(5) for the calculation of the expectation value of the potential, applying the ZDO approximation and supposing that SLMOs are orthogonal, i.e., neglecting nonorthogonality terms, we get the following simplified expression

$$V(\mathbf{r}) = -2\sum_i \sum_a c_{ai}^2 \int h_{ai}^2(1)/|\mathbf{r} - \mathbf{r}_1|\, dv_1 + \sum_a \frac{Z_a^{eff}}{|\mathbf{R}_a - \mathbf{r}|} \tag{6}$$

where $Z_a^{eff}$ is an effective nuclear charge and $\mathbf{R}_a$ is the position vector of nucleus $a$. Derivating Eq. (6) we get the molecular electrostatic field (MEF).[17] $c_{ai}$ coefficients in Eq. (6) for $\sigma$- and $\pi$-orbitals are obtained from calculations on suitable model molecules and may be stored allowing rapid calculation of the MEP and MEF even for very large molecules, like proteins.[18]

We have compared the results from Eq. (6) with *ab initio* STO-3G minimal basis set calculations.[17] It has been shown that for saturated systems the calculated potentials and fields are systematically overestimated. However, they reflect correct trends and therefore can be applied for comparative purposes. For $\pi$-systems some problems arise since the minima under and above the ethylene and benzene planes are predicted to be positive instead of being negative. This deficiency is, however, absent if a heteroatom is present, therefore the approximate MEP can be used with sufficient care to interpret various phenomena depending on electrostatic interactions, between heteroaromatic molecules and small ligands.

In order to consider inductive effects, i.e., to optimize $AO$ coefficients in Eqs. (2) and (3) simple secular equations were derived within the CNDO/2 approximation.[14,19] We write for the vector of coefficients of the $i$th bond

$$\mathbf{F}_i\mathbf{c}_{mi} = \varepsilon_{mi}\mathbf{c}_{mi} \tag{7}$$

where the Fockian is given as follows

$$F_{aa,i} = H_{aa,i}^{eff} + \sum_m P_{mm,i}(ai;ai\,|\,mi;mi) - \frac{1}{2}P_{aa,i}(ai;ai\,|\,ai;ai) \tag{8b}$$

$$F_{ab,i} = H_{ab,i}^{eff} - \frac{1}{2}P_{ab,i}(ai;ai\,|\,bi;bi) \tag{8b}$$

$\mathbf{H}^{eff}$ is an effective core Hamiltonian including the Coulomb repulsion between bond $i$ and other bonds

$$H_{aa,i}^{eff} = H_{aa,i} + \sum_{j\neq i}\sum_m P_{mm,j}(ai;ai\,|\,mj;mj) \tag{9a}$$

$$H_{ab,i}^{eff} = H_{ab,i} \tag{9b}$$

$\mathbf{P}$ is the density matrix, $H_{aa,i}$, and $H_{ab,i}$ are core matrix elements within the CNDO/2 parametrization. $(ai;ai\,|\,mj;mj)$ denotes the Coulomb integral in the $(11\,|\,22)$ convention. Equation (7) involves the solution of a coupled set of at most $m$-dimensional secular equations where $m$ denotes the maximum number of SLMO centers in Eqs. (1)–(3). This feature considerably reduces the computational work especially for saturated sys-

tems composed of one-center lone pairs and two-center $\pi$-bonds. The total wavefunction $\Psi^I$ has now the same form as $\Psi^T$ in eq. (5), but coefficients of Eqs. (2) and (3) are replaced by those obtained from Eq. (7).

In the third level of approximation we partition the molecular system under study into a central part, where delocalization effects are important, and a rigid environment where coefficients from Eq. (7) are used. We neglect charge transfer and inductive effects between the central fragment and the environment and expand the wavefunction of the former, $\Psi^{D(C)}$, on the basis of SLMOs. Applying the variation principle to the total CNDO/2 energy of the central fragment and making use of the special, block-diagonal form of the density matrix, the following secular equation can be derived[20]

$$\mathbf{F}^C\mathbf{a}_m = \varepsilon_m^C\mathbf{a}_m \tag{10}$$

with

$$F_{ij} = H_{ij}^{\text{eff}} + \sum_{k,l\in C} P_{kl}\left[(ij\,|\,kl) - \frac{1}{2}(ik\,|\,jl)\right] \tag{11}$$

$$H_{ij}^{\text{eff}} = H_{ij} + 2\sum_{k\in C}(ij\,|\,kl) \tag{12}$$

Summation in Eqs. (11) and (12) runs over SLMO basis functions inside and outside the central part, respectively. The wavefunction is now written as

$$\psi^{D(C)} = \det|\psi_i(j)| \tag{13}$$

where the $\psi_i$ molecular orbitals are expanded in terms of SLMOs belonging to the central fragment

$$\psi_i = \sum_k a_{ij}\varphi_k \tag{14}$$

We called the above procedure the Fragment SCF method where separation of the environment from the central fragment reduces the dimensionality of the secular equation to a relatively small number that is independent of the size of the environment. Note that our method, though revealing some similarity in the philosophy, is essentially different from the Fragment Molecular Orbital theory of Christoffersen.[21] As a result, we were able to study really large systems like a model of $\alpha$-chymotrypsin containing 58 atoms and 157 valence orbitals.[22]

## PROGRAMS

Our package consists of two main programs PCMEP and FSCF. PCMEP, a user-friendly, modified version of the QCPE program ELPO,[23] is available for the IBM PC microcomputer.[24] It calculates electrostatic potentials and fields using Eq. (6) for molecules with up to 600 atoms. If the molecule under study contains one or more $\pi$-systems, CNDO/2 calculations for suitable models of the aromatic moiety have to be done in order to obtain $\pi$-orbital coefficients. Otherwise, the program needs only specification and Cartesian coordinates of atoms and hypothetical centers defining lone pair orientations, furthermore the molecular connectivity as input. FSCF is installed on an IBM 3031 computer.[25] Its capacity is 200 atoms in the transferable region ($T$) and 80 orbitals in the inductive ($I$) and central ($C$) regions; cf. Eqs. (5), (7), and (10), respectively. The input includes specification and Cartesian coordinates of all atoms and difiniton of the inductive and central regions by giving serial numbers and connectivity of the relevant atoms. A user-friendly version will be available in the near future.

There are further three programs being specialized versions of PCMEP or FSCF. PROTPOT[26] processes coordinate holdings of the Protein Data Bank to an input for ELPO.[24] It generates hydrogen atoms and hypothetical lone-pair centers using standard geometries, assigns coefficients to $\pi$-centers of unsaturated side chains using stored transferable fragments. Optionally, any desired side chain or residue can be excluded from the input; dangling bonds are then saturated by hydrogen atoms. This feature allows us to calculate electrostatic potentials and fields at given atomic sites (cf. proton NMR chemical shifts for BPTI in the next section). Ionizable side chains can be treated in their protonated and unprotonated forms, as well. The program will be adapted for the IBM PC.

We wrote a program, ASI, for the IBM 3031 that uses FSCF for calculations on models of amorphous silicon (a-Si).[27] The bulk is modeled by pseudosilicon atoms ($Si^*$) at the boundary, as proposed by László,[28,29] within the CNDO SCF approximation utilizing canonical orbitals. It is especially simple to define $Si^*$ atoms in the SLMO framework. Depending on their adjacency (1 or 2) one or two $sp^3$ hybrids are assigned to them, each filled

by just one electron. Since all the parameters for these hybrids (principal quantum number, orbital exponent, and core matrix elements) are the same as for a real Si atom, solving Eq. (7) for diamond-like structures yields exactly zero net charges on Si and Si* atoms, as well. Thus the spurious accumulation of charges, observed in case of the conventional SCF formalism[28,29] can be avoided. ASI is able to handle models of various atomic crystal lattices and surfaces with up to 100 centers.

We have started writing a further program, PCGEOM, that will serve for the construction of molecular geometries. Optionally, PCGEOM will use bond lengths, bond angles, and torsional angles as input or may construct the geometry from stored fragments. Through continuous display of the molecule, the desired conformations can be defined and specific files will be produced for input to PCMEP and FSCF.

## APPLICATIONS

### Hydration of the β-Trypsin-BPTI Complex

Analysis of MEF maps may help in constructing the first hydration shell around molecules (cf., e.g., Ref. 17). In order to explore the adequacy of our method we attempted to find a relationship between the value of the electrostatic field at sites near the contact region of the β-trypsin-BPTI complex and the presence or absence of a bound water molecule at this site. We calculated the MEF values by the PROTPOT program at water (oxygen) positions given by the Protein Data Bank for the β-trypsin-BPTI complex,[30] for β-trypsin,[31] and BPTI,[32] respectively. Our results are listed in Table I. The smallest field (for W413) is 3.9 V/nm corresponding to a binding energy of 15 kJ/mol in reasonable agreement with experimental and theoretical estimates for the lower bound of H-bond energies.[33] The binding energy of a water molecule was calculated modeling it by a dipole of a moment of $6.48 \times 10^{-30}$ C.m (1.94 D).

We postulate that if the MEF at a given site outside the van der Waals envelope of a protein molecule, as calculated by the PROTPOT program, is larger than or equal to 3.9 V/nm, the oxygen of a water molecule will be bound there. If the MEF is smaller than this value, no hydration occurs. The reliability of this estimation can be judged from Table I. There are four possible hydration sites (W495, W607, and W403 for trypsin, W416 for BPTI) where the fields are larger than 3.9 V/nm, but no bound water could be detected by X-ray

**Table I.** MEF values (in V/nm) for bound water molecules (oxygen atoms) as located by X-ray diffraction around the β-trypsin-BPTI complex and its components. Neighboring residues within a distance of 400 pm (by italics for BPTI) are also indicated.

| Complex | | β-Trypsin | | BPTI | |
|---|---|---|---|---|---|
| Water (Residue)[30] | Field | Water (Residue)[31] | Field | Water (Residue)[32] | Field |
| **414** (Asp-189, Gly-219, *Lys-15*) | 25.1 | **414** (Asp-189, Gly-219) | 7.8–11.4 | **223** (Lys-15)[d] | 5.9[d] |
| **402** (Asp-189) | 18.6 | **704, 705** (Asp-189) | 3.9–8.5 | - | 3.7[b] |
| **416** (Ser-190, *Lys-15*) | 16.4 | **416** (Ser-190) | 6.9–8.1 | - | 4.2[a,b] |
| **415** (Asp-189, Ser-217, Ala-221) | 12.5 | **415** (Asp-189 Ser-217, Ala-221) | 11.2–11.8 | - | 0.6[b] |
| **400** (*Cys-14*) | 9.8 | - | 2.6[b] | **156** (Cys-14) | 11.5 |
| **445** (Asp-189) | 9.3 | **562** (Asp-189) | 7.0–7.4 | - | 0.1[b] |
| **495** (Trp-141, *Arg-17*) | 7.9 | - | 8.5[c] | - | 1.9[b] |
| **607** (Tryp-141, *Arg-17*) | 6.6 | - | 6.8[c] | - | 2.6[b] |
| **403** (Gln-192, Gly-216, *Pro-13*) | 6.4 | - | 5.6–6.0[c] | **145** (Pro-13) | 4.6 |
| **503** (*Pro-13*) | 5.9 | - | 1.1[b] | **145** (Pro-13) | 5.5 |
| **413** (*Arg-17*) | 3.9 | - | 2.3[b] | - | 3.8[a,b] |

[a]Fluctuating side chain.
[b]Small field.
[c]Outlier.
[d]A. Wlodawer, J. Deisenhofer, and R. Huber, *J. Mol. Biol.*, **193**, 145 (1987).

crystallography. For BPTI, this is a consequence of the strong fluctuation of side chains in Lys-15 and Arg-17 making that even if one or more water molecules were strongly bound here they could be located by X-ray diffraction with some difficulty since the corresponding electronic densities are smeared.[34] The same reasoning may be true for W495 and W607 around trypsin that are located near Trp-141 which has an extended side chain. However, no direct experimental evidence is available to decide whether the fluctuation of Trp-141 or other important factors, not considered in this study, are responsible for the failure of our predictions. W403 is clearly an outlier, in contrast to the relatively large calculated field here; no associated water can be detected. Our predictions are valid for hypothetical W400, W413, and W500 sites in trypsin and W402, W413, W415, W445, W495, and W607 sites in BPTI, where the calculated fields are small and, in fact, no bound water could be located experimentally.

### Proton NMR Chemical shifts in BPTI

It is known that variations in proton net charges, due to electrostatic field effects may play an important role in determining NMR chemical shifts ($\delta$).[35] In the absence of ring current effects the change in $\delta$ for a proton in the XH bond depends linearly on $E_z$, the external field component along this bond. Since proteins produce strong electrostatic fields, it is expected that variations of $\delta$ for NH and $C^{\alpha}H$ protons in BPTI can be explained in terms of $E_z$ at the site of the proton.

The SLMO formalism allows us to omit just one or a few bonds from the calculation; therefore it was simple to get the electrostatic field of BPTI at proton sites. To calculate $E_z$ for residue $i$, we dropped all bonds of this residue and, additionally, the $N(i)—C(i-1)$, $C(i)—N(i+1)$, $N(i+1)—H$ and $N(i+1)—C(i+1)\sigma$-bonds and the lone pair at $N(i+1)$ from the summation. Dropping a one- or two-center bond means that in Eq. (6) the corresponding SLMO is not counted in the first sum and the nuclear charge(s) belonging to this bond are reduced by two or one, respectively. In case of delocalized $\pi$-systems, all corresponding $\sigma$- and $\pi$-SLMOs and nuclei should be omitted. Otherwise, all other bonds of BPTI were accounted for in Eq. (6). We considered ionizable side chains to be completely shielded, i.e., being neutral.[18] Positive values of $E_z$ refer to a vector directed from atom N or $C^{\alpha}$ to H.

In Figure 1 we plotted $\Delta\delta$ vs. $E_z$ for BPTI.[36] $\Delta\delta$ is the observed NH or $C^{\alpha}H$ chemical shift at pH 3.5 minus the random-coil and ring-current corrections (cf. Tables 3 and 4 in Ref. 36). We did not consider NH shifts for residues Tyr-10, Cys-14, Cys-38, and Lys-41 where hydrogen bonding to structural water molecules strongly influences the magnitude of $\Delta\delta$. For the rest of $\Delta\delta$-$E_z$ pairs the following linear regression equations were derived

$$\Delta\delta(\mathrm{NH}) = 0.0915E_z - 2.71 \quad r = 0.814 \tag{15}$$

$$\Delta\delta(C^{\alpha}H) = 0.164E_z - 1.50 \quad r = 0.745 \tag{16}$$

The correlation in Eq. (15) is better than that found by Pardi et al.[36] who correlated $\Delta\delta$ with $d_X^{-3}$, where $d_X$ is the hydrogen bond length between the NH proton and a neighboring H-bond acceptor, and obtained $r = 0.75$. As for Eq. (16), the maximum deviation between experimental and calculated values is relatively small, 0.57 ppm. The reason for the

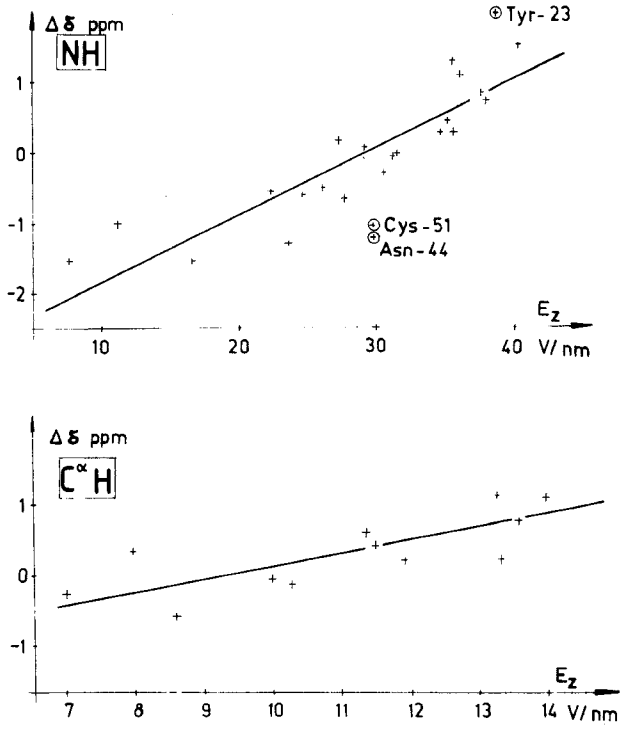


**Figure 1.** Dependence of reduced proton chemical shifts, $\Delta\delta$, in BPTI on the MEF component along the XH bond, $E_z$. Upper graph: NH protons, Eq. (15); lower graph: $C^{\alpha}H$ protons, Eq. (16). Outliers where the difference between computed and experimental values is larger than 1 ppm, are encircled.

improvement is clear; Pardi et al. approximated $E_z$ by the field of a point dipole centered at the H-bond acceptor atom. Our bond increment approximation is more sophisticated, calculated MEF values correlate fairly with *ab initio* minimum basis set results.[17]

### Charge Distribution in Silicon Clusters

In order to determine charge distribution in a-Si clusters theoretically, we started with diamond-like models and mimicked the bulk by $Si^*$ atoms at the boundary. As we have mentioned our model avoids spurious accumulation of charges in these symmetric models. We applied our ASI program solving Eq. (7) to get the net charges and first studied size effects on the charge distribution.

We have found that in clusters containing 35 Si atoms and 36 $Si^*$ centers (Si-Si and Si-$Si^*$ distances: 235 pm) the charges accumulating as the result of the displacement of the central atom, Si(C), are less than 0.1 millielectron (1%) on atoms separated by more than two bonds from Si(C). From this result we concluded that charge accumulation in amorphous silicon clusters is a three-atom effect and can be traced back to bond angle distortions. In a triad of Si atoms $Si_K$, $Si_L$, and $Si_M$, forming two bonds $Si_LSi_M$ and $Si_KSi_M$ with an $Si_KSi_MSi_L$ angle of $\vartheta$, the charge depends linearly on the deviation of the actual bond angle from the ideal tetrahedral value, $\Delta\vartheta = \vartheta - 109.47°$. Accordingly, the charges are obtained from the following equations

$$q_M = 2A\Delta\vartheta \qquad (17a)$$

$$q_K = q_L = -A\Delta\vartheta \qquad (17b)$$

Generalization of Eq. (17) to a diamond-like cluster, where each Si atom has just four neighbours, gives

$$q_M = A\left(2\sum_{i=1}^{6}\Delta\vartheta_j - \sum_{j=1}^{12}\Delta\vartheta_j\right) + B \qquad (18)$$

where $\vartheta_i = XMY\sphericalangle$ and $\vartheta_j = MXZ\sphericalangle$ ($X$ and $Y$ are bonded to $M$, $Z$ to $X$ or $Y$). We checked the validity of Eq. (18) on three 35-atomic, diamond-like clusters where the central atom, Si(C), was displaced by 20 pm in various directions. Considering net charges calculated for Si(C) and for those 16 atoms that are separated by one or two bonds from Si(C), we got a very good linear correlation with $A = -0.717$ and $r = -0.981$. The value of $q_M$ was given in millielectrons. The intercept is very close to zero, $B = -0.015$ millielectrons. Equation (18) is analogous, though not equivalent to the relation proposed by Guttman et al.[37] (Fig. 2).

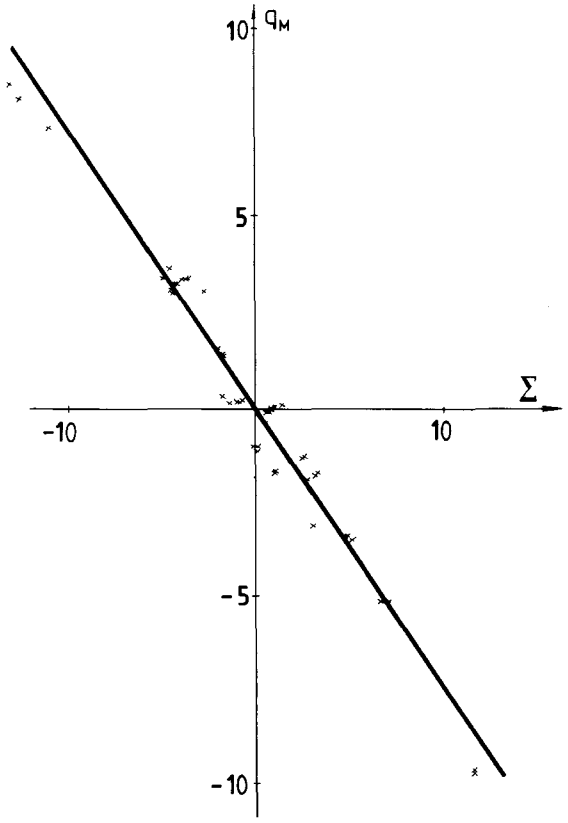


**Figure 2.** Graphical representation of Eq. (18). $\Sigma = 2\Sigma_{i=1}^{6}\Delta\vartheta_i - \Sigma_{j=1}^{12}\Delta\vartheta_j \cdot q_M$ in millielectrons.

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