The GROMOS Software for (Bio)Molecular Simulation

Volume 3: Force Field and Topology Data Set

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Contents

CHAPTER 1

Introduction

In this volume the molecular model and the force field used in GROMOS are described. The GROMOS package comes with a number of standard data files. The ones involving the definition of a force field parameter set fall into two categories: interaction function parameter files ($*$.ifp) and molecular topology building block files ($*$.mtb). At least one of each of these types of files are required to build a molecular topology.
This chapter continues with a short overview of the history of the GROMOS force field and a description of the background for its various versions. Chap. 2 summarizes the physical potential energy terms used in the GROMOS force fields. A detailed description of the Hamiltonian can be found in Vol. 2. The parameters contained in the interaction function parameter files of the 45A4 (45B4)[1–4] and 54A7 (54B7)[5–8] versions of the GROMOS force field are presented in Chap. 3. The corresponding molecular topology building blocks for the 54A7 force field are described in Chap. 4. Standard configurations of molecules or molecular systems are listed in Chap. 5.

1.1. GROMOS Force Fields

The GROMOS force field is continuously being tested and, if necessary, improved. From time to time a new version is brought out. The historic sequence of GROMOS force fields is the following:

- the 26C1 force field of June 1981
- the 37C2 (and 37D2) force field(s) of January 1983 (extended in November 1983)
- the 37C4 (and 37D4) force field(s) of November 1983 (revised in December 1985)
- the 43A1 (and 43B1) force field(s) of July 1996
- the 43A2 force field of October 2000
- the 45A3 (and 45B3) force field(s) of January 2001
- the 45A4 (and 45B4) force field(s) of July 2003
- the 53A5 (and 53B5) force field of July 2003
- the 53A6 (and 53B6) force field of July 2003
- the 54A7 (and 54B7) force field of April 2011

The A-version of a force field is the basic force field designed for molecules in solution or in crystalline form. The B-version is derived from the A-version in order to be used for simulating molecules in vacuo, where the dielectric screening effect of the environment is neglected. The atomic charges and van der Waals parameters are changed such that atom charge groups with a non-zero total charge are neutralized while maintaining the hydrogen-bonding capacity of the individual atoms.

Since the functional form of the 43A1 and 43B1 force fields differs from that of the previous versions and the GROMOS file structure and formats were substantially changed in 1996, the force field versions older than 1996 have not been converted and have not been kept in the GROMOS package. For every force-field version, the complete set of interaction function parameters can be found in the corresponding file $*$.ifp. Building blocks of the 43A1 and 43A2, and the 43B1 and 43B2 force fields are given in the files 43a1.mtb and 43b1.mtb, respectively, and 45a3.mtb and 45b3.mtb present building blocks for the 45A3 and 45B3 force fields. In the newer versions of the GROMOS force field, building blocks are supplied via more than one file. These files contain building blocks that are categorized according to the kind of (sub)molecule they represent. For example, 45A4 building blocks can be found in: 45a4.mtb (α-amino acids, lipids, nucleotides and solvents), 45a4_carbo.mtb (carbohydrates and sugars), 45a4_beta.mtb (β-amino acids) and 45a4_cof.mtb (cofactors and other types of molecules).

Since the introduction of the 43A1 and 43B1 versions, the basic functional form of the GROMOS force field has been kept constant. It is described in Chap. 2-5 to Chap. 2-8 of Vol. 2. Chap. 3 and Chap. 4 of this Volume present the force field parameters and building blocks of the 54A7 force field. In the remaining of the current chapter, the events leading up to these force fields are sketched.

1.2. Development of the GROMOS Force Field

In the first GROMOS force field, 26C1, only 26 atom types were defined[9,10]. The molecular topology building block file contained only amino acid residues and a heme group. It was meant for simulation of proteins in aqueous solution or crystalline form.

The 37C2 force field was an extension of the 26C1 force field in order to allow for simulation of nucleotides, sugars, etc. Eleven new atom types were added. Some interaction function parameters were slightly changed, which made the version number change from 1 to 2. The molecular topology building block file contained many more building blocks. It was meant for simulation of proteins, DNA, sugars in aqueous solution or crystalline form.

The 37D2 force field was the one corresponding to the 37C2 one, but adapted in order to be used for simulations of molecules in vacuo.

In the previous force fields the repulsive part of the van der Waals interaction between third neighbour atoms (1-4 interaction) was too large, in case one or both of the atoms involved was an extended (CH1, CH2, CH3, CR1) carbon atom and the torsion angle 1-2-3-4 was in a cis-conformation. This effect was redressed by changing the programs such that for 1-4 or third-neighbour interactions, van der Waals parameters can be used which are different from the normal ones. These extra 1-4 van der Waals parameters had to be given on the interaction function parameter file. This change made the force field version number change from 2 to 4. It was meant for simulation of proteins, DNA, sugars, etc. in solution or crystalline form.

The 37D4 force field was the one corresponding to the 37C4 one, but adapted in order to be used for simulations of molecules in vacuo.

The 43A1 force field constitutes a significant change with respect to the 37C4 one, and differs from it in a number of aspects.

1. The non-polar solute atoms appeared to be slightly too hydrophilic[11]. Therefore, the C12(I,J) van der Waals parameter, where I denotes a non-polar atom type and J denotes a water oxygen, was enlarged.
2. The description of aromatic rings which was based on the use of united atoms, was improved by introducing explicit hydrogen atoms on some aromatic rings[11].
3. In order to reduce the rotational motion of the peptide plane, the dihedral angle torsional force constants for the φ, ψ dihedrals were slightly increased.
4. The force field parameters in the heme-group were slightly changed.
5. The functional forms of the covalent bond-stretching interaction and bond-angle bending interaction were changed in order to improve computational efficiency and to avoid singularities in the forces for (ideal) bond angles of 180° (see section Sec. 2.3).
6. The nomenclature (definition of improper dihedral angles) of the Leu and Val side chains was changed such that it corresponds to the IUPAC-IUB convention.
7. Due to the introduction of the distinction between mass atom types and non-bonded van der Waals atom types and by relinquishing the use of non-bonded atom types for the definition of bond, bond-angle and (improper) dihedral- angle types, the number of different (van der Waals) atom types could be reduced from 37 to 22.
8. New van der Waals atom types were added, especially to allow for the use of different solvents (apart from water). This brought the number of non-bonded (van der Waals) atom types to 43 .

Shortly after the release of the 43A1 and 43B1 force fields, some small changes in the torsional-angle parameters and the third-neighbour-van der Waals interaction were introduced, in order to better reproduce the distribution of the torsional-angle values in short aliphatic chains. This modification resulted in the

43A2 parameter set[12].
As it was then shown that the density for the longer alkanes was too high, a reparametrisation of the aliphatic united atoms followed, introducing two additional atom types for branched and cyclic alkanes. This resulted in the 45A3 and 45B3 set of parameters[1].
Several parametrisation efforts on different classes of molecular systems were subsequently collected in the 45A4 and 45B4 set of parameters. The most important changes involved

- Charges and torsional dihedral angles in nucleotides and common co-factors[3]
- Charges and torsional dihedral angles in carbohydrates[4]
- Charges and torsional dihedral angles in lipids[2]
- Modifications in the choice of polar/nonpolar C12 interaction parameters for atom type 6 (NT)
- Correction to the van der Waals interaction parameters for atom type 31 (BR)
- Modifications to the heme group covalent interactions
- A new definition of the molecular topology building block at the end of polypeptide, polynucleotide or polysaccharide chains

The 53A5 and 53A6 force fields[5] are the result of a complete reparametrisation of the non-bonded interaction parameters for condensed phase simulations of pure liquids of small molecules (53A5) and solutions of molecular systems in water or apolar solvents (53A6). All interaction types have been redefined in these force fields, which also include parameters for additional solvents. In addition, bond types, bond-angle types, dihedral-angle types and atom-types have been renumbered in 53A5 and 53A6.

The recent 54A7 force field[6–8]

- The 53A6 helical propensities are corrected through new phi/psi torsional angle terms and a modification of the N-H, C=O repulsion.
- A new atom type for a charged -CH3 in the choline moiety is added.
- The Na+ and Cl- ions are modified to reproduce the free energy of hydration.
- Additional improper torsional angle types for free energy calculations involving a chirality change are introduced.

Solvent models that are consistent with the GROMOS biomolecular force fields are available for much used (co)-solvents[13]:

- water[14, 15]
- methanol[16]
- DMSO[17]
- chloroform[18]
- carbontetrachloride[19]
- urea[20]
- acetonitrile[21]

CHAPTER 2

Physical Forces: GROMOS Force Field

2.1. Introduction

This chapter summarizes the functional form of the GROMOS force field terms, which are described in detail in the following chapters of Vol. 2: The bonded interaction force-field terms are described in Chap. 2-5; van der Waals interactions are described in Chap. 2-6; Electrostatic interactions are described in Chap. 2-7; The special force-field terms are described in Chap. 2-8.

2.2. Bond stretching force-field terms

The potential energy (force-field) term associated with *bond stretching interactions* is the term $\mathcal{V}^{(b)}(\boldsymbol{r};\mathbf{s})$ in Eq. 2.1. It is given by

$$\mathcal{V}^{(b)}(\boldsymbol{r};\mathbf{s}) = \sum_{n=1}^{N^{(b)}} V^{(b)}(b_n; k_n^{(b)}, b_n^0) \ , \tag{2.1}$$

where $N^{(b)}$ is generally equal to the total number of all covalent bonds present in the system, *i.e.* each covalent bond is associated with one and only one stretching term in the GROMOS force-field, and $V^{(b)}$ is the function describing the potential energy associated with the stretching of a single bond. The quantity $b_n \doteq b_n(\boldsymbol{r})$ represents the length of bond n in the given system configuration, *i.e.* the distance between the two atoms $i \doteq i(n)$ and $j \doteq j(n)$ connected by the covalent bond n (minimum-image distance if PBC is applied). The quantities $k_n^{(b)}$ and b_n^0 represent force-field parameters, force constant and reference length, respectively characteristic for the specific bond n, as encoded by a corresponding *bond type code* $M_n^{(b)}$, *i.e.* one may write $k_n^{(b)} \doteq k^{(b)}(M_n^{(b)},\mathbf{s})$ and $b_n^0 \doteq b^0(M_n^{(b)},\mathbf{s})$. Two different expression can be used for the function $V^{(b)}$ in GROMOS (see Sec. 2-5.1.1), a quartic function with force constant $k^{(b)}$ and a harmonic function with force constant $k^{(b,h)}$.

For reasons of ease of analysis, the list of $N^{(b)}$ covalent bonds is split into two lists, one of bonds involving hydrogen atoms (defined as having mass atom type code 1, see Tab. 3.1), and one involving the other bonds. These lists are kept in the molecular topology file (see Vol. 4). The first list contains NBONH bonds involving hydrogen atoms. Three items are stored: IBH, JBH[1..NBONH] are the atom sequence numbers of the atoms forming bond i-j as a function of the bond sequence number n, and ICBH[1..NBONH] is the bond-type code, denoting the parameters $k_n^{(b)}$, $k_n^{(b,h)}$ and b_n^0 , as a function of the bond sequence number n. The list for the bonds involving no hydrogen atoms contains corresponding items denoted by IB, JB, ICB[1..NBON]. The force field parameters $k_n^{(b)}$, $k_n^{(b,h)}$ and b_n^0 for the various types of covalent bonds are stored in CB[1..NBTY], HB[1..NBTY] and B0[1..NBTY], as a function of the bond-type code (ICBH or ICB). They can be found in the interaction function parameter files ∗.ifp. For the GROMOS force fields 45A4 and 45B4 they are listed in Tab. 3.2, for force fields 54A7 and 54B7 they are listed in Tab. 3.17.

PROMD and MD++ read in values for $k_n^{(b)}$, $k_n^{(b,h)}$ and b_n^0 from the BONDSTRETCHTYPE block in the molecular topology file (∗.top), also if the BONDTYPE block is given as well. If the BONDTYPE block is given in the topology file instead of the BONDSTRETCHTYPE block, only $k_n^{(b)}$ values are read in, and use of equation (Eq. 2-17.3) to (Eq. 2-17.4) to calculate covalent-bond interaction and forces is not supported.

2.3. Bond-angle bending force-field terms

The potential energy (force-field) term associated with *bond-angle bending interactions* is the term $\mathcal{V}^{(\theta)}(\boldsymbol{r};\mathbf{s})$ in Eq. 2.2. It is given by

$$\mathcal{V}^{(\theta)}(\boldsymbol{r};\mathbf{s}) = \sum_{n=1}^{N^{(\theta)}} V^{(\theta)}(\theta_n; k_n^{(\theta)}, \theta_n^0) \ , \tag{2.2}$$

where $N^{(\theta)}$ is generally equal to the total number of all covalent bond-angles present in the system, *i.e.* each definable covalent bond-angle is associated with one and only one bending term in the GROMOS force field, and $V^{(\theta)}$ is the function describing the potential energy associated with the bending of a single bond angle. The quantity $\theta_n \doteq \theta_n(\boldsymbol{r})$ represents the value of bond angle n in the given system configuration, *i.e.* the angle formed by the three atoms $i \doteq i(n)$, $j \doteq j(n)$ and $k \doteq k(n)$ defining the covalent bond angle n (minimum-image triplet if PBC is applied). The quantities $k_n^{(\theta)}$ and θ_n^0 represent force-field parameters, force constant and reference bond angle, respectively, characteristic for the specific bond angle n, as encoded by a corresponding *bond-angle type code* $M_n^{(\theta)}$ *i.e.* one may write $k_n^{(\theta)} \doteq k^{(\theta)}(M_n^{(\theta)},\mathbf{s})$ and $\theta_n^0 \doteq \theta^0(M_n^{(\theta)},\mathbf{s})$. Two different expression can be used for the function $V^{(\theta)}$ in GROMOS (see Sec. 2-5.1.2), a cosine-harmonic function with force constant $k^{(\theta)}$ and a harmonic function with force constant $k^{(\theta,h)}$.

For reasons of ease of analysis, the list of $N^{(\theta)}$ bond angles is split into two lists, one of bond angles involving hydrogen atoms (defined as having mass atom type code 1, see Tab. 3.1), and one involving the other bond angles. These lists are kept in the molecular topology file (Volume 4). The first list contains NTHEH bond angles involving hydrogen atoms. Four items are stored: ITH, JTH, KTH[1...NTHEH] are the atom sequence numbers of the atoms forming bond angle i-j-k as a function of the bond-angle sequence number n, and ICTH [1...NTHEH] is the bond-angle type code, denoting the parameters $k_n^{(\theta)}$, $k_n^{(\theta,h)}$ and θ_n^0 as a function of the bond-angle sequence number n. The list for the bond angles involving no hydrogen atoms contains corresponding items denoted by IT, JT, KT, ICT[1...NTHE]. The force field parameters $k_n^{(\theta)}$, $k_n^{(\theta,h)}$ and θ_n^0 for the various types of bond angles are stored in CT[1...NTTY], CHT[1...NTTY] and T0[1 ... NTTY] as a function of the bond-angle type code (ICTH or ICT). They can be found in the interaction parameter files $*$.ifp. For the GROMOS force fields 45A4 and 45B4, they are listed in Tab. 3.3, for force fields 54A7 and 54B7 they are listed in Tab. 3.18.

PROMD and MD++ read in values for $k_n^{(\theta)}$, $k_n^{(\theta,h)}$ and θ_n^0 from the BONDANGLEBENDTYPE block in the molecular topology file ($*$.top), also if the BONDANGLETYPE block is given as well. If the BONDANGLETYPE block is given in the topology instead of the BONDANGLEBENDTYPE block, only values $k_n^{(\theta)}$ are read in, and use of equations (Eq. 2-17.8) to (Eq. 2-17.10) to calculate covalent-bond angle-bend interaction and forces is not supported.

2.4. Improper dihedral-angle bending force-field term

The potential energy (force-field) term associated with *improper dihedral-angle bending interactions*, *i.e.* typically controlling out-of-plane or out-of-tetrahedron distortions, is the term $\mathcal{V}^{(\xi)}(\boldsymbol{r};\mathbf{s})$ in Eq. 2.3. It is given by

$$\mathcal{V}^{(\xi)}(\boldsymbol{r};\mathbf{s}) = \sum_{n=1}^{N^{(\xi)}} V^{(\xi)}(\xi_n; k_n^{(\xi)}, \xi_n^0) \ , \tag{2.3}$$

where $N^{(\xi)}$ generally corresponds to a subset of all possibly definable improper dihedral angles in the system (see below; note, however, each definable covalent improper dihedral angle is associated with at most one bending term in the GROMOS force field), and $V^{(\xi)}$ is the function describing the potential energy associated with the bending of a single improper dihedral angle. The quantity $\xi_n \doteq \xi_n(\boldsymbol{r})$ represents the value of improper dihedral angle n in the given system configuration, *i.e.* the dihedral angle formed by the four atoms $i \doteq i(n)$, $j \doteq j(n)$, $k \doteq k(n)$ and $l \doteq l(n)$ defining the covalent improper dihedral angle n (minimum-image quadruplet if PBC is applied). The quantities $k_n^{(\xi)}$ and ξ_n^0 represent force-field parameters, force constant and reference improper dihedral-angle, respectively, characteristic for the specific improper dihedral angle n, as encoded by a corresponding *improper dihedral-angle type code* $M_n^{(\xi)}$ *i.e.* one may write $k_n^{(\xi)} \doteq k^{(\xi)}(M_n^{(\xi)},\mathbf{s})$

and $\xi^0_n \doteq \xi^0(M^{(\xi)}_n, \mathbf{s})$. The function $V^{(\xi)}$ is always a *harmonic* function in GROMOS.
The improper dihedral angle definitions can be found in the molecular topology building block files ∗.mtb.

For reasons of ease of analysis, the list of $N^{(\xi)}$ improper dihedral angles is split into two lists, one of improper dihedrals involving hydrogen atoms (defined as having mass atom type code 1, see Tab. 3.1), and one involving the other one involving the other improper dihedrals. These lists are kept in the molecular topology file (Volume 4). The first list contains NQHIH improper dihedral angles involving hydrogen atoms. Five items are stored: IQH, JQH, KQH, LQH[1...NQHIH] are the atom sequence numbers of the atoms forming improper dihedral i-j-k-l as a function of the improper dihedral sequence number n, and ICQH[1...NQHIH] is the improper dihedral type code, denoting the parameters $k^{(\xi)}_n$ and ξ^0_n , as a function of the improper dihedral sequence number n. The list for the improper dihedral angles involving no hydrogen atoms contains corresponding items denoted by IQ, JQ, KQ, LQ, ICQ[1...NQHI]. The force field parameters $k^{(\xi)}_n$ and ξ^0_n for the various types of improper dihedrals are stored in CQ[1...NQTY] and Q0[1...NQTY] as a function of the improper dihedral type code (ICQH or ICQ). They can be found in the interaction parameter files ∗.ifp. For the GROMOS force fields 45A4, 45B4, 54A7 and 54B7 they are listed in Tab. 3.4 (and Tab. 3.19).

2.5. Proper dihedral-angle torsion force-field term

The potential energy (force-field) term associated with *proper dihedral-angle bending interactions*, *i.e.* typically controlling, in balance with non-bonded interactions, the rotational barriers around covalent bonds, is the term $\mathcal{V}^{(\varphi)}(\boldsymbol{r};\mathbf{s})$ in Eq. 2.4. It is given by

$$\mathcal{V}^{(\varphi)}(\boldsymbol{r};\mathbf{s}) = \sum_{n=1}^{N^{(\varphi)}} V^{(\varphi)}(\varphi_n; k^{(\varphi)}_n, \varphi^0_n, m^{(\varphi)}_n) \ , \tag{2.4}$$

where $N^{(\varphi)}$ generally corresponds to a subset of all possibly definable proper dihedral angles in the system and $V^{(\varphi)}$ is the function describing the potential energy contribution of the term to the torsion of the corresponding proper dihedral angle. The quantity $\varphi_n \doteq \varphi_n(\boldsymbol{r})$ represents the value of proper dihedral angle n in the given system configuration, *i.e.* the dihedral angle formed by the four atoms $i \doteq i(n)$, $j \doteq j(n)$, $k \doteq k(n)$ and $l \doteq l(n)$ defining the covalent proper dihedral angle n (minimum-image quadruplet if PBC is applied). Note that the sign of the dihedral angle as defined by Eq. 2-5.19 follows the IUPAC-IUB convention**22**, and that the proper dihedral angle is undefined if either $r_{im'} = 0$ or $r_{in'} = 0$. The quantities $k^{(\varphi)}_n$, φ^0_n and $m^{(\varphi)}_n$ represent force-field parameters (force constant, reference dihedral-angle, and multiplicity, respectively; the reference dihedral angle is also called the phase shift; the multiplicity is a positive non-zero integer) characteristic for the specific proper dihedral angle term n, as encoded by a corresponding *proper dihedral-angle type code* $M^{(\varphi)}_n$. Two different expression can be used for the function $V^{(\varphi)}$ in GROMOS (see Sec. 2-5.1.4).

The torsional dihedral angle definitions can be found in the molecular topology building block files ∗.mtb (see Vol. 4). Examples of the special definitions involving sugar or phosphor atoms can be found in the building blocks DADE or NADPH.

PROMD and MD++ read in values for $k^{(\varphi)}_n$, φ^0_n and $m^{(\varphi)}_n$ from the TORSDIHEDRALTYPE block in the molecular topology file (∗.top), also if the DIHEDRALTYPE block is given as well. If the DIHEDRALTYPE is given in the topology instead of the TORSDIHEDRALTYPE, only cos φ_n values (instead of φ_n values) are read in, and use of equations (Eq. 2-17.19) to (Eq. 2-17.21) to calculate dihedral angle torsion interactions and forces is not supported in PROMD.

For reasons of ease of analysis, the list of $N^{(\varphi)}$ torsional dihedral angles is split into two lists, one of dihedrals involving hydrogen atoms (defined as having mass atom type code 1, see Table Tab. 3.1), and one involving the other dihedrals. These lists are kept in the molecular topology file (Vol. 4). The first list contains NPHIH dihedral angles involving hydrogen atoms. Five items are stored: IPH, JPH, KPH, LPH[1..NPHIH] are the atom sequence numbers of the atoms forming dihedral i-j-k-l as a function of the dihedral sequence number n, and ICPH[1..NPHIH] is the dihedral type code, denoting the parameters $k^{(\varphi)}_n$, φ^0_n and $m^{(\varphi)}_n$, as a function of the dihedral sequence number n. The list for the dihedrals involving no hydrogen atoms contains corresponding items denoted by IP, JP, KP, LP, ICP[1..NPHI]. The force field parameters $k^{(\varphi)}_n$, φ^0_n and $m^{(\varphi)}_n$ for the various types of torsional dihedrals are stored in CP[1..NPTY], NP[1..NPTY] and PD[1..NPTY] as a function of the torsional dihedral type code (ICPH or ICP). They can be found in the interaction parameter files ∗.ifp. For the GROMOS force fields 45A4 and 45B4, they are listed in Tab. 3.5, for the GROMOS force fields 54A7 and 54B7, they are listed in Tab. 3.20.

As an additional feature in MD++, the specification at so-called cross-dihedral terms is supported. The corresponding expression for this type of interaction reads

$$\begin{aligned} V^{trig,cross}(\mathbf{r};s) &= \sum_{n=1}^{N_c} V_n^{\;trig,cross}\;(\varphi_n;\psi_n;K_{c_n};\delta_n;m_n) \\ &= \sum_{n=1}^{N_c} K_{c_n}\;[1+\cos\;(m_n(\varphi_n+\psi_n)-\delta_n)] \end{aligned} \tag{2.5}$$

The summation runs over the set of $n = 1, \ldots, N_c$ of coupled dihedral angles φ_n and ψ_n, as specified by atoms a-b-c-d and e-f-g-h, respectively, which are specified in the CROSSDIHEDRALH and CROSSDIHEDRAL blocks in the molecular topology file (∗.top). These blocks specify coupled dihedral angles that do involve hydrogens and do not involve hydrogens, respectively. In addition, the type of cross-dihedral term n is specified in the same blocks in the topology file, defining the force constant K_{c_n}, phase-shift δ_n and multiplicity m, as read from the TORSDIHEDRALTYPE block in the molecular topology file. Accordingly, the specification of cross-dihedral terms is only possible if the TORSDIHEDRALTYPE block is specified.

The forces on atoms a, b, c, d of dihedral φ_n and atoms e, f, g, h of dihedral ψ_n due to the n-th in (Eq. 2.5) are

$$\begin{aligned} \mathbf{f}_a &= -\frac{\partial V^{\;trig,cross}}{\partial\varphi_n}\frac{\partial\varphi_n}{\partial\mathbf{r}_a} \\ &= K_{c_n} m_n sin(m_n(\varphi_n+\psi_n)-\delta_n)\frac{r_{cb}}{r^2_{mb}}\;\mathbf{r}_{mj} \end{aligned} \tag{2.6}$$

$$\begin{aligned} \mathbf{f}_d &= -\frac{\partial V^{\;trig,cross}}{\partial\varphi_n}\frac{\partial\varphi_n}{\partial\mathbf{r}_d} \\ &= -K_{c_n} m_n sin(m_n(\varphi_n+\psi_n)-\delta_n)\frac{r_{cb}}{r^2_{mb}}\;\mathbf{r}_{nc} \end{aligned} \tag{2.7}$$

$$\begin{aligned} \mathbf{f}_b &= -\frac{\partial V^{\;trig,cross}}{\partial\varphi_n}\frac{\partial\varphi_n}{\partial\mathbf{r}_b} \\ &= \left[\frac{(\mathbf{r}_{ab}\;\cdot\;\mathbf{r}_{cb})}{r^2_{cb}}\;-1\right]\;\mathbf{f}_i\;-\frac{\mathbf{r}_{cd}\;\cdot\;\mathbf{r}_{cb}}{r^2_{cb}}\mathbf{f}_d \end{aligned} \tag{2.8}$$

$$\mathbf{f}_c = -\mathbf{f}_a\;-\mathbf{f}_b\;-\mathbf{f}_d \tag{2.9}$$

$$\begin{aligned} \mathbf{f}_e &= -\frac{\partial V^{\;trig,cross}}{\partial\psi_n}\frac{\partial\psi_n}{\partial\mathbf{r}_e} \\ &= K_{c_n} m_n sin(m_n(\varphi_n+\psi_n)-\delta_n)\frac{r_{gf}}{r^2_{mf}}\;\mathbf{r}_{mf} \end{aligned} \tag{2.10}$$

$$\begin{aligned} \mathbf{f}_h &= -\frac{\partial V^{\;trig,cross}}{\partial\psi_n}\frac{\partial\psi_n}{\partial\mathbf{r}_h} \\ &= -K_{c_n} m_n sin(m_n(\varphi_n+\psi_n)-\delta_n)\frac{r_{gf}}{r^2_{ng}}\;\mathbf{r}_{ng} \end{aligned} \tag{2.11}$$

$$\begin{aligned}\mathbf{f}_f &= -\frac{\partial V^{\ trig,cross}}{\partial \psi_n}\frac{\partial \psi_n}{\partial \mathbf{r}_f} \\ &= \left[\frac{(\mathbf{r}_{ef}\ \cdot\ \mathbf{r}_{gf})}{r_{gf}^2}\ -1\right]\ \mathbf{f}_e - \frac{(\mathbf{r}_{gh}\ \cdot\ \mathbf{r}_{gf})}{r_{gf}^2}\mathbf{f}_h\end{aligned} \tag{2.12}$$

$$\mathbf{f}_g = -\mathbf{f}_e\ -\mathbf{f}_f\ -\mathbf{f}_h \tag{2.13}$$

where

$$\mathbf{r}_{mb} = \mathbf{r}_{ab}\ \times\ \mathbf{r}_{cb} \tag{2.14}$$
$$\mathbf{r}_{nc} = \mathbf{r}_{cb}\ \times\ \mathbf{r}_{cd} \tag{2.15}$$
$$\mathbf{r}_{mf} = \mathbf{r}_{ef}\ \times\ \mathbf{r}_{gf} \tag{2.16}$$
$$\mathbf{r}_{ng} = \mathbf{r}_{gf}\ \times\ \mathbf{r}_{gh} \tag{2.17}$$

and

$$sin(m_n(\varphi_n + \psi_n) - \delta_n) = \sqrt{1 - cos^2(m_n(\varphi_n + \psi_n) - \delta_n)} \tag{2.18}$$

2.6. Non-Bonded Interactions

The term in the interaction function that represents the *non-bonded interaction* is a sum of contributions from van der Waals and electrostatic interactions,

$$\begin{aligned}&V^{nonb}(\mathbf{r}^{\mathbf{N}}; s) = \\ &\sum_{\substack{nonbonded\\ pairs(i,j)}} \{V^{LJ}(r_{ij}; C_{12}(i,j), C_6(i,j), R_{cp}, R_{cl}) \\ &\qquad +V^{CRF}(r_{ij}; q_i, q_j, R_{cp}, R_{cl}, R_{rf}, \varepsilon_1, \varepsilon_2, \kappa)\}\end{aligned} \tag{2.19}$$

with

$$V^{LJ} = \left[\frac{C_{12}(i,j)}{(r_{ij})^6} - C_6(i,j)\right]\frac{1}{(r_{ij})^6} \tag{2.20}$$

and

$$V^{CRF} = \frac{q_i q_j}{4\pi\varepsilon_0\varepsilon_1}\left[\frac{1}{r_{ij}} - \frac{\frac{1}{2}C_{rf}(r_{ij})^2}{R_{rf}^3} - \frac{1-\frac{1}{2}C_{rf}}{R_{rf}}\right] \tag{2.21}$$

The van der Waals interactions are discussed in Chap. 2-6 and the electrostatic interactions are discussed in Chap. 2-7.

2.6.1. van der Waals parameters. The non-bonded interaction van der Waals parameters C_{12}(i,j) and C_6(i,j) in formula (Eq. 2.19) depend on the atom type or more specifically the integer atom codes I = IAC[i] and J = IAC[j] of the atoms with atom sequence numbers i and j. The integer atom codes of the various types of atoms in the GROMOS force fields 45A5 and 45B4 are listed in Tab. 3.6, for GROMOS force fields 54A7 and 54B7, they are listed in Tab. 3.21.

Lists of integer atom codes are kept in the molecular topology file (Volume 4). For the NRP atoms of the “solute” part of the molecular topology the integer atom codes are stored in IAC[1..NRP]. The integer atom codes of the NRAM solvent atoms are stored in IACS[1..NRAM]. The van der Waals parameters are kept in the molecular topology file (see Volume 4). For the NRATT atom types, C12[1 .. NRATT∗(NRATT+1)/2] contains the coefficient C_{12} in (Eq. 2.19) as a function of the occurring pair codes; the sequence of atom pairs with integer atom codes ranging from 1 to NRATT is:

1-1, 1-2, 2-2, ..., 1-NRATT, 2-NRATT, ..., NRATT-NRATT.

The coefficients C_6 in (Eq. 2.19) are kept likewise in C6[1 .. NRATT∗(NRATT+1)/2]. In this way it is possible to change the van der Waals interaction between each pair of atom types independently. Basically, the GROMOS van der Waals parameters for an atom pair with integer atom codes I and J are derived from single atom van der Waals parameters using the relations

$$C_6(I,J) = \sqrt{C_6^{\frac{1}{2}}(I,I)C_6^{\frac{1}{2}}(J,J)} \tag{2.22}$$

and

$$C_{12}(I,J) = \sqrt{C_{12}^{\frac{1}{2}}(I,I)C_{12}^{\frac{1}{2}}(J,J)} \tag{2.23}$$

For the GROMOS force fields 45A4 and 45B4, the single atom van der Waals parameters $(\mathrm{C6(I,I)})^{1/2}$ and $(\mathrm{C_{12}(I,I)})^{1/2}$ are given in the third and fourth column of Tables Tab. 3.7 and Tab. 3.8 as a function of integer atom code or non-bonded atom type. For the GROMOS force fields 54A7 and 54B7, they are given in the third and fourth column of Tables Tab. 3.22 and Tab. 3.23.

GROMOS also offers a possibility to specify the van der Waals parameters for a specific atom pair, thereby overruling the interaction parameters as derived from the normal (or third-neighbour) interaction parameters. This can be done by introducing a LJEXCEPTIONS block in the molecular topology file (see Vol. 4).

2.6.2. Atomic Charges and Charge Groups. Lists of atomic charges are kept in the molecular topology file (see Volume 4). For the NRP atoms in the “solute” part of the molecular topology atomic charges are stored in CG[1..NRP] (multiplied by $(4\pi\varepsilon_0)^{-1/2}$). The atomic charges of the NRAM solvent atoms are stored in CGS[1..NRAM] (multiplied by $(4\pi\varepsilon_0)^{-1/2}$).

When the (partial) atomic charges of a group of atoms add up to exactly zero, the leading term of the electrostatic interaction between two such groups of atoms is of dipolar ($1/\mathrm{r}^3$) character. The sum of the 1/r monopole contributions of the various atom pairs to the group-group interaction will be zero. Therefore, the range of the electrostatic interaction can be considerably reduced when atoms are assembled in so-called charge groups, which have a zero net charge, and for which the electrostatic interaction with other (groups of) atoms is either calculated for all atoms of the charge group or for none.

The GROMOS force fields make use of this *concept of charge groups*. The atoms that belong to a charge group are chosen such that their partial atomic charges add up to zero. For groups of atoms with a total charge of $+e$ or $-e$, like the sidechain atoms of Arg or Asp, the partial atomic charges of the charge group may add up to $+e$ or $-e$. In GROMOS, the non-bonded interactions are calculated between charge groups only. When a cut-off radius is used, the distance between two charge groups must be defined. The *position of a charge group* is defined differently for a charge group belonging to the “solute” part of the molecular topology and one in the “solvent” part of the molecular topology.

- The position of a “solute” charge group is taken to be its centre of geometry:

  $$R_{cg} = \sum_{i=1}^{N_{cg}} \mathbf{r}_i \; / N_{cg} \tag{2.24}$$

  where the number of atoms belonging to the charge group is denoted by N_{cg}.
- The position of a “solvent” charge group is taken to be the position of the first atom of a solvent molecule. A “solvent” molecule may only contain one charge group.

Since each solvent molecule consists of one charge group, the “solvent” part of the molecular topology file does not need to contain information on “solvent” charge groups. In the “solute” part of the molecular topology file the charge group information is kept in the following way. It is assumed that atoms belonging to one charge group have sequential atom sequence numbers. The last atom of any charge group is denoted by a charge group code value of 1. All other atoms have a charge group code value of 0. This requirement of atoms of a charge group to have sequential atom sequence numbers is a less elegant restriction to choosing the atom sequence when defining molecular topology building blocks or molecular topologies (see Vol. 4).

The atomic charges and charge group definitions for the GROMOS force fields are given in the molecular topology building block files ∗.mtb (Chap. 3). The atomic charges and charge group definitions for amino acid residues, various solvents and nucleotides of the 45A4 and 45B4 GROMOS force fields are listed in Tables Tab. 3.12-Tab. 3.16. For the GROMOS force fields 54A7 and 54B7 they are listed in Tables Tab. 3.27-Tab. 3.31.

The charges for the B-versions of the force field are given between parentheses. The atoms for which no changes are listed have zero partial charge and form single atom or multiple atom charge groups.