ATTEMPTS TOWARD THE AUTOMATED CHEMICAL SYNTHESIS OF BRANCHED OLIGORIBONUCLEOTIDES pdf

1: Computational chemistry - Wikipedia

NucleicAcids Research, , Vol. 20, No. 24 Solid-phase synthesis of branched oligoribonucleotides related to messenger RNAsplicing intermediates Masad www.enganchecubano.com, Kanjana Ganeshan.*

How to Cite Abstract Oligonucleotides are usually prepared in lab scale on a solid support with the aid of a fully automated synthesizer. Scaling up of the equipment has allowed industrial synthesis up to kilogram scale. In spite of this, solution-phase synthesis has received continuous interest, on one hand as a technique that could enable synthesis of even larger amounts and, on the other hand, as a gram scale laboratory synthesis without any special equipment. The synthesis on a soluble support has been regarded as an approach that could combine the advantageous features of both the solution and solid-phase syntheses. The critical step of this approach is the separation of the support-anchored oligonucleotide chain from the monomeric building block and other small molecular reagents and byproducts after each coupling, oxidation and deprotection step. The techniques applied so far include precipitation, extraction, chromatography and nanofiltration. As regards coupling, all conventional chemistries, viz. Several of protocols developed for the soluble-supported synthesis allow the preparation of both DNA and RNA oligomers of limited length in gram scale without any special equipment, being evidently of interest for research groups that need oligonucleotides in large amounts for research purposes. However, none of them has really tested at such a scale that the feasibility of their industrial use could be critically judged. The coupling reaction may take place either at oxidation level III or V of phosphorus. General principle of oligonucleotide synthesis. Alternative coupling methods used in the synthesis of oligonucleotides. Jump to Scheme 1 To achieve coupling, phosphoramidites are activated with azoles [6] , such as tetrazole [7] , its derivatives 2-ethyl- and 2-benzylthiotetrazole [8] or 4,5-dicyanoimidazole [9]. The activator has a dual role donating a proton to the departing dialkylamino group and attacking as an anionic species on phosphorus [10]. Nucleoside H-phosphonates are, in turn, converted in situ to reactive mixed anhydrides with acyl chlorides or chlorophosphates []. On applying the phosphoramidite chemistry, the phosphite triesters obtained are oxidized to phosphate triesters in each coupling cycle, whereas the H-phosphonate diesters may be stable enough to become oxidized only at the end of chain assembly. Compared to oligodeoxyribonucleotides ODNs , the synthesis of oligoribonucleotides ORNs is complicated by the presence of an additional nucleophilic functionality, viz. For this purpose, numerous protecting groups have been proposed [18,19] , the fluoride ion labile tert-butyldimethylsilyl TBDMS [20] and triisopropylsilyloxymetyl TOM [21] groups being most widely used. Otherwise, the synthetic strategies are similar to those of ODNs. Since then, this solid-supported phosphoramidite chemistry has almost exclusively used for the preparation of oligonucleotides from lab scale [3,22] to industrial synthesis up to kilogram scale [23]. In spite of the obvious success of this methodology, synthesis in solution phase has received continuous interest as an alternative for large-scale synthesis, and the recent advances in the development of therapeutic oligonucleotides targeting either pre-mRNA [24,25] , mature mRNA [] or noncoding microRNA [29,30] have even increased this interest. It has been repeatedly argued that i the synthesis in solution could be carried out with a smaller excess of building blocks, ii the scale up procedure would be more straightforward and iii expensive solid support material is not needed. In addition, the possibility to characterize the growing chain by mass or NMR spectroscopy after each coupling is an attractive feature, although not possible with all soluble supports. While major advances in the large scale solid-phase technology have been taken, the difference in the consumption of building blocks in solution and on a solid-support is not necessarily as substantial as previously assumed; the phosphoramidite-chemistry-based synthesis has been optimized to the level that building blocks are required only in a moderate excess, 1. The obvious challenge is the separation of the support-anchored ON chain from small molecular reagents after each coupling cycle, a step that on a solid-support can be carried out by simple washing. Precipitation, chromatography, extraction and nanofiltration have been considered to be feasible approaches. Even if the synthesis on a soluble support fails

to compete with industrial solid-phase synthesis, it may still play an important role in up to gram scale laboratory synthesis, since no special equipment is usually needed. Spectroscopic studies on structure, dynamics and recognition of ONs by other biopolymers, small molecules or metal complexes, for example, may consume ONs in amounts that cannot be conveniently reached by lab-scale solid-phase synthesizers. In addition to synthesis on a soluble support, impressive examples of classical convergent synthesis [] and exploitation of solid-supported reagents in solution [35,36] have been reported. The present review, however, surveys only the progress of ON synthesis on a soluble support. Review Synthesis of oligodeoxyribonucleotides by phosphotriester chemistry The pioneering syntheses of ONs on a soluble support were carried out by the phosphotriester strategy. Although this coupling chemistry is seldom used on a solid support where small molecule reagents and wastes can be removed by simple washing, the avoidance of the oxidation step due to use of P V synthons markedly simplifies the coupling cycle. This is a marked advantage in case of solution synthesis where the excess of reagents and wastes must be removed by a more laborious technique. The first synthesis of a reasonably long ODN, viz. Evidently, the MSNT activation had resulted in displacement of O6 by the 3-nitro-1,2,4-triazolyl group [38]. The oligomer was released from the support and deprotected by successive treatments with syn-pyridinecarbaldoxime and tetramethylguanidine in aq dioxane [39] and aq ammonia, and purified by ion-exchange chromatography on DEAE cellulose. Jump to Scheme 2 To avoid the modification of dGibu during the MSNT treatment, activation by 1-hydroxybenzotriazole, as originally introduced by Marugg et al. Otherwise, the protocol was similar to the previous one. No base modification reactions were now detected. Owing to the symmetrical structure of the support, NMR and mass spectroscopic characterization is possible at any stage of the chain assembly. Detritylation was catalyzed with HCl in a 1: Precipitations were achieved by fold dilution with MeOH. All small-molecule compounds remained in solution. Removal of the 2-chlorophenyl protections with the tetramethylguanidium salt of E nitrobenzaldoxime in aqueous dioxane, followed by ammonolysis, removal of the support by precipitation and conversion to the sodium salt, completed the synthesis. The advantages of such a tetrapodal support appear to be good atomic economy, i. However, only short oligomers have been so far prepared on this support. Support loaded with longer fully protected oligomers may precipitate less quantitatively or interchain aggregation may reduce the coupling efficiency. Synthesis of ODNs on a precipitative tetrapodal support by phosphotriester chemistry using 1-hydroxybenzotriazole activation [42]. Synthesis of ODNs on a precipitative tetrapodal support by phosphotriester chemistry using 1-hydrox Such phosphoramidites are widely used for the assembly of ODNs useful in protein engineering by oligonucleotide directed mutagenesis []. Silica gel chromatographic purification and conventional phosphitylation with 1-chloro 2-cyanoethoxy -N,N-diisopropylphosphoramidite gave the desired building blocks, the applicability of which in a solid-phase synthesis was demonstrated [45]. Synthesis of oligodeoxyribonucleotides by phosphoramidite chemistry As mentioned above, phosphoramidite chemistry is nowadays the method of choice for the solid-supported synthesis of oligonucleotides both in small and large scale. The first attempt to apply the phosphoramidite chemistry to synthesis on a soluble support dates back to Both the support PEG and overall strategy of chain assembly were in this pioneering study of Bonora et al. In other words, the support-bound material was separated from the low molecular weight substances by precipitation from Et2O and recrystallization from a mixture of MeCN and Et2O. Phosphite triesters were oxidized to phosphate triesters after each coupling with tert-butyl hydroperoxide in MeCN [52]. Jump to Scheme 4 The essentially same approach was later applied to the synthesis of a PEG-conjugated mer antisense ODN [53] and a mer purine-rich triple-helix forming sequence [54]. The Fmoc protecting group was first removed and the peptide was assembled on the exposed amino function. Since the peptide moiety did not contain acid labile side chain protections, the oligonucleotide sequence could then be assembled by the protocol discussed above. Another precipitative support that has been used for the synthesis of ODNs is the tetrapodal tetrakis-O-[4- azidomethyl phenyl]pentaerythritol-derived support discussed above [43]. Two precipitations from MeOH were carried out in each coupling cycle: The detritylation was carried out with HCl in a 1: The acid was neutralized with slight

excess of pyridine. Couplings were carried out in a 1: The resulting phosphite triesters were converted to phosphate esters by conventional aq iodine oxidation. Precipitation by dilution with MeOH removed all traces of reagents and monomeric nucleoside derivatives. Release and deprotection of the oligomer by conventional ammonolysis were accompanied by precipitation of the support. Synthesis of ODNs on a precipitative tetrapodal support by conventional phosphoramidite chemistry [43]. Jump to Scheme 5 Besides precipitation, extraction offers a possible approach for the separation of the soluble-supported oligonucleotides from small molecular materials. The underlying idea is to keep the growing oligonucleotide chain sufficiently hydrophobic to enable removal of the excess of building blocks, activators and wastes by water extraction, but still allow removal of highly hydrophobic substances, above all DMTrOMe, by extraction with very nonpolar solvents. After HCl catalyzed detritylation in a 6: The polar phase was concentrated, diluted with a 5: Standard base moiety protections dABz, dCBz, dGibu were employed, with the exception of thymine, which was used as a 3-pivaloyloxymethyl derivative to ensure sufficient hydrophobicity. Synthesis of ODNs by an extractive strategy on an adamantylacetyl support [57]. The support precipitates from a 1: The couplings were carried out with 1. Unreacted phosphoramidites were quenched by EtOH and the support was precipitated before the oxidation step, repeatedly when needed. The precipitate was dissolved in MeCN and conventional aq I2 oxidation was performed. After bisulfite quenching, the mixture was diluted with chloroform and washed with water to remove salts. The product was, however, still partly tritylated, and the detritylation had therefore to be repeated. The longest oligomer synthesized was a thymidine tetramer. Synthesis of ODNs by a combination of extractive and precipitative strategy [58]. Jump to Scheme 7 Although chromatographic separation appears to be a tedious procedure compared to precipitation or extraction, it has been successfully applied to the synthesis of ODNs on a soluble support. Owing to poor solubility of the support into MeCN, elongation of the branches by tetrazole promoted coupling of nucleoside phosphoramidites was carried out in pyridine under argon. The mixture was concentrated and subjected to gel permeation chromatography in MeOH to remove the low molecular weight compounds. The pooled fractions containing the support-bound oligonucleotides were concentrated and oxidized with tert-butyl hydroperoxide. The excess of oxidizing agent was removed by coevaporation with THF and MeOH, and the residue was dissolved into an After neutralization with Et3N, the chromatographic separation was repeated. Conventional ammonolysis was used for the release from the support. Assembly from dimeric phosphoramidites was additionally attempted, but the chromatographic separation was not efficient enough to remove the excess of the dimeric building block. Synthesis of ODNs by phosphoramidite chemistry on a N1,N3,N5-tris 2-aminoethyl benzene-1,3,5-tricarboxamide support by making use of chromatographic separation [59]. The 1-methoxymethylethyl group may be removed by acid-catalyzed methanolysis approximately as readily as the DMTr group, but it gives only volatile products. The subsequent flash chromatographic purification was, in turn, rather straightforward owing to the hydrophobic support. After ammonolytic release and deprotection, the methylated cyclodextrin support could be removed by simple extraction with DCM. Synthesis of oligoribonucleotides by the phosphoramidite chemistry Three different protocols, all based on separation of the support-bound oligonucleotide from low-molecular weight compounds by precipitation, have been utilized for the synthesis of oligoribonucleotides by phosphoramidite chemistry. After completion of the coupling, oxidation to the phosphate ester was carried out in the same pot by addition of 2-butanone peroxide in DCM. Dilution with MeOH precipitated the support. With 15â€”mer oligomers, some support-bound material, however, remained in solution and was recovered by adsorption to Ccoated silica gel. Cleavage and deprotection was conventional:

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2: Synthesis of oligonucleotides on a soluble support

This paper describes the full detail of the chemical synthesis of branched oligoribonucleotides by use of appropriately protected adenosine 2',3'-diphosphate derivatives (13 and 30), as key.

Every effort has been made to ensure the accuracy of the following information. Should you find any errors please contact us via e-mail at: Isomerization of tert-butyldimethylsilyl protecting groups in ribonucleosides. Journal of Photochemistry and Photobiology. Nucleosides, Nucleotides and Nucleic Acids. Canadian Journal of Microbiology. Antimicrobial Agents and Chemotherapy. Preparation and rearrangement of 6-methoxyglyceropurines. Canadian Journal of Chemistry. Methods in Molecular Biology. Nucleic Acids Symposium Series. Treatment with 9- [2-hydroxy hydroxymethyl ethoxy]methyl guanine. Journal of Organic Chemistry. Journal of the American Chemical Society. Journal of Chromatography A. Sources of error in the quantitative analysis of alkylsilyl derivatives of nucleosides. A comparison of condensing agents in the coupling of silybted ribonucleosides. The mass spectra of pyrimidine 2,2-anhydronucleosides and their derivatives. Pure and Applied Chemistry. Biochimica et Biophysica Acta. A comparison of protecting groups in the dichloridite procedure. Journal of the Chemical Society - Chemical Communications. Journal of the Chemical Society D: Research Triangle Park, N. Nucleosides, nucleotides, and their biological applications: Journal of Medicinal Chemistry. Advances in Mass Spectrometry. Developments in syntheses of oligodeoxyribonucleotides and their organic derivatives. Comparisons between the mass spectra of 3,5-substituted, isomeric pairs of 2,2-anhydrouridines. Biochemical and Biophysical Research Communications. Biochemical and biophysical research communications. Harry Steenbock Symposium 4th: Nucleic acid structure and conformation and protein-nucleic acid interactions: European Journal of Biochemistry. The use of silyl protecting groups in nucleoside and nucleotide chemistry. Synthesis of a ribozyme sequence. Journal of carbohydrates, nucleosides, nucleotides. Negative ions of subunits in the stepwise synthesis of a heptaribonucleotide. Fundamental and Applied Toxicology. Atlantic Institute for Market Studies; vi, 39 p. Negative ions of dinucleoside monophosphates. Advances in mass spectrometry. The synthesis of a hexadecamer by a block condensation approach. Synthesis of oligothymidylates via phosphotriester intermediates. Journal of Heterocyclic Chemistry. American Journal of Veterinary Research. Drugs of the Future.

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3: USA1 - Cationic sirnas, synthesis and use for rna interference - Google Patents

Synthesis of segment A (Fig. 4, step I) was performed using the standard procedure of automated RNA synthesis. The branching nucleotide was incorporated with small changes to the standard protocol. The branching nucleotide was incorporated with small changes to the standard protocol.

The process is particularly suited to the large scale synthesis of nucleotides. The acetonitrile may be removed from the solid support by one or both of drying and by washing with solvents. Preferred washing solvents comprise trialkylamines. These applications, in their entirety, are incorporated herein by reference. Much of the work has been carried out on a micromolar or even smaller scale, and automated solid phase synthesis involving monomeric phosphoramidite building blocks Beaucage, S. Indeed, high molecular weight DNA and relatively high molecular weight RNA sequences can now be prepared routinely with commercially available synthesisers. These synthetic oligonucleotides have met a number of crucial needs in biology and biotechnology. Whereas milligram quantities have generally sufficed for molecular biological purposes, gram to greater than gram quantities are required for clinical trials. Several oligonucleotide analogues that are potential antisense drugs are now in advanced clinical trials. If, as seems likely in the very near future, one of these sequences becomes approved, say, for the treatment of AIDS or a form of cancer, kilogram, multikilogram or even larger quantities of a specific sequence or sequences will be required. Many of the oligonucleotides currently of interest in the phamaceutical industry are analogues of natural oligonucleotides which comprise phosphorothioated-internucleoside linkages. A large number of protocols for the synthesis of oligonucleotides employ acetonitrile as a solvent for the reagents employed. Acetonitrile is attractive as a solvent because it is inert towards the reagents and oligonucleotide product, it has good solvation properties and is environmentally acceptable. Commonly, for large-scale syntheses, a high concentration of acetonitrile is present during the stage when the oligonucleotide product is cleaved from the solid support. Hitherto, this has been acceptable for large scale synthesis because of the perceived inert nature of acetonitrile. However, during the course of the studies resulting in the present invention, it has now been surprisingly found that higher purity oligonucleotides can be obtained by reducing the concentration of acetonitrile present during the cleavage stage. The phosphorothioate oligonucleotides can be assembled by known techniques for solid phase synthesis, for example using H-phosphonate or particularly phosphoramidite chemistry. For the phosphoramidite approach, commonly, the sequence employed is: This cycle is then repeated as often as is necessary to assemble the desired sequence of the oligonucleotide. On completion of the assembly, and prior to cleavage from the support, the supported oligonucleotide is commonly washed with acetonitrile in order to remove traces of unreacted reagents. Acetonitrile can be removed by drying of the supported oligoncleotide, optionally under reduced pressure. The process according to the first aspect of the present invention is employed for large scale synthesis of oligonucleotides. Large scale synthesis of oligonucleotides is often regarded as being at or above a batch size of 10 mmol oligonucleotide, commonly at or above 15 mmol, often at or above 25 mmol, for example greater than 50 mmol, and especially greater than 75 mmol of oligonucleotide. In many embodiments, the process of the present invention is employed for oligonucleotide synthesis at a scale in the range of from â€” mmol. On completion of the assembly of the desired product, the product may be cleaved from the solid support. Cleavage methods employed are those known in the art for the given solid support. When the product is bound to the solid support via a cleavable linker, cleavage methods appropriate for the linker are employed, for example, contact with methylamine, aqueous methylamine solution, liquified ammonia, gaseous ammonia and particularly contact with concentrated aqueous ammonia solution. Following cleavage, the product can be purified using techniques known in the art, such as one or more of ion-exchange chromatography, reverse phase chromatography, and precipitation from an appropriate solvent. Further processing of the product by for example ultrafiltration may also be employed. Solid supports that are employed in the process according to the present invention are substantially insoluble in the solvent

employed, and include those supports well known in the art for the solid phase synthesis of oligonucleotides. Examples include silica, controlled pore glass, polystyrene, copolymers comprising polystyrene such as polystyrene-poly ethylene glycol copolymers and polymers such as polyvinylacetate. Additionally, microporous or soft gel supports, especially poly acrylamide supports, such as those more commonly employed for the solid phase synthesis of peptides may be employed if desired. Preferred poly acrylamide supports are amine-functionalised supports, especially those derived from supports prepared by copolymerisation of acryloyl-sarcosine methyl ester, N,N-dimethylacrylamide and bis-acryloylethylenediamine, such as the commercially available Polymer Laboratories support sold under the catalogue name PL-DMA. The procedure for preparation of the supports has been described by Atherton, E. A Practical Approach, Publ. The functional group on such supports is a methyl ester and this is initially converted to a primary amine functionality by reaction with an alkyl diamine, such as ethylene diamine. According to a second aspect of the present invention, there is provided a process for the synthesis of phosphorothioate oligonucleotides which comprises: The washing regime employs one or more solvent washes. When the washing regime comprises a single wash, the solvent employed is free from acetonitrile and dioxane. When more than one solvent wash is employed, acetonitrile and dioxane may be employed in the wash stages other than the final wash. However, it is preferred that acetonitrile and dioxane are not employed in any stage of the washing regime. Solvents which can be employed are preferably inert solvents which do not degrade the oligonucleotide under the conditions under which the solvent is employed. Examples of inert solvents that can be employed include inert organic solvents and inert aqueous solvents. Organic solvents which can be employed include aromatic hydrocarbons, for example toluene; aliphatic hydrocarbons, for example cyclohexane; haloalkanes, particularly dichloromethane; esters, particularly alkyl esters such as ethyl acetate and methyl or ethyl propionate; alcohols, particularly aliphatic alcohols such as C alkyl alcohols, for example methanol, ethanol or isopropanol; amides, such as dimethylformamide and N-methylpyrollidinone; basic, nucleophilic solvents such as pyridine or alkylamines, especially tri alkyl , such as tri Calkyl amines; polar ethers such as tetrahydrofuran; and sulphoxides, for example dimethylsulphoxide. Aqueous solvents that can be employed include water, aqueous buffer solutions, mixtures of water and water miscible inert organic solvents, especially those solvents described above. Solid supports that may be employed are those described with the respect to the first aspect of the present invention. In many embodiments, it may be preferred to employ an organic solvent when the support is hydrophobic, such as poly styrene. In other embodiments, it may be preferred to employ an aqueous solvent when the support is hydrophilic, such as controlled pore glass or silica. In further embodiments, when the support is microporous, it may be preferred to employ a solvent which swells the support. In certain preferred embodiments, the solvent employed serves to remove protecting groups from the oligonucleotide, particularly betacyanoethyl protecting groups from the internucleotide linkages, and nucleobase protecting groups. Preferred solvents are alkylamines, especially tri alkyl amines, such as tri Calkyl amines, and most preferably triethylamine. The oligonucleotides can be assembled, and after washing, cleaved from the solid support, by the methods described above in respect of the first aspect of the present invention. An especially preferred embodiment of the present invention comprises assembling an oligonucleotide bound to a solid support in the presence of acetonitrile, air drying the supported oligonucleotide, contacting the dried supported oligonucleotide with a trialkylamine, preferably triethylamine, for sufficient time to deprotect the oligonucleotide, and subsequently cleaving the oligonucleotide from the solid support. In a related embodiment of the present invention, there is provided a process for the synthesis of phosphorothioate oligonucleotides which comprises: One or more solvent washes may be employed. It is preferred that acetonitrile is not employed in any of the solvent washes. The synthesis of oligonucleotides using phosphoramidite chemistry wherein the oilgonucleotide is synthesised supported on a microporous support is believed to be novel. Accordingly, in a third aspect of the present invention, there is provided a process for the preparation of an oligonucleotide which comprises coupling a nucleoside or oligonucleotide phosphoramidite with a nucleoside or oligonucleotide comprising a free hydroxy group supported on a solid

support to form an oligonucleotide phosphite triester, characterised in that the solid support is a microporous support. Microporous supports are preferably poly acrylamide supports, such as those more commonly employed for the solid phase synthesis of peptides, may be employed if desired. The functional group on amine-functionalised supports is a methyl ester and this is initially converted to a primary amine functionality by reaction with an alkyl diamine, such as ethylene diamine. The microporous supports are preferably employed in the form of polymeric beads. The process according to the third aspect of the present invention is preferably carried out in the presence of a solvent which swells the microporous support. Examples of such solvents include haloalkanes, particularly dichloromethane; esters, particularly alkyl esters such as ethyl acetate and methyl or ethyl propionate; ethers such as tetrahydrofuran; and preferably amides, such as dimethylformamide and N-methylpyrollidinone. The most preferred solvent is dimethylformamide. Commonly, the phosphoramidite is a betacyanoethyloxy phosphoramidite. Preferred protecting groups are pixyl and trityl, especially dimethoxytrityl, groups. The nucleoside or oligonucleotide comprising a free hydroxy group is commonly bound to the solid support via a cleavable linker. The coupling of the nucleoside or oligonucleotide phosphoramidite with a nucleoside or oligonucleotide comprising a free hydroxy group takes place in the presence of a suitable activator. Examples of such activators are those known in the art for conventional phosphoramidite oligonucleotide synthesis, and include tetrazole, thioethyltetrazole, nitrophenyltetrazole and dicyanoimidazole. Commonly, the nucleoside or oligonucleotide phosphoramidite is employed as a solution in the solvent employed to swell the microporous support. Advantageously, the phosphoramidite solution is mixed with the swollen support comprising the free hydroxy group prior to addition of the activator as a solution in the solvent employed to swell the microporous support. The oligonucleotide phosphite triester produced in the process of the third aspect of the present invention is commonly oxidised or sulphurised to form an oligonucleotide phosphate or phosphorothioate. Oxidising agents employed are those known in the art for conventional phosphoramidite oligonucleotide synthesis, and include iodine and t-butylhydroperoxide. Sulphurising agents employed are those known in the art for conventional phosphoramidite oligonucleotide synthesis, and include xanthane hydride, phenylacetyl disulphide and Beaucage reagent. The oxidising or sulphurising agents are commonly employed as a solution in the solvent employed to swell the microporous support. A capping treatment, employing capping agents known in the art, for example a mixture of pyridine and acetic anhydride and a mixture of pyridine and N-methylimidazole, may be employed. Advantageously, the capping agents are employed in the presence of the solvent employed to swell the microporous support. Preferably, the dichloroacetic acid is employed as a solution in the solvent employed to swell the microporous support, for example dichloromethane or advantageously and amide, particularly dimethylformamide or N-methylpyrrolidinone. Removal of the pixyl or trityl protecting groups produces a free hydroxyl group which can then be employed for further coupling. Further couplings can be carried out in order to assemble the desired sequence. On completion of the assembly of the desired sequence, the product can be cleaved from the solid support using techniques appropriate to the linker employed. The processes according to the present invention can be employed to synthesise phosphorothioated deoxyribonucleotides and ribonucleotides. The nucleotides may comprise bases, protecting groups and other modifications known in the nucleotide art. Other bases which may be present include hypoxanthine, inosine and 2,6-diaminopurine. Protecting groups which may be present include base-protecting groups, such as benzyl, acetyl, phenoxyacetyl and isobutyryl groups, and hydroxy-protecting groups, such as pixyl and trityl, especially dimethoxytrityl, groups. Other modifications, including inverted nucleosides, abasic nucleosides and L-nucleosides may also be present. In many embodiments, the processes of the present invention are employed to prepare oligonucleotides having from 1 to , often from 5 to 75, preferably from 8 to 50 and particularly preferably from 10 to 30 internucleoside linkages. Examples of cleavable linkers that may be employed in the processes of the present invention include those well known in the art for the solid phase synthesis of oligonucleotides, such as urethane, oxalyl, succinyl, and amino-derived linkers. Succinyl linkers are preferred. The invention will now be illustrated without limitation by the following examples. The product

was produced trityl-on on a polystyrene support. After completion of the assembly and sulphurisaton, the supported nucleotide was washed with acetonitrile. Three samples of the supported oligonucleotide were treated as follows. For Example 1, the supported oligonucleotide was air dried on a filter funnel. For Example 2, the sample was washed with triethylamine. For Example 3, the sample was washed with 2. In each of Examples 2 and 3, the washing took place on a filter funnel under slightly reduced pressure, but operated so as to minimise evaporation of acetonitrile. The products of Examples 1 to 3 were cleaved using standard ammonolysis conditions using concentrated aqueous ammonia to obtain the oligonucleotide product. For Comparison A, a further sample of the supported oligonucleotide was cleaved under the same conditions, but without a drying or washing treatment.

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4: Profile - Ogilvie, Kelvin Kenneth

Thesis: Attempts Toward the Automated Chemical Synthesis of Branched Oligoribonucleotides [(c)] Solid-Phase Synthesis of Branched Oligoribonucleotides Related to m-RNA Splicing Intermediates.

However, achieving targeted tissue and cellular delivery, stabilization in vivo, and cost effective large scale synthesis of RNA are significant bottlenecks in the development of RNAi technology. The reality of mainstream RNAi based therapeutics is rapidly approaching and the demand for these compounds on large scale may soon exceed the capability of manufacturers. Methods in Enzymology , ; Alvarado-Urbina, G. Science ,]. The most commonly used group used for this purpose is an acetyl ester. This process is repeated until an oligomer of the desired length and sequence is obtained. Cleavage of the oligomer from the solid support and removal of the protecting groups from the sugars, phosphates and nucleobases provides the desired target oligomer, which is then separated from shorter failure sequences by ion exchange high pressure liquid chromatography HPLC , ion-pair reverse phase HPLC, or polyacrylamide gel electrophoresis PAGE. The full length oligomer is then characterized by mass spectrometry. The same iterative method may be applied toward the synthesis of DNA and RNA oligonucleotides in solution, for example as described recently by Donga et al. The use of ionic soluble supports allows for selective precipitations of the growing oligonucleotide over all other reagents used in the oligonucleotide synthesis cycle. To date, there have been many attempts to design protecting groups and methods that embody the conditions required for the construction of high quality oligoribonucleotides [for reviews, see Beaucage, S. Tetrahedron Letters 15,]. This protecting group is removed at the end of RNA chain assembly in the presence of fluoride ions. Protocols for Oligonucleotides and Analogs: The Humana Press Inc. Tetrahedron Letters 45,]. Silyl isomerization is characteristic of other 0-silyl ether protecting groups. In all cases the synthesis of oligoribonucleotides is an elaborate multistep process, which entails assembly of the oligonucleotide chain typically from monomeric phosphoramidite building blocks e. Nevertheless, there have been several reports describing the synthesis of RNA through block coupling condensation reactions. Pays-Bas, 97, 73]. J, and Ogilvie, K. Solid-phase RNA synthesis is carried out almost exclusively using monomeric phosphoramidite synthons. Given the efficiency of the phosphoramidite chemistry, it is highly desirable to have access to block dimer and trimer phosphoramidites for RNA synthesis, as these would permit longer chain extensions at each step during chain assembly, significantly shortening the time required for synthesis. However, while solid-supported synthesis overcomes the limitation of purification by allowing excess reagents to be washed away, it can be quite restricting in terms of scale. While it is true that current large scale methods of producing oligonucleotides in the kilogram scale utilize solid phase approaches, the mechanical requirements for this type of manufacturing are very specialized and costly. Therefore, an ideal method of large scale synthesis is in solution. In attempts to overcome this limitation, a variety of soluble polymer-based supports have been developed [Gravert, D. They can be selectively removed by perfluorinated solvents. This is a very efficient process, but requires many specialized and expensive materials [Horvath, I. It is also desirable therefore to have improved methods for solution phase RNA synthesis. These building blocks allow longer chain extensions at each coupling stage of RNA synthesis, significantly reducing the total number of steps required in the synthesis of a target RNA oligomer. Additionally, the block coupling strategy disclosed herein produces crude RNA oligomers that are more readily separated from shorter failure sequences. The procedure is illustrated by the synthesis of UpU, ApA, and UpUpU blocks and their use in the assembly of oligoribonucleotide chains via a phosphoramidite coupling method. The disclosed compounds and processes benefit two critical aspects of siRNA manufacturing: In another aspect, methods for the synthesis of blockmer dimer, trimer, tetramer, etc. These building blocks allow longer chain extensions at each coupling stage of DNA synthesis, significantly reducing the total number of steps required in the synthesis of a target DNA oligomer. Additionally, the block coupling strategy disclosed herein produces crude DNA oligomers that are more readily separated from shorter failure

sequences. There are provided herein methods for the synthesis of ionically tagged linkers for, but not limited to, the synthesis of oligoribonucleotides, oligodeoxyribonucleotides, oligopeptides and oligosaccharides, which can be orthogonally cleaved in the presence of all other standard protecting groups. Tag-linker combinations provided herein make it possible to grow oligonucleotides in solution using stepwise iterative couplings, utilizing the ionic properties of the tags to selectively precipitate a growing oligonucleotide at each step, in order to remove coupling reagents and reactants. This can be utilized for, but not limited to, converting an oligomer dimer, trimer, tetramer, etc. Additionally, the block coupling strategy produces crude RNA or DNA oligomers that are readily separable from shorter, undesired sequences that arise during synthesis. It is also envisioned that, in some embodiments, tag linkers can be used in place of standard ester protecting groups, to provide both a mild cleavage alternative as well as a means to selectively precipitate a desired molecule and circumvent the use of costly and time consuming chromatography. In one aspect, there is provided a compound of formula II: In another aspect, there is provided a process for preparing a compound of formula II: In an aspect, there is provided herein an ionic tag linker comprising a gamma ketoester moiety, an ionic moiety and a linker. In one embodiment, the ionic tag linker has the structure of formula K: The linker may be, for example, alkyl, glycol or functionalized alkyl. In some embodiments, alkyl is C1 to C6 alkyl. The ionic moiety may be, for example, an imidazolium or phosphonium group. It should be understood that an ionic moiety in an ionic tag linker of the invention may comprise any salt, such as but not limited to a phosphonium salt, an imidazolium salt, etc. Many salts are known in the art and are within the capacity of a skilled technician. Further non-limiting examples include organic salts comprising a heterocyclic or substituted heterocyclic quaternary nitrogen-containing organic cation, a heterocyclic or substituted heterocyclic quaternary phosphonium containing organic cation, or a heterocyclic or substituted heterocyclic trivalent sulfonium containing organic cation; and an anion balancing the charge on the organic cation. In a more particular embodiment an organic cation is selected from the group consisting of N-substituted pyridine and 1,3-disubstituted imidazole. Other suitable anions could also be used and are well within the capacity of a skilled technician. In an embodiment, an ionic moiety in an ionic tag linker of the invention is a zwitterionic phosphonium salt of Formula I: For example, the zwitterionic phosphonium salt may have the following structure: In an embodiment, a gamma ketoester moiety is cleavable with hydrazine. In another aspect, there is provided herein an ionic tag linker comprising a photolabile moiety, an ionic moiety and a linker. The photolabile moiety may be, for example, a nitrobenzyl derivative. In an embodiment, the ionic tag linker has the structure of formula P: The linker may be alkyl, glycol or functionalized alkyl. The ionic moiety may be an imidazolium or phosphonium group. In one embodiment, the photolabile moiety is cleavable by photolysis. In some embodiments, ionic tag linkers provided herein are orthogonally cleavable. Ionic tag linkers may be selectively cleavable under conditions which do not cleave other oligoribonucleotide or oligodeoxyribonucleotide protecting groups. Ionic tag linkers may also be cleavable under conditions which do not cause isomerisation of, e. In an embodiment, an ionic tag linker is selected from: In another embodiment, an ionic tag linker is selected from: In an embodiment, an ionic tag linker comprises a diethoxy group or a dithiophenyl group. In a particular embodiment, an ionic tag linker comprises a dithiophenyl group and a phosphonium salt. In another embodiment, an ionic tag linker comprises a dithiophenyl group and an imidazolium salt. In yet another embodiment, an ionic tag linker comprises a diethoxy group and a phosphonium salt. In a further embodiment, an ionic tag linker comprises a diethoxy group and an imidazolium salt. In another aspect, there are provided herein compounds of formula II: In an embodiment, n is 1, 2, or 3. In another embodiment, R3 is and R5 is a protecting group. In a still further embodiment, R is isopropyl. In another embodiment, a N-protecting group is selected from levulinyl, acetyl, difluoroacetyl, trifluoroacetyl, isobutyryl, benzoyl, 9-fluorenylmethoxycarbonyl, phenoxyacetyl, dimethylformamidine, and N,N-diphenyl carbamate. In some embodiments, R3 is substituted with an ionic tag linker provided herein. In embodiments, R3 is or a protecting group, and may or may not be substituted with an ionic tag linker provided herein. In another embodiment, the protecting group is a levulinyl group Lev , or is an ionic tag linker

provided herein, e. In another aspect, there are provided herein processes for preparing compounds disclosed herein. In an embodiment, a compound has the structure: In an embodiment, R3 is H. In another embodiment, R3 is a protecting group, and the process further comprises: In an embodiment, the protecting group is a levulinyl Lev group. In another embodiment, the protecting group is an ionic tag linker provided herein. In other embodiments, processes of the invention further comprise phosphitylation of the product of step b or c to form a compound of formula IIa: Processes may also comprise phosphitylation of the product of step d to form a compound of formula IIa: In an embodiment, R1 is TBDMS; R5 is selected from DMTr and MMTr; Rp is selected from methyl Me , 2-cyanoethyl CNEt , ortho-chlorophenyl o-ClPh , and para-chlorophenyl p-ClPh ; R is selected from isopropyl, methyl, and ethyl; and B is a nucleobase protected on at least one nitrogen by a suitable N-protecting group, wherein the N-protecting group is selected from levulinyl, acetyl, difluoroacetyl, trifluoroacetyl, isobutyryl, benzoyl, 9-fluorenylmethoxycarbonyl, phenoxyacetyl, dimethylformamidine, and N,N-diphenyl carbamate. In further aspects, there are provided herein methods for synthesizing an oligomer, the methods comprising: In an embodiment, the oligomer is an oligopeptide, an oligosaccharide or an oligonucleotide. In a particular embodiment, the oligonucleotide is an oligoribonucleotide. In another embodiment, the oligonucleotide is an oligodeoxyribonucleotide. In one embodiment, there is provided a method for synthesizing an oligoribonucleotide, the method comprising: In some embodiments, methods provided herein further comprise a step of isolating an oligomer, oligoribonucleotide or oligodeoxyribonucleotide before cleaving an ionic tag linker from the oligomer, oligoribonucleotide or oligodeoxyribonucleotide. For example, an oligomer, oligoribonucleotide or oligodeoxyribonucleotide may be isolated by precipitation, based on ionic properties of an ionic tag linker. In some embodiments, novel dimer and trimer blocks are provided for the synthesis of RNA or DNA oligonucleotides on solid supports. In another embodiment, a tetramer block is provided.

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Regiospecific Solid-Phase Synthesis of Branched Oligoribonucleotides That Mimic Intronic Lariat RNA Intermediates The Journal of Organic Chemistry Katolik, Johnsson, Montemayor, Lackey, Hart, and Damha.

Advanced Search Abstract CAG repeats occur predominantly in the coding regions of human genes, which suggests their functional importance. In some genes, these sequences can undergo pathogenic expansions leading to neurodegenerative polyglutamine poly-Q diseases. The mutant transcripts containing expanded CAG repeats possibly contribute to pathogenesis in addition to the well-known pathogenic effects of mutant proteins. One of the structures has been determined at atomic resolution 0. The duplexes include non-canonical Aâ€”A pairs that fit remarkably well within a regular A-helix. The main effect on the helix conformation is a local unwinding. The CAG repeats and the previously examined CUG structures share a similar pattern of electrostatic charge distribution in the minor groove, which could explain their affinity for the pathogenesis-related MBNL1 protein. Most of the TREDs are triggered by expanded CAG repeat tracts that occur in protein-coding regions of specific single genes that are transcribed and translated into functionally unrelated proteins. These disorders are also known under the common name of polyglutamine poly-Q diseases because the CAG repeat tracts encode polyglutamine, that results in altered protein structure, shown in numerous studies to be involved in pathogenesis 2 , 3. Over this decade, several authors have proposed that also mutant transcript having expanded CAG repeat may contribute to pathogenesis of polyglutamine diseases 4â€”9. Moreover, it was shown using repeats expressed from suitable genetic constructs that expanded non-translated CAG repeats were capable of triggering neurodegeneration in vivo in the Drosophila eye model of SCA3 8. The CAG repeat tracts composed of six or more repeat units are present in about human genes and these sequences are strongly overrepresented in exons, which suggests their positive selection and functional importance Little is known about physiological roles of CAG repeats in transcripts but their structural characterisation is more advanced. Most of the relevant structural studies have been carried out using biochemical methods on CAG repeats buried in sequence context of mRNAs of genes implicated in poly-Q disease 15â€” Short CAG repeat tracts were shown to be single-stranded, but longer repeats formed fairly stable hairpins in which alternating Aâ€”A interactions occurred between the Gâ€”C and Câ€”G base pairs Also structures formed by pure CAG repeats were compared with those formed by other triplet repeats, using both biochemical 10 , 20 and biophysical 19 , 20 methods. The CAG repeats were shown to form considerably more stable hairpins than CUG repeats of the same length 20 but the specific structural factor responsible for this difference could not be identified. The study addresses the issue of the detailed structure as well as similarities and differences between the CAG and CUG repeat structures. The details of deprotection and purification of oligoribonucleotides were described previously The size of the crystal was 0. X-ray data collection, structure solution and refinement X-ray diffraction data were collected: Although the cell parameters of the two crystal forms were similar, the space groups were different: H and P32 details in Supplementary Data. The program Coot 27 was used for visualisation of electron density maps 2Foâ€”Fc and Foâ€”Fc and for manual rebuilding of the atomic model. During the refinement of the rhombohedral structure, anisotropic temperature factors was implemented and hydrogen atoms were added to the model. The last few cycles were performed using all data, including the Rfree set. The final cycles of the refinement were carried out without stereochemical restraints. The trigonal model was refined using isotropic B-factors and TLS strategy. The helical parameters were calculated using 3DNA All pictures were drawn using PyMOL v0. The accession codes are 3NJ6 and 3NJ7. The second strand of the duplex is symmetry-related via a crystallographic 2-fold axis. In the trigonal structure, the asymmetric unit contains tree duplexes: All the duplexes stack end-to-end, forming semi-infinite columns parallel to the c cell edge. The RNA interacts with ordered water molecules and sulphate anions. The models are summarized in Table 1 and Supplementary Table S1. Crystal lattice interactions are discussed in Supplementary Data.

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6: Oligonucleotide synthesis - Wikipedia

Described is the first automated solid-phase synthesis of a branched oligosaccharide by stepwise assembly from monosaccharides. Cap tetrasaccharide 1, found as part of the cell surface lipophosphoglycan (LPG) of the protozoan parasite Leishmania, was readily prepared using glycosyl phosphate and glycosyl trichloroacetimidate building blocks.

History[edit] Building on the founding discoveries and theories in the history of quantum mechanics , the first theoretical calculations in chemistry were those of Walter Heitler and Fritz London in The books that were influential in the early development of computational quantum chemistry include Linus Pauling and E. With the development of efficient computer technology in the s, the solutions of elaborate wave equations for complex atomic systems began to be a realizable objective. In the early s, the first semi-empirical atomic orbital calculations were performed. Theoretical chemists became extensive users of the early digital computers. A very detailed account of such use in the United Kingdom is given by Smith and Sutcliffe. For diatomic molecules, a systematic study using a minimum basis set and the first calculation with a larger basis set were published by Ransil and Nesbet respectively in The first configuration interaction calculations were performed in Cambridge on the EDSAC computer in the s using Gaussian orbitals by Boys and coworkers. Of these four programs, only Gaussian, now vastly expanded, is still in use, but many other programs are now in use. At the same time, the methods of molecular mechanics , such as MM2 force field , were developed, primarily by Norman Allinger. Computational chemistry has featured in several Nobel Prize awards, most notably in and Walter Kohn , "for his development of the density-functional theory", and John Pople , "for his development of computational methods in quantum chemistry", received the Nobel Prize in Chemistry. In theoretical chemistry, chemists, physicists, and mathematicians develop algorithms and computer programs to predict atomic and molecular properties and reaction paths for chemical reactions. Computational chemists, in contrast, may simply apply existing computer programs and methodologies to specific chemical questions. Computational chemistry has two different aspects: Computational studies, used to find a starting point for a laboratory synthesis, or to assist in understanding experimental data, such as the position and source of spectroscopic peaks. Computational studies, used to predict the possibility of so far entirely unknown molecules or to explore reaction mechanisms not readily studied via experiments. Thus, computational chemistry can assist the experimental chemist or it can challenge the experimental chemist to find entirely new chemical objects. Several major areas may be distinguished within computational chemistry: The prediction of the molecular structure of molecules by the use of the simulation of forces, or more accurate quantum chemical methods, to find stationary points on the energy surface as the position of the nuclei is varied. Storing and searching for data on chemical entities see chemical databases. Identifying correlations between chemical structures and properties see quantitative structureâ€”property relationship QSPR and quantitative structureâ€”activity relationship QSAR. Computational approaches to help in the efficient synthesis of compounds. Computational approaches to design molecules that interact in specific ways with other molecules e. Accuracy[edit] The words exact and perfect do not apply here, as very few aspects of chemistry can be computed exactly. However, almost every aspect of chemistry can be described in a qualitative or approximate quantitative computational scheme. Molecules consist of nuclei and electrons, so the methods of quantum mechanics apply. Therefore, a great number of approximate methods strive to achieve the best trade-off between accuracy and computational cost. Accuracy can always be improved with greater computational cost. Significant errors can present themselves in ab initio models comprising many electrons, due to the computational cost of full relativistic-inclusive methods. This complicates the study of molecules interacting with high atomic mass unit atoms, such as transitional metals and their catalytic properties. For geometries, bond lengths can be predicted within a few picometres and bond angles within 0. The treatment of larger molecules that contain a few dozen atoms is computationally tractable by more approximate methods such as density functional theory DFT. There is some dispute within the field whether or not the latter methods are

sufficient to describe complex chemical reactions, such as those in biochemistry. Large molecules can be studied by semi-empirical approximate methods. Even larger molecules are treated by classical mechanics methods that use what are called molecular mechanics MM. Methods[edit] One molecular formula can represent more than one molecular isomer: Each isomer is a local minimum on the energy surface called the potential energy surface created from the total energy i. A stationary point is a geometry such that the derivative of the energy with respect to all displacements of the nuclei is zero. A local energy minimum is a stationary point where all such displacements lead to an increase in energy. The local minimum that is lowest is called the global minimum and corresponds to the most stable isomer. If there is one particular coordinate change that leads to a decrease in the total energy in both directions, the stationary point is a transition structure and the coordinate is the reaction coordinate. This process of determining stationary points is called geometry optimization. The determination of molecular structure by geometry optimization became routine only after efficient methods for calculating the first derivatives of the energy with respect to all atomic coordinates became available. Evaluation of the related second derivatives allows the prediction of vibrational frequencies if harmonic motion is estimated. More importantly, it allows for the characterization of stationary points. The frequencies are related to the eigenvalues of the Hessian matrix , which contains second derivatives. If the eigenvalues are all positive, then the frequencies are all real and the stationary point is a local minimum. If one eigenvalue is negative i. If more than one eigenvalue is negative, then the stationary point is a more complex one, and is usually of little interest. When one of these is found, it is necessary to move the search away from it if the experimenter is looking solely for local minima and transition structures. This leads to the evaluation of the total energy as a sum of the electronic energy at fixed nuclei positions and the repulsion energy of the nuclei. A notable exception are certain approaches called direct quantum chemistry , which treat electrons and nuclei on a common footing. Density functional methods and semi-empirical methods are variants on the major theme. For very large systems, the relative total energies can be compared using molecular mechanics. The ways of determining the total energy to predict molecular structures are: Ab initio methods[edit] Main article: This does not imply that the solution is an exact one; they are all approximate quantum mechanical calculations. It means that a particular approximation is rigorously defined on first principles quantum theory and then solved within an error margin that is qualitatively known beforehand. Diagram illustrating various ab initio electronic structure methods in terms of energy. Spacings are not to scale. The simplest type of ab initio electronic structure calculation is the Hartreeâ€"Fock method HF , an extension of molecular orbital theory , in which the correlated electron-electron repulsion is not specifically taken into account; only its average effect is included in the calculation. As the basis set size is increased, the energy and wave function tend towards a limit called the Hartreeâ€"Fock limit. Many types of calculations termed post-Hartreeâ€"Fock methods begin with a Hartreeâ€"Fock calculation and subsequently correct for electron-electron repulsion, referred to also as electronic correlation. To obtain exact agreement with experiment, it is necessary to include relativistic and spin orbit terms, both of which are far more important for heavy atoms. In all of these approaches, along with choice of method, it is necessary to choose a basis set. This is a set of functions, usually centered on the different atoms in the molecule, which are used to expand the molecular orbitals with the linear combination of atomic orbitals LCAO molecular orbital method ansatz. Ab initio methods need to define a level of theory the method and a basis set. The Hartreeâ€"Fock wave function is a single configuration or determinant. In some cases, particularly for bond breaking processes, this is inadequate, and several configurations must be used. Here, the coefficients of the configurations, and of the basis functions, are optimized together. The total molecular energy can be evaluated as a function of the molecular geometry ; in other words, the potential energy surface. Such a surface can be used for reaction dynamics. The stationary points of the surface lead to predictions of different isomers and the transition structures for conversion between isomers, but these can be determined without a full knowledge of the complete surface. A particularly important objective, called computational thermochemistry , is to calculate thermochemical quantities such as the enthalpy of formation to chemical accuracy. To reach that

accuracy in an economic way it is necessary to use a series of post-Hartreeâ€"Fock methods and combine the results. These methods are called quantum chemistry composite methods. Density functional methods[edit] Main article: Density functional theory Density functional theory DFT methods are often considered to be ab initio methods for determining the molecular electronic structure, even though many of the most common functionals use parameters derived from empirical data, or from more complex calculations. In DFT, the total energy is expressed in terms of the total one- electron density rather than the wave function. In this type of calculation, there is an approximate Hamiltonian and an approximate expression for the total electron density. DFT methods can be very accurate for little computational cost. Some methods combine the density functional exchange functional with the Hartreeâ€"Fock exchange term and are termed hybrid functional methods. Semi-empirical quantum chemistry methods Semi-empirical quantum chemistry methods are based on the Hartreeâ€"Fock method formalism, but make many approximations and obtain some parameters from empirical data. They were very important in computational chemistry from the 60s to the 90s, especially for treating large molecules where the full Hartreeâ€"Fock method without the approximations were too costly. The use of empirical parameters appears to allow some inclusion of correlation effects into the methods. Primitive semi-empirical methods were designed even before, where the two-electron part of the Hamiltonian is not explicitly included. Molecular mechanics In many cases, large molecular systems can be modeled successfully while avoiding quantum mechanical calculations entirely. Molecular mechanics simulations, for example, use one classical expression for the energy of a compound, for instance the harmonic oscillator. All constants appearing in the equations must be obtained beforehand from experimental data or ab initio calculations. The database of compounds used for parameterization, i. A force field parameterized against a specific class of molecules, for instance proteins, would be expected to only have any relevance when describing other molecules of the same class. These methods can be applied to proteins and other large biological molecules, and allow studies of the approach and interaction docking of potential drug molecules. Computational chemical methods in solid state physics Computational chemical methods can be applied to solid state physics problems. The electronic structure of a crystal is in general described by a band structure , which defines the energies of electron orbitals for each point in the Brillouin zone. Ab initio and semi-empirical calculations yield orbital energies; therefore, they can be applied to band structure calculations. Since it is time-consuming to calculate the energy for a molecule, it is even more time-consuming to calculate them for the entire list of points in the Brillouin zone. The potential representing the interatomic interaction is given by the potential energy surfaces. In general, the potential energy surfaces are coupled via the vibronic coupling terms.

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