'ValleyScan': A new two-bond drive technique for the calculation of potential energy surfaces with less computational effort

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SUMMARY

A novel, CPU-time inexpensive two-bond drive technique, called 'ValleyScan' [1], is described. It makes it possible to omit the chemically nonrelevant points of high energy, which are normally part of a two-dimensional (2D) grid calculation. The new procedure works well for the calculation of the ring inversion of cyclic molecules, but should also be useful for other 'two-bond' problems e.g. side-chain movements in larger molecules (e.g. proteins). The algorithm is based upon pseudocode description and can easily be included in any molecular modelling software with an open user interface. Starting from an energy minimum, the calculation scans the potential surface in all directions up to a user-defined energy limit. With this strategy, attention is paid only to the area close to the stationary points – energetically higher structures do not have to be calculated. We applied the procedure to the test molecules 1,3-cyclohexadiene (**4**), 2H-pyran (**5**) and 6H-dibenzo[b,d]pyran (**6**). The extension of this method to the variation of more than two dihedral angles for more complex problems, e.g. sterically more hindered rotation, is in progress.

INTRODUCTION

Two-bond drive techniques [2,3] based on force-field methods [4] are standard procedures for the calculation of inversion barriers of ring molecules. Difficulties can arise when the ring has reached a certain size and thus flexibility [5]. Further problems may originate when ring inversion is inhibited by nonbonded interactions. In this paper, we describe an efficient two-bond drive technique that is characterized by fewer calculations. Such a procedure became necessary for the

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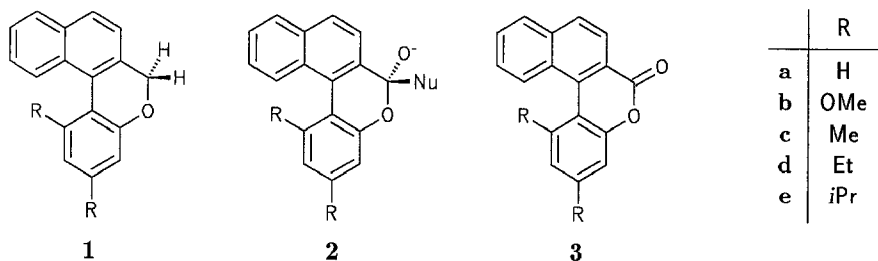* To whom correspondence should be addressed.

Fig. 1. The benzo[b]naphtho[1,2-d]pyrans **1** and related bridged biaryls.

benzo[b]naphtho[1,2-d]pyrans of type **1** [6,7] (Fig. 1), useful intermediates in the directed, i.e., regio- and even stereoselective synthesis of important biaryl compounds [8,9].

These compounds can easily be prepared by intramolecular aryl coupling and are subject to a more or less rapid helimerization equilibrium $(M)-1 \rightleftharpoons (P)-1$, out of which they may be opened stereoselectively, i.e., under directed formation of only one of the two possible atropisomers. Furthermore, these cyclic ethers constitute simplified models for analogous lactolates **2**, the postulated [6,7] intermediates in the stereocontrolled atropisomer-selective ring opening of the corresponding lactones **3**. Hence, a detailed knowledge of the ring inversion process is of crucial interest for mechanistic investigations of this unprecedented ring opening process.

FUNDAMENTAL CONCEPT

For the geometry of the transition state between the two chiral species $(M)-1$ and $(P)-1$, a planar (i.e., achiral) structure might be expected in the simplest possible case. On the basis of this assumption, the calculated activation enthalpy $\Delta H^{\neq}$ for helimerization was calculated to be 223.05 kJmol^{-1}, the energy difference between the minimum and planar structure. The large deviation from the experimental value of 81.71 kJmol^{-1}, as determined by DNMR experiments [10], reveals that a nonplanar – thus chiral – transition state is more likely. Unlike a planar structure, this kind of transition state is impossible to locate theoretically.

Normally, when trying to force a severely distorted molecule like **1** into a planar conformation, several torsional constraints have to be defined for the 'minimization' of the resulting structure. For calculation of the energy of the flattened structure for **1**, up to seven of these constraints had
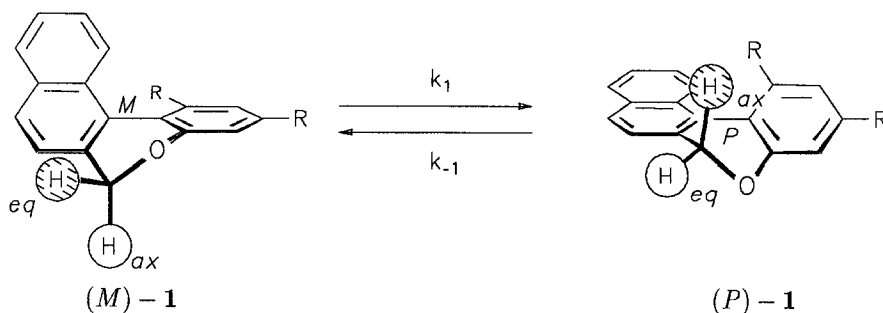

Fig. 2. The ring inversion of the benzo[b]naphtho[1,2-d]pyrans **1**.

to be set. This demonstrates that a *multiple* bond-drive technique has to be used to calculate the complete helimerization process. This makes it possible to pay attention to the participation of each important dihedral angle that varies during helimerization. The problem thus gets extra dimensions with respect to the potential energy surface describing the reaction pathway. As mentioned before, the localization of the chemically relevant transition state also becomes more complicated. In order for such a procedure to be practicable, the number of single point calculations, which is expected to increase exponentially with the number of the dihedral angles varied, had to be limited.

For this reason, we have developed a new approach which confines the calculation of the potential surface to the area close to the stationary points, ignores energetically high points, and thus limits the number of the structures to be calculated. The basic idea of the method is to start the calculation at an energy minimum and to scan the potential surface in all directions within a chosen energy window. We have therefore named this procedure 'ValleyScan'. In order to facilitate the elaboration of such a novel approach, the new procedure was first developed as a two-bond drive technique, and will later be extended to a corresponding multibond-drive technique.

THE METHOD

First of all, the procedure ValleyScan (Fig. 3) determines the 'origin' of the calculation by minimizing the starting geometry, which should describe the conformation of a minimum. Then the first dihedral angle, ω_1, is incremented step-by-step and the subroutine RowScan is used until the starting point for the subroutine RowScan lies outside the energy window. Subsequently, ω_1 is decreased analogously, starting from the origin again.

The subroutine RowScan (Fig. 4) first creates a starting geometry from the values ω_1 and $\omega_{2,start}$, as delivered by ValleyScan. Starting from this geometry, a new row of values is calculated by increasing ω_2 in positive and negative directions, until the energy exceeds the defined window.

```
Procedure ValleyScan (EnergyWindow, Incr)
BEGIN
    CalculateMinimumGeometry ( )
    GetTorsionalAngleOfMinimumGeometry ( )
    ω₁ = ω₁,Minimum
    ω₂ = ω₂,Minimum
    WHILE (ω₂ < EXIT)
        ω₂ = RowScan (ω₁,ω₂,Incr)
        ω₁ = ω₂ + Incr
    ENDWHILE
    LoadMinimumGeometry ( )
    ω₁ = ω₁,Minimum − Incr
    ω₂ = ω₂,Minimum
    WHILE (ω₂ < EXIT)
        ω₂ = RowScan (ω₁,ω₂,Incr)
        ω₁ = ω₂ − Incr
    ENDWHILE
END
```

Fig. 3. Pseudocode description of the ValleyScan procedure.

```
Subroutine RowScan (ω₁,ω₂,Start,Incr) : ω₂
BEGIN
    ω₁ = ω₂,Start
    ActualEnergy = CalculateStructure (ω₁,ω₂)
    IF (ActualEnergy > EnergyWindow)
        RETURN (EXIT)
    ENDIF
    SaveStartGeometry ( )
    WHILE (ActualEnergy < EnergyWindow)
        SaveStructures (Structures[i],Energies[i],Angles[i])
        i = i + 1
        ω₂ = ω₂ + Incr
        ActualEnergy = CalculateStructure (ω₁,ω₂)
    ENDWHILE
    ω₂ = ω₂,Start
    ActualEnergy = LoadStartStructure ( )
    WHILE (ActualEnergy < EnergyWindow)
        SaveStructures (Structures[i],Energies[i],Angles[i])
        i = i + 1
        ω₂ = ω₂ - Incr
        ActualEnergy = CalculateStructure (ω₁,ω₂)
    ENDWHILE
    ω₂ = FindRowMinimum (Energies[ ],Angles[ ])
    RETURN (ω₂)
END
```

Fig. 4. Pseudocode description of the RowScan subroutine.

The subroutine FindMinimum ascertains the point of lowest energy in the row just calculated and provides the corresponding value for ω_2. This value serves as starting value for ω_2 in the next run of RowScan. The subroutine CalculateStructure calculates the geometry at the point (ω_1,ω_2) by first defining the appropriate torsional constraints. After minimization of the geometry, the energy of this point is stored in the variable ActualEnergy and the constraints are removed. The subroutine SaveStructures saves the calculated geometries and stores their energies and torsional angles, ω_2, in the data arrays Energies[] and Angles[], respectively. The number of points to be calculated depends on the level of the chosen energy window, the incremental values, and especially on the shape of the potential surface. The shape, i.e., the steepness of the surface, fixes how easily the reaction valley can be cut out of the 2D grid. The advantage of this method is greater for a steep potential surface and smaller for a flat one. In no case was the computational effort required for the new algorithm greater than that for conventional two-bond drive techniques.

We implemented the ValleyScan method within the molecular modelling software SYBYL 5.41 (Tripos Associates, Inc.) by using the SYBYL programming language. The default settings for the minimizer MaxiMin2 were employed, except for the use of the BFGS-method for minimization, the termination option GRADIENT, and the rms gradient 0.001 for termination. Calculations were performed on a Silicon Graphics IRIS 4D/310GTX computer system.
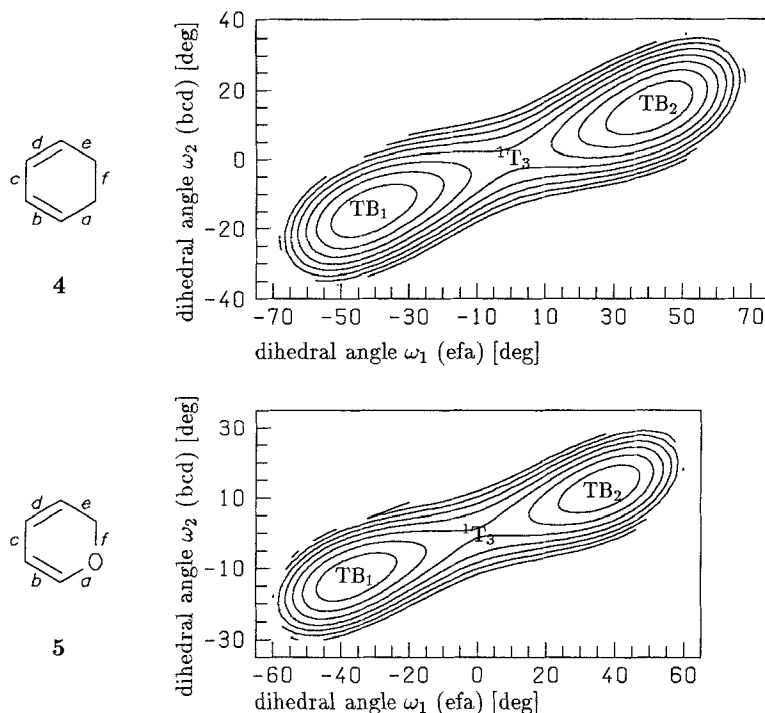
Fig. 5. Calculated potential surfaces of 1,3-cyclohexadiene (4) and 2H-pyran (5).

RESULTS AND DISCUSSION

To test the procedure, we first chose simple molecules as models for the pyrans 1, such as 1,3-cyclohexadiene (4) and 2H-pyran (5). Theoretical data for 4 [11–18] and 5 [19,20] concerning geometry and energy of minima and transition states are already known in the literature. Experimental data, however, are available only for 1,3-cyclohexadiene (4) [21–26], since 2H-pyran (5) has not been synthesized as yet [27–30].

In agreement with the literature [12], a double minimum potential surface was found for both molecules (Fig. 5). The minima TB_1 and TB_2 correspond to twisted conformations, whereas the transition states ^1T are planar and are located 7.70 kJmol^{-1} (for 4) and 4.77 kJmol^{-1} (for 5) above the minima.

For 6H-dibenzo[b,d]pyran (6), the potential surface found (Fig. 6) is already significantly influenced by nonbonded interactions between the *ortho-* and *ortho'-H*-atoms. This hypersurface is characterized by the presence of two distorted transition states that have to be passed during the interconversion of the two helimeric forms. These are again highly twisted in the energy minima, TB_1 and TB_2. This suggests two different enantiomeric reaction pathways that connect the two energy minima, TB_1 and TB_2, via the two nonplanar and thus chiral enantiomeric transition states, $^1T_3$ and $^1T_4$. These are located 23.63 kJmol^{-1} above the energy minima. In contrast, the planar geometry ($^2T_5$) represents an energy maximum, which is located 25.23 kJmol^{-1} above TB_1/TB_2 and thus lies energetically higher than $^1T_3$ and $^1T_4$.
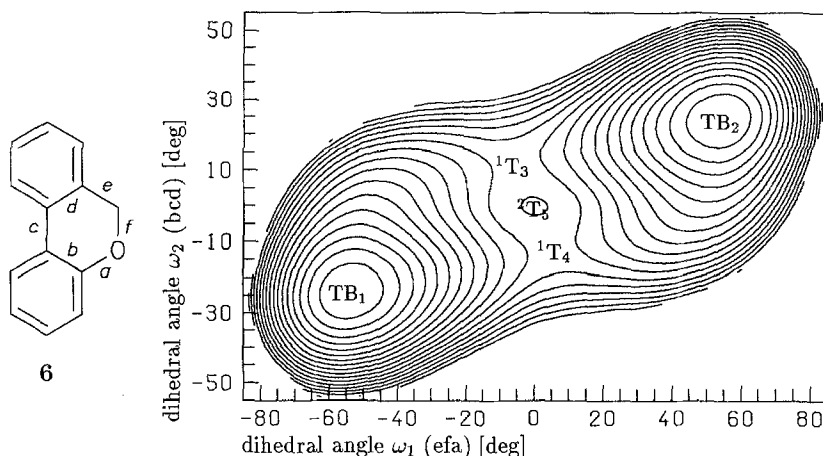
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Fig. 6. Potential surface of 6H-dibenzo[b,d]pyran (**6**).

In order to judge the real value of the new algorithm better, it was compared to analogous calculations using the GridSearch algorithm within SYBYL, on the same molecules under otherwise identical conditions, i.e., using the same range of dihedral angles and the same step size. For this comparison, the maximum energy for ValleyScan was allowed to be 0.4 kJmol^{-1} above the energy of the planar structure. The improvements of ValleyScan with respect to the conventional two-bond drive technique are documented in Table 1. For a better comparison, the percentages of saved CPU time versus the number of calculated points are listed.

As expected, the ValleyScan algorithm led to a smaller amount of calculated points and thus to a saving in CPU time. This tendency was further improved by the fact that structures near stationary points, such as minima, are faster to calculate. Smaller potential surfaces combined with a lower energy window, i.e., for cyclohexadiene (**4**) and 2H-pyran (**5**), are faster to calculate because of the lower mean CPU time *per point*. Thus, the CPU time saved when using ValleyScan instead of GridSearch was up to 75%, i.e., the conventional grid search requires four times more CPU time than the new algorithm now described. For a larger potential surface combined with an increased energy window, i.e., for 6H-dibenzo[b,d]pyran (**6**), this effect is smaller, and the CPU time is shorter because fewer points are calculated.

TABLE 1
ADVANTAGES OF VALLEYSCAN COMPARED TO GRIDSEARCH

	Saved amount [%] of		
	Calc. points	CPU time per point	Total CPU time
1,3-cyclohexadiene (**4**)	65.1	29.3	75.3
2H-pyran (**5**)	65.0	20.5	72.2
6H-dibenzo[b,d]pyran (**6**)	43.0	1.3	43.7

CONCLUSION

In summary, the new method, ValleyScan, allows the calculation of potential energy surfaces with less computational effort. In this paper, the presented procedure was tested with simplified model molecules, and showed that the computational effort was reduced compared with methods described in the literature. This makes it now possible to extend this method to molecules with more steric hindrance, by using more than two torsional angles, since the method should then be able to compute more complicated helimerization processes. This work is currently in progress.

ACKNOWLEDGEMENTS

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