Dimorphs of 4′-amino-4-hydroxy-2′-methylbiphenyl: Assessment of likelihood of polymorphism in flexible molecules†

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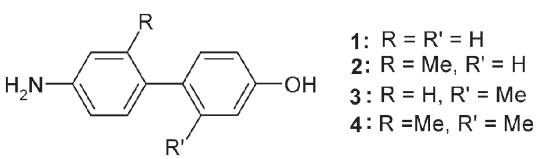
Received (in CAMBS) 24th April 2006, Accepted 17th May 2006
First published as an Advance Article on the web 25th May 2006
DOI: 10.1039/b605751a

The less stable polymorph of the title compound has the better synthon while the more stable polymorph the better packing. The possibility of polymorphism in a closely related isomer is examined computationally.

Introduction

Polymorphism and crystal structure prediction (CSP) are related aspects of crystal engineering.[1–3] Both these phenomena are useful to the understanding of the complex events underlying crystallisation. Observed crystal structures often result from kinetically favoured intermediates and contain preferred interactions and synthons.[4] The thermodynamic crystal may be elusive in many cases. When the kinetic and thermodynamic crystals are identical, polymorphism would not normally be possible under standard conditions. With increasing attention being paid to these subjects, polymorphs are now being discovered for very well-known compounds (*sym*-trinitrobenzene,[5] benzamide[6] and maleic acid[7]). We have studied substituted aminophenols for nearly a decade and have published the crystal structures of at least 25 of them.[8–11] There are around another 25 aminophenol crystal structures in the CSD (version 5.27, Jan 2006 update).[12] Despite the fact that we crystallised many of these compounds from several solvents during the course of our investigations, we never found a single case of polymorphism in this family. Neither do exist reports from others concerning polymorphism in aminophenols. Of course, it is very difficult to assert that a particular group of compounds will not be polymorphic (proving the negative) but we have related the absence of polymorphism in this family to the presence of flexible groups that are also hydrogen bond donors and acceptors.[10] Here, we report the first example of polymorphism in aminophenols, in particular for the compound 4′-amino-4-hydroxy-2′-methylbiphenyl, **2**. There is a salient difference in the molecular backbone of **2** when compared to other aminophenols we have studied previously, in terms of ease of rotation around the central biphenyl C–C bond. In this context, we have explored the present system (compounds **1–4**) computationally.



1: R = R′ = H
2: R = Me, R′ = H
3: R = H, R′ = Me
4: R =Me, R′ = Me

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† Electronic supplementary information (ESI) available: Experimental details. See DOI: 10.1039/b605751a

Experimental

1. Synthesis

Melting points were recorded on a DSC (A Mettler Toledo). ^{1}H NMR spectra were recorded on a Bruker-AC-400 spectrometer (dmso-d6). All reactions were carried out using standard techniques and literature procedures. All compounds were purified by column chromatography and diffraction quality single crystals were obtained by slow evaporation from 1 : 1 EtOAc–MeCN.

4′-Amino-4-hydroxy-2′-methylbiphenyl, (2). The commercially available 4-methoxybenzeneboronic acid was subjected to Suzuki coupling with 2-bromo-5-nitrotoluene as described elsewhere.[9] The resulting biaryl derivative was reduced with Pd/C and $N_2H_4 \cdot H_2O$ in EtOH and lastly O-methoxy deprotection was performed with BBr_3/DCM at −78 °C followed by work-up and column chromatography to give **2** in 65% yield. Mp 177.43 °C. ^{1}H NMR: δ 9.25 (s, 1H), 7.01 (d, J 8, 2H), 6.75 (m, 3H), 6.37 (m, 2H), 4.91 (s, 2H) and 2.07 (s, 3H).

4′-Amino-4-hydroxy-2-methylbiphenyl, (3). The synthetic route is similar. But the starting material (2-methyl-4-methoxybenzenboronic acid) is not commercially available. Accordingly, it was prepared according to the literature.[13] The final yield of **3** after three steps was 50%. Mp 155.6 °C. ^{1}H NMR: δ 9.13 (s, 1H), 6.89 (m, 3H), 6.65 (m, 4H), 4.99 (s, 2H) and 2.12 (s, 3H) (see ESI for NMR spectrum, Fig. S1).†

2. X-Ray crystallography

X-Ray data for the polymorphs of compound **2** were collected on a Bruker SMART diffractometer using Mo Kα radiation.

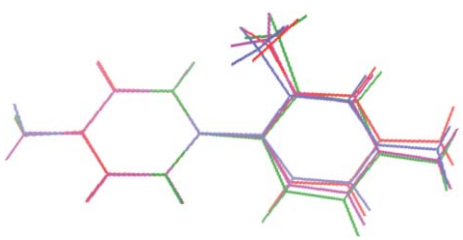

Fig. 1 Overlay diagram of the four conformations of biphenyl **2** in its dimorphs. The colour codes are as follows: Form I (red and green); Form II (blue and magenta).

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The structure solution and refinements were carried out using SHELXTL programs.[14] In all cases the hydroxy and amino H-atoms were located in difference Fourier maps and refined isotropically. The other hydrogen atoms were fixed in geometrically sensible positions. CCDC reference numbers 605385 and 605386. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b605751a

3. Computational

Ab initio potential energy scan (PES). The b3lyp/6–31g (d,p) method in the Gaussian package[15] was used. The PES was carried out for **1–4** at 5° intervals within the torsion angle range 0–90° around the central C–C single bond.

Lattice energy scan (LES). All simulations were carried out with version 4.8 of the Cerius[2] molecular modelling[16] environment running on Silicon Graphics workstations. The DMol3 (Quality: fine, Fuctional: LDA, PWC, Basis set: DNP) module in MS Modelling v3.2[17] (PC based client) was used for the starting model generation. The seven models were investigated at 15° intervals in the torsion angle range 0–90° and the electrostatic potential (ESP fitted) charges were calculated. The Polymorph Predictor (PP) module was used for this calculation and the PP runs were carried out in the six common space groups $P2_1/c$, $C2/c$, $P\bar{1}$, $P2_1$, $P2_12_12_1$, $Pbca$ and $Pna2_1$ using three different force field (FF), Dreiding, Compass, cff95 (ESI Table S2†). Default options were used for the fine search in the Monte Carlo simulation and for clustering. The COSET program was used for all the PP analyses.

Results and discussion

The dimorphs of compound, **2** were discovered accidentally and in separate experiments although the same solvent mixture was used in both cases. The relevant crystallographic, packing and energy details of the two forms are given in Table 1. This is a case of conformational polymorphism. There are two molecules in the asymmetric unit in both morphs. The biphenyl torsion angles of the four conformations are in the range 44–67° and an overlay diagram is given in Fig. 1.

The crystal structure of the dimorphs of aminophenol **2** may be understood by a consideration of the crystal structure of the unsubstituted derivative **1** which crystallises in a single form. Aminophenol **1** takes the so-called β-As structure[18] which consists of the kinetically favoured O–H···N–H···O–H··· infinite chain synthon[11] which is cross-linked with similar chains to give a supramolecular cyclohexane chair with alternating O–H···N and N–H···O hydrogen bonds (Fig. 2). This structure is favoured by sterically unhindered aminophenols in which the hydroxy and amino groups are located at opposite ends of the molecule. It is seen, for example, in 4-aminophenol and even in the 1 : 1 molecular complex of hydroquinone and phenylenediamine. The hydrogen bonds within the supramolecular cyclohexane chair are mutually stabilised by cooperative effects.

Table 1 Relevant crystallographic data, energy and synthon for compound **2**

	Form I	Form II
Chemical formula	$C_{13}H_{13}NO$	$C_{13}H_{13}NO$
Solvent of crystallization	EtOAc–MeCN (1:1)	EtOAc–MeCN (1:1)
Crystal system	Monoclinic	Monoclinic
Space group	$\boldsymbol{P2_1/c}$	$P2_1/n$
a/Å	11.1587(4)	11.1587(2)
b/Å	18.9115(7),	9.5748(2)
c/Å	10.3217(4),	19.9175(4),
B/°	109.83	96.33
Z	8	8
V/Å^3	2048.98(13)	2115.05(7)
D_{calc}/mg m^{-3}	1.292	1.251
R_1 [$I > 2\sigma(I)$]	0.0420	0.0406
wR_2	0.1172	0.1171
GOF	1.019	0.958
Synthon	O–H···N–H···O infinite chain	Supramolecular cyclohexane chair with O–H···O and N–H···N interactions.
Lattice energy[a]/ kcal mol^{-1}	−34.419	−35.910

[a] Lattice energy minimization were carried out with COMPASS force field and charge equilibrium charge model with rigid body assumption.

Form I of aminophenol **2** contains the infinite O–H···N–H···O–H··· chain (Fig. 3a) but steric hindrance from the Me groups prevents the close approach of chains which would be required for the cross-linking of interactions which would lead to the supramolecular cyclohexane chair, and the chains remain isolated. Form II has a supramolecular cyclohexane chair (Fig. 3b), but this is not the pattern seen in the β-As structure, in that it contains O–H···O and N–H···N interactions both of which are extremely uncommon in aminophenols because they do not lead to the cooperative advantage obtained in the O–H···N–H···O–H··· chain.[10] This disadvantage is offset by the crystal packing in which the packing of the phenyl groups accommodates the methyl groups nicely

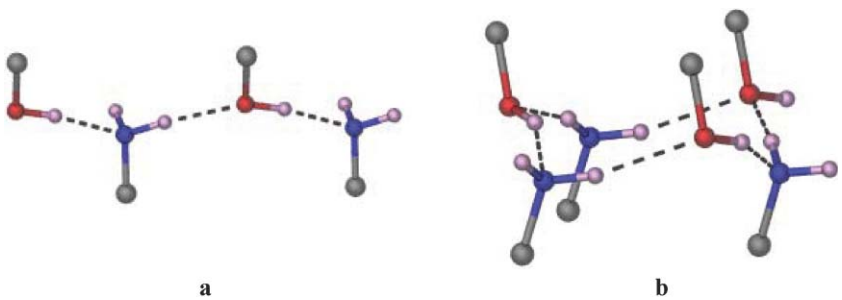

Fig. 2 Supramolecular synthons in the β-As structure of aminophenols: (a) infinite O–H···N–H···O–H··· chain; (b) supramolecular cyclohexane chair constituted with O–H···N and N–H···O hydrogen bonds.

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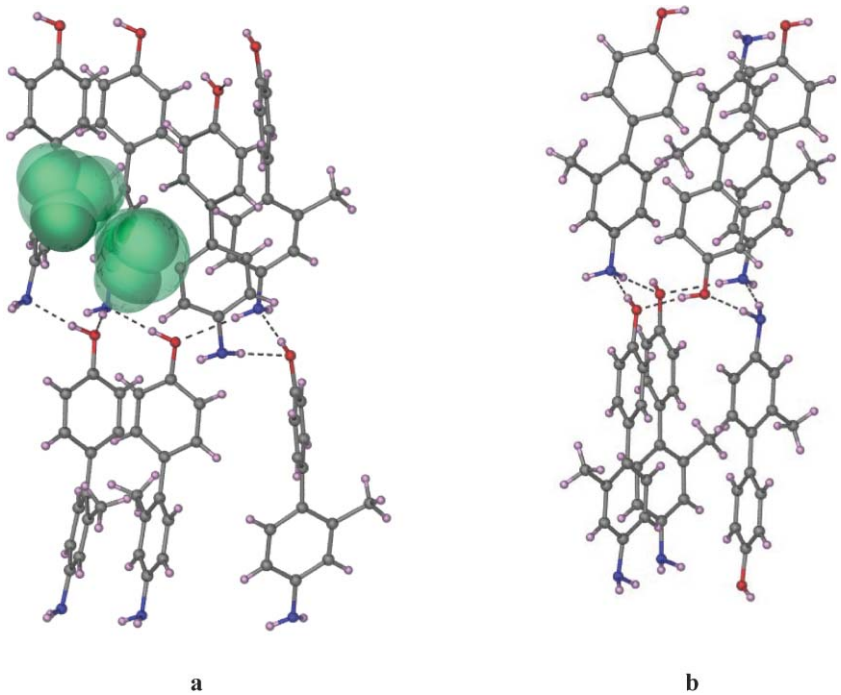

Fig. 3 Dimorphs of 4′-amino-4-hydroxy-2′-methylbiphenyl: (a) Form I, showing steric hindrance between methyl groups and the isolated ···O–H···N–H···O–H···N–H chains. (b) Form II, showing supramolecular cyclohexane chair that is constructed not only with O–H···N and N–H···O interactions as is usual in this family but also with the disfavoured O–H···O and N–H···N interactions.

(Fig. 3b). Interaction metrics for both polymorphs are given in Table S1 in ESI.†

The rationalization of polymorphism in compound **2** is as follows. The molecules have an awkward shape and it is difficult to assemble them in the crystal, retaining both the best interactions and the best packing. The best (kinetically favoured) interaction pattern is the O–H···N–H···O–H··· chain, which is seen across a wide variety of compounds among the 25 or so aminophenols we have studied.[8–11] Form I, a kinetic crystal which retains this pattern is a result of this fact. Alternatively, and to achieve the most favourable crystal packing for a linear aminophenol like **2** (this packing being *any* supramolecular cyclohexane chair), the system dispenses with the infinite O–H···N–H···O–H··· chain, and the unexpected O–H···O and N–H···N interactions make their appearance. Form II is a manifestation of these effects, and one might term it as the thermodynamic polymorph or as approaching the thermodynamic polymorph. Lattice energy calculations support this hypothesis in that polymorph II is more stable than polymorph I by 1.5 kcal mol^{-1}. We have shown clearly in our previous publications that the infinite O–H···N–H···O–H chain is the kinetically most favoured synthon in the aminophenols[9,10] and the formation of the dimorphs of **2** follows this notion. The less stable polymorph **I** has the better synthon while the more stable polymorph II has the better packing. A pertinent observation, in this context, is that both forms have $Z' = 2$, and this hints that the thermodynamic crystal is still to be found.[19,20]

We next considered 4′-amino-4-hydroxy-2-hydroxybiphenyl, **3**, which we qualitatively expected would be polymorphic by analogy with compound **2**. Aminophenol **3** was obtained pure after a 4-step synthesis but the sample was of limited crystallinity and the PXRD (see ESI†) of poor quality. Further, we could never obtain a single crystal suitable for X-ray analysis despite several attempts. The problem could have to do with decomposition of the compound in solution (observed in a few aminophenols) such that each crystallisation degrades the sample further. The compound was investigated with DSC and hot stage microscopy (see ESI†) but there was no evidence of polymorphism. It is difficult to assert the polymorphic behaviour of any compound without reliable experimental data but considering that compounds **2** and **3** are so similar, we decided to explore this system computationally.

We set up a methodology for polymorph (conformational) screening of a compound. This is closely related to the most difficult problem within CSP, namely CSP of a flexible molecule. This has been a classical problem in crystal engineering wherever the molecular structure and the crystal structure affect each other implicitly, and it has been referred to as *conformational polymorphism*.[21] Nowadays, special attention has been paid to this problem because many, if not most, commercially important pharmaceutical molecules are flexible.[22] Predicting the crystal structures of such molecules becomes especially difficult because the force field has to properly and simultaneously parameterize both the intra- and the intermolecular energy terms. Success in such an endeavour therefore depends very much on force field quality.

A major concern in the computational study of a flexible molecule is the selection of the starting conformation. Two recent studies by Price and co-workers on aspirin[23] and piracetam,[24] illustrate different facets of this issue. In aspirin, it was assumed (correctly) that the gas phase and the crystal conformations are similar. This represents a lower level of difficulty because one is looking for a new polymorph in the

correct region of conformational space. Piracetam represents a higher level of difficulty in that the gas phase conformation is different from what is obtained in the (at the time) three known crystal forms of the compound. In the present case, we are dealing with biphenyls which are known to be notorious as regards the differences between *ab initio* and crystal conformations.[25]

The question under consideration here is different from that in aspirin and piracetam. Firstly, we are not attempting CSP. We wish to address the more limited question, as to whether compound **3** will give polymorphs given the fact that compound **2** is polymorphic. However, the main problem is the same as that encountered in piracetam, namely how does one screen the vast conformational space and arrive at plausible starting conformations? An additional difficulty in this case is that no experimental information is available (unlike in piracetam) on *any* crystal form of compound **3**. Accordingly, we decided to address the issue by first comparing experimental and gas phase conformations in related biphenyls. The CSD was accessed and nine compounds were selected (ESI Table S3†). *Ab initio* calculations [Gaussian, b3lyp, 631-G (d,p)] were performed to obtain the gas phase conformations. This study shows that when all the *ortho* positions are blocked with substituents (ZZZMBS), there is little difference between the gas phase and crystal conformations. When two positions are blocked (BUWCAX) there is a slight difference (5°) between the two conformations. When there are no *ortho* substituents, there is a wide variation between the gas phase and crystal conformations ranging from 9° in NEHFAH to 40° in DOHDPH. We conclude that if only one *ortho* substituent is present (as in compounds **2** and **3**), the gas phase and crystal conformations may show variation. These observations are certainly not novel, and are stated here only in the context of the computational methodology that we employed.

In any system of conformational polymorphism, the basic assumption is that there will be a shallow crystal energy surface (1–2 kcal mol^{-1}) that covers a wide range of torsion angles; in other words, the angle ranges for minimum conformational energy and lattice energy are comparable *and large*. For example, in compound **2** the torsion angle ranges from 44 to 67°. For this study, we included two more compounds, **1** (which is in the CSD) and **4** (which has not been made as yet). The idea is to assess if **1**, **3** and **4** are capable of exhibiting polymorphism. The computational methodology consists of the following steps: (1) *ab initio* potential energy scan (PES) to determine the gas phase conformation; (2) lattice energy scan (LES) across conformational space, in other words the generation of hypothetical crystal structures with different torsion angles. Operationally, the average of the 10 lowest energy structures at a particular torsion angle is taken as the lattice energy for that particular conformation (see ESI Table S4†). The force field (FF) selection was carried out by simulation of the known crystal structure of compound **1** with COMPASS, DREIDING and cff95. The COMPASS FF was selected based on its better performance (ESI Table S2†). The efficacy of this FF with respect to aminophenols has already been demonstrated by us.[10] We cross checked the validation of the FF with lattice energy calculations of the dimorphs of compound **2**.

We next quantified the observations made from the CSD on compounds **1–4**. Fig. 4 shows the variation of gas phase conformational energies as a function of torsion angle for biphenyls **1–4**. The results are as expected. Molecule **1** can exist, *in vacuo*, in any conformation. For compounds **2** and **3**, torsion angles between 35–90° are accessible. For compound **4** the range of torsion angles is narrower, 60–90°. The next step is to carry out LES at certain discrete values of the torsion angle with the Polymorph Predictor (PP) module of Cerius[2]. The different starting models with different torsion angles were generated by DMol3 in MS modelling. The Compass FF and ESP-fitted charges (as calculated by DMol3) were used for PP calculation.

As mentioned previously, the most difficult task for PP of flexible molecules is the simultaneous parameterization of intra- and intermolecular energy terms. So, we performed PP with the rigid body assumption but with free hydroxy and amino groups. The reason for this is that in all aminophenols studied by us previously the H-atom of the hydroxy group is generally out of the phenyl ring plane whereas in the *ab initio* conformation, it is almost always in this plane. However, a disadvantage of the rigid body assumption is that it does not take into account the intramolecular energy term in the energy minimization step. Since this term is significant in comparison to the intermolecular terms, this is a major drawback. Accordingly, we decided to re-minimize each of the 10 lowest energy structures for each conformation, keeping the torsion angle fixed and this average energy is plotted in Fig. 5. For this purpose, however, we used the cff95 FF with charge equilibrium charges and there is literature precedent for this.[26]

The results in Fig. 5 are revealing. We assumed that any structure within 2 kcal mol^{-1} of the global minimum is experimentally accessible under normal conditions. For compound **1**, torsion angles between 0 and 15° could lead to stable structures and the experimental structure (PITZAT) is within this range (2.5°). However, the minimum at 0° is not particularly shallow. Accordingly, even though the gas phase energy variations (Fig. 4) are minor, polymorphism may not

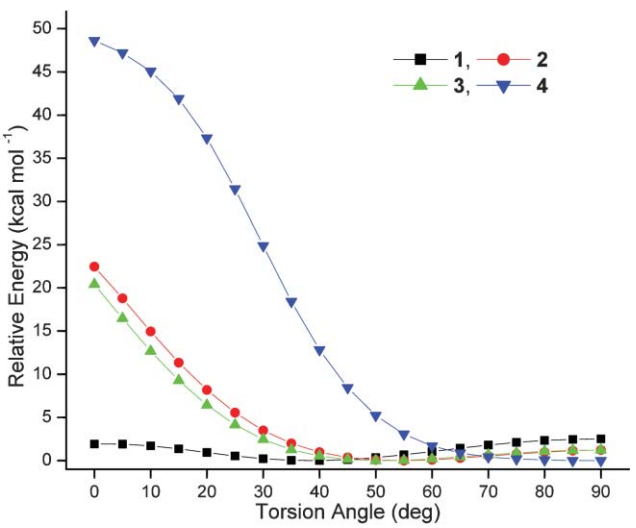

Fig. 4 *Ab initio* potential surface energy scans for biphenyls **1–4**. Gaussian, b3lyp/631-G (d,p) was used for these calculations.

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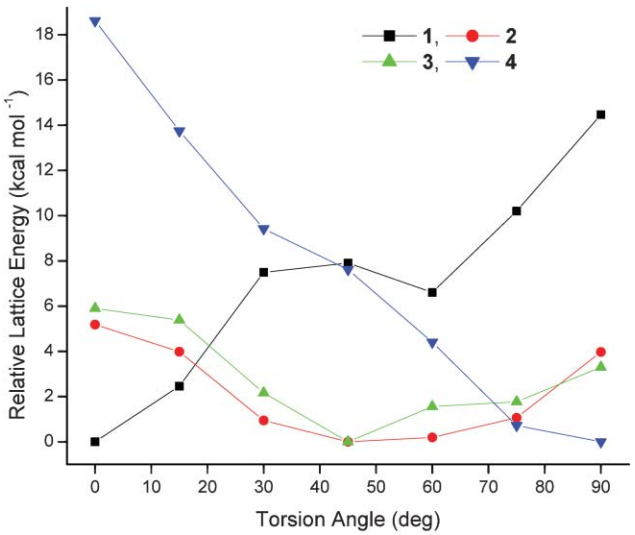

Fig. 5 Lattice energy scan with re-minimized energy for aminophenols **1–4**.

be so easy. In other words, this result tells us that while the molecule is flexible, it is locked in a near 0° conformation because of strong hydrogen bonding (β-As sheet) and appropriate close packing. Compound **4** is at the other extreme. The range of conformational space is reduced (60–90°), and the actual conformations that may be accessed are further reduced to 70–90° because of crystal packing effects. For a different reason therefore, we feel that the possibility of polymorphism is low.

An overlap between the torsional angle low energy window and a shallow crystal energy surface is important to achieve polymorphism in these amino hydroxy biphenyls. This feature is seen in compound **2** where a shallow lattice energy valley of 1–2 kcal mol^{-1} corresponds to a large range (25–75°) of torsion angles. Indeed, the polymorphism of **2** is experimentally observed and all four torsion angles in the dimorphs lie within the above mentioned range. Compound **3** is similar but the torsion angle range is slightly less (30–70°). Accordingly, the possibility of polymorphism is high.

Conclusions

Conformational dimorphs of 4′-amino-4-hydroxy-2′-methylbiphenyl have been isolated and their crystal structures determined. This is the first report of polymorphism among the 50 or so aminophenols studied so far by us[8–11] and others.[19,27] Polymorphism in this compound is explained by the conflicting demands of good interactions (kinetic structure) and good packing (thermodynamic structure). The related compound 4′-amino-4-hydroxy-2-methylbiphenyl has been synthesised but no experimental evidence could be obtained for the presence or absence of polymorphs. The possibility of polymorphism in this latter compound has been assessed by a computational method which addresses the match between a wide torsional angle window and a shallow energy valley for the corresponding crystal structures. On this basis, we conclude that there is a good chance that aminophenol **3** will be polymorphic. Such a computational method is expected to be useful in the examination of conformational space in the crystals of flexible molecules, a problem that is not expected to yield quick results with brute force computation. Our method seems to work well for molecules with a single rotatable bond; how it will perform for molecules with higher degrees of flexibility still remains to be seen.

Acknowledgements

A.D. thanks the CSIR for the award of a SRF. G.R.D. thanks DST for financial support. We are indebted to Dr C. K. Broder and Prof. J. A. K. Howard for single crystal data and to Dr J. A. Chisholm for providing us with the COSET program. We thank the UGC (UPE) for providing computational facilities (CMSD).

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