Solid state nuclear bromination with *N*-bromosuccinimide. Part 2. Experimental and theoretical studies of reactions with some substituted benzaldehydes †

Jagarlapudi A. R. P. Sarma,*[a] Akula Nagaraju,[a] Kanak K. Majumdar,[b] Purnima M. Samuel,[b] Indira Das,[b] Sujit Roy[b] and Alistair J. McGhie[c]

[a] *Molecular Modeling Group, Organic Division-I,* [b] *Metallo-Organic Laboratory, Inorganic Division, Indian Institute of Chemical Technology, Hyderabad 500 007, India*
[c] *Central Research & Development Department, Experimental Station, E. I. DuPont De Nemours & Co., Inc., Wellington, USA*

N-Bromosuccinimide reacts with aromatic aldehydes in the solid state to yield exclusively nuclear brominated products while a similar reaction in the solution phase produces a number of products under varied conditions. The reactivity and regioselectivity have been studied in terms of the energies of HOMO, HOMO–LUMO difference, reaction free energy, reaction conditions and crystal packing. Single crystal X-ray structural analysis of 3,4-dihydroxybenzaldehyde has been carried out. Crystal packing energies of some of the reactive and unreactive benzaldehydes indicate the importance of molecular bromine diffusion in the solid state.

Introduction

Chemoselective, kinetically fast, operationally simple and high yielding organic transformations in the solid state environment are entered enthusiastically into the practising organic chemist's work-book in which *N*-bromosuccinimide (NBS) has been used as one of the reagents for bromination and/or oxidation.[1–4] In the solution phase, apart from regular use as a reagent for the bromination of allylic and benzylic systems, NBS was also used as an oxidising agent in the reaction of primary or secondary alcohols in polar media and in the conversion of sulfides to sulfoxides where methanol was used as a solvent, or to form α-bromo sulfides in anhydrous solvents.[5,6] It was also used in the conversion of benzaldehydes to the corresponding benzoyl bromides and for the bromolactonisation of unsaturated acids and their derivatives.[7–9] In allylic and benzyl systems, the side chain bromination is commonly mediated by free radical initiators while the nuclear bromination requires metal chlorides or sulfuric acid as catalysts.[10,11] Employing a homogeneous or heterogeneous acid catalyst, nuclear bromination was also carried out to some extent on some aromatic compounds substituted with electron withdrawing groups.[12] However, electron-rich aromatic compounds are easily brominated by NBS either in the solid state or to some extent in acetonitrile in the dark.[3,4,13] Irradiation of the solution phase reaction mixture leads to the formation of multiple products. In CCl₄ solvent, reaction of similar aldehydes with either NBS or Br₂, however, leads to the formation of acid bromides.[7,14] Thus in solution, NBS reacts with aromatic aldehydes to yield different products and at times multiple products too are obtained under varied conditions. However, based on our earlier observations, in the solid state substituted phenols or anilines can be readily brominated with reasonably good selectivity whereas nitro aromatic compounds do not react at all.[4] As the electron withdrawing nature of the aldehyde group (Hammett constant, σ^- of 0.35–0.42 depending on the position) is less than that of the nitro group (0.71–0.78), it is interesting to study the NBS reactivity of such systems especially in the presence of other groups such as chloro (0.23–0.37), methoxy (0.12 to −0.27), hydroxy (0.12 to −0.37), or amino groups (−0.16 to −0.66) which are increasingly more electropositive in character.[15] In the earlier study, while some electron donating groups were considered as constants other groups were varied to study their reactivity.[4] However, this report describes NBS reactivity towards substituted benzaldehydes.

Computational methodology

The AM1 method in the MOPAC package was used to calculate the molecular orbital energies and reaction free energies, and density functional theory (DFT) and semi-empirical (MOPAC) modules of *Cerius*[2] were used with default values for the geometry optimisation and to calculate electrostatic potential charges (ESP).[4] DFT calculations were performed with a BLYP parameter set with frozen inner core electrons employing medium grid and double numerical polarisation (DNP) settings. While the solid state reaction conditions and observed products are given in Table 1, free energies of the solution and solid state reactions are given in Table 2. Crystallographic data of some of the reactive (**2R**, **5R**, **7R**) and unreactive (**17U**, **24U**, **27U**, **29U**) aldehydes were retrieved from the Cambridge Structural Database (CSD). Single crystal X-ray structural analysis of 3,4-dihydroxybenzaldehyde, **3R**, was carried out. The crystal data of **3R**: $C_7H_6O_3$, mol. wt. 138.12, monoclinic, $P2_1$, $a = 3.780(1)$, $b = 7.621(1)$, $c = 10.581(2)$ Å, $\beta = 90.20(1)°$, $V = 304.8$ Å³, $Z = 2$, $D_{exp} = 1.505$ g cm⁻³, temp. 173 K, Mo-Kα, $R = 0.04$, $R_w = 0.031$. Other details along with atomic coordinates and atomic displacement parameters are given as supplementary material‡ in the form of a CIF file. The *Crystal Builder* and *Crystal Packer* modules of the *Cerius*[2] program suite were used to study the crystal packing patterns and packing potential energies and results are given in Table 3.

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† IICT Communication No. 3585. For Part 1, see ref. 4.

‡ CCDC reference number 188/233. See http://www.rsc.org/suppdata/p2/a9/a905468e/ for crystallographic files in .cif format.

Table 1 Reaction details with the observed/expected products in the solid state reactions

Starting compound	Melting point/°C	Reaction conditions		Observed products[a]	Yield (%)
		Time/ min	Temp./ °C		
1R	56	2.0	0	3-Br[b]	94
2R	81	2.5	27	5-Br	83
3R	153	4.0	60	5-Br	78
4R	73	3.0	27	3-Br	79
5R	117	4.5	27	3,5-Br	40
6R	40	2.0	0	5-Br	84
7R	40	2.5	0	5-Br	91
8R	42	2.0	27	5-Br	38
9R	126	3.5	27	5-Br	82
10R	73	3.0	27	6-Br	85
11R	69	2.5	27	5-Br	60
12R	45	2.5	0	4-Br	60
13R	51	2.0	0	5-Br	45
14R	37	2.0	0	5-Br	76

[a] In some of the compounds such as **2R**, **4R**, **7R**, **10R** and **25U**, a mixture of products along with benzoyl bromides were obtained in a solution reaction and the nature of the products and their relative yields vary with solvent and reaction conditions such as temperature and exposure to light. Thus for the calculations of free energy of reactions in both media, benzoyl bromide was considered as a product which was observed in many cases. [b] In **1R**, a side chain product, 5-CH₂Br-salicaldehyde is formed in a solution phase reaction along with benzoyl bromide[14] while in **25U** a similar product, 4-CH₂Br-benzaldehyde, benzoyl bromide and starting material were obtained in a solution reaction.
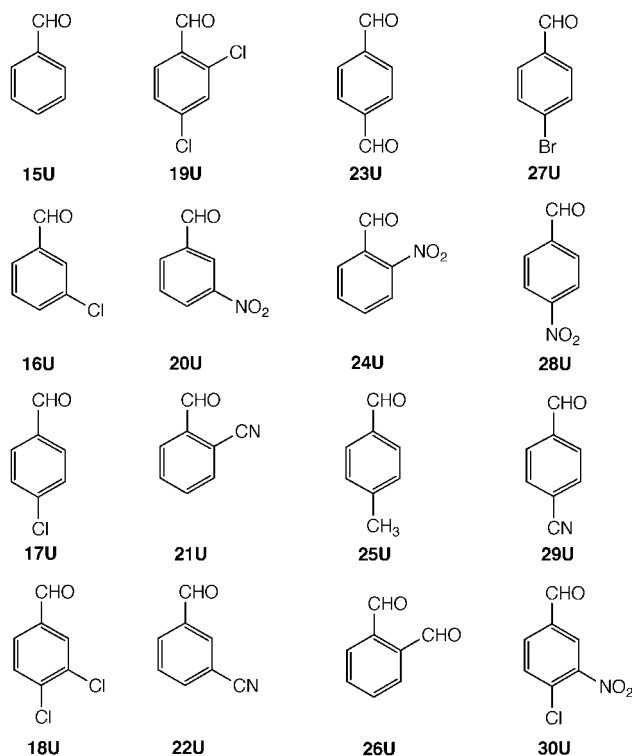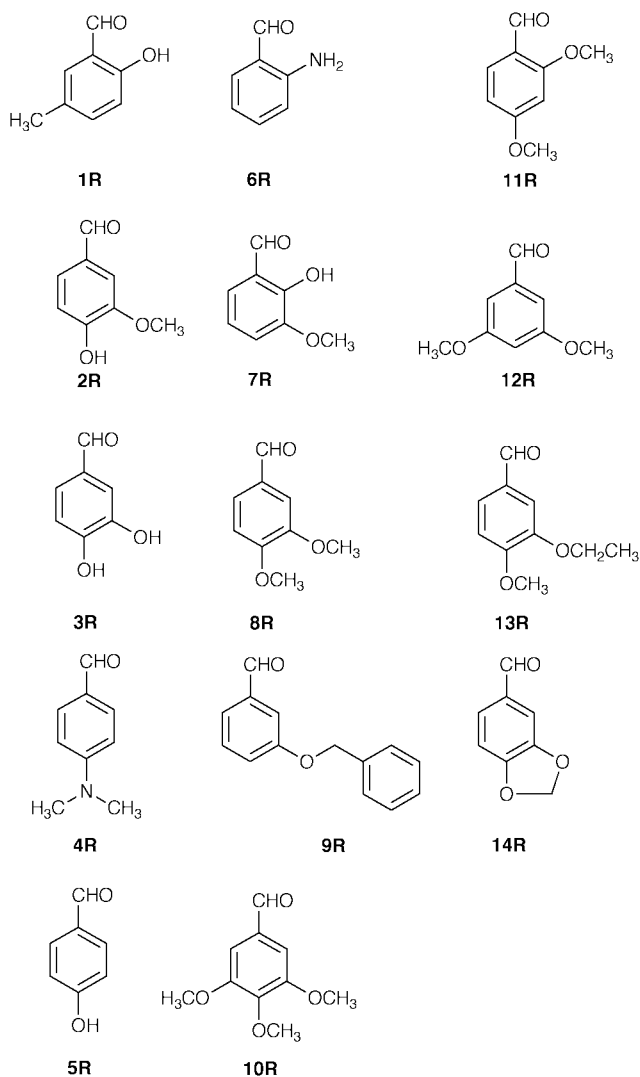
Results and discussion

NBS reacts readily with any electron-rich benzaldehydes in the solid state to produce nuclear bromo products with high regioselectivity. In many cases, the regioselectivity is in accordance with the normally observed electronic effects of the substituents on the aromatic ring, namely, *meta* to the aldehyde group and/or *ortho* or *para* to the electron donating substituent. The specificity decreases with the loss of crystallinity of the reactant or when the reaction is carried out nearer to the melting range of the reactant. However, when only Cl, Br, and/or NO₂ groups are present, reactivity was not observed even after two hours or at higher temperatures. The presence of an electron donating group on the benzaldehyde is essential for the reactivity for the nuclear bromination.

Solid state *vs.* solution reactivity

Reaction was observed when single crystals of reactive benzaldehydes were loosely held in contact with crystals or powder of NBS. When a mixture of **10R** and NBS was subjected to *in situ* scanning, no EPR signal was observed. In terms of the product selectivity, reaction in solution generally differs from that in the solid state. With controlled addition of NBS, **2R**, **4R**, **7R** or **10R** slowly reacts (0.5 h in the dark and acetonitrile solvent at 0 °C) to yield products similar to that of a solid state reaction. The product selectivity is lost with increase in temperature and the other conditions such as exposure to light and solvent. This is evident as **7R** yielded a mixture of products at 30 °C in acetonitrile in the dark for 0.5 h and **10R** in CCl₄ on irradiation (500 W sunlamp) for 12 h afforded a mixture of 2-bromo-3,4,5-trimethoxybenzaldehyde and 3,4,5-trimethoxybenzoyl bromide along with reactant aldehyde. Similarly, on irradiation at 40 °C for 6 h in CCl₄, **25U** yielded a mixture containing 4-methylbenzoyl bromide and 4-(bromomethyl)-benzaldehyde and unchanged aldehyde. It is interesting to note that **25U** is unreactive in the solid state but forms different products in solution. From these observations, it is clear that the reaction pathway in solution differs from that in the solid state with added dimensions in the form of light and solvent. It is obvious that on exposure to light the solution reaction may

Table 2 Reaction free energies of the solution and solid state reactions and the energy values of HOMO and of LUMO relative to HOMO

Compound	Solid state ΔG_f°/kcal mol^{-1}	Solution ΔG_f°/kcal mol$^{-1\,a}$	HOMO/eV	Δ(LUMO − HOMO)/eV
1R	−32.0	−26.3, −30.9^b	−9.24	8.83
2R	−34.1	−29.4	−9.02	8.55
3R	−33.5	−31.5	−9.13	8.59
4R	−21.4	−21.1	−8.41	8.34
5R	−66.9^c	−27.7	−9.48	9.04
6R	−31.6	−25.5	−8.80	8.64
7R	−35.8	−29.3	−9.02	8.50
8R	−29.8	−27.9	−8.94	8.54
9R	−32.7	−31.7	−9.33	8.83
10R	−29.6	−28.2	−9.15	8.62
11R	−31.1	−30.4	−9.35	8.91
12R	−28.3	−27.8	−9.14	8.66
13R	−29.3	−28.9	−8.90	8.51
14R	−30.4	−28.1	−9.28	8.63
15U	−32.1	−28.7	−10.04	9.57
16U	−32.9	−27.9	−9.87	9.19
17U	−31.5	−27.6	−9.90	9.17
18U	−30.3	−27.7	−9.90	8.96
19U	−28.3	−28.0	−10.07	9.05
20U	−28.7	−26.0	−10.88	9.48
21U	−34.2	−27.8	−10.26	9.28
22U	−32.3	−28.0	−10.32	9.90
23U	−31.4	−28.8	−10.31	9.20
24U	−32.1	−29.2	−10.74	9.50
25U	−31.9	−31.5, −31.6^b	−9.72	9.27
26U	−36.3	−28.6	−10.23	9.64
27U	−32.7	−28.4	−9.94	9.12
28U	−28.9	−27.0	−10.84	9.16
29U	−31.5	−30.5	−10.35	9.19
30U	−30.6	−28.0	−10.62	9.10

^{a} Reaction free energies for benzoyl bromide products at room temperature. ^{b} Free energies for side chain products (**1R**, **25U**). ^{c} For monobromo product, the energy is −26.98 kcal mol^{-1}.

Table 3 Electrostatic potential charges of unsubstituted aromatic ring C-atoms of reactive aldehydes derived from MOPAC and density functional theory (DFT) calculations. For reasons of clarity the charges of other atoms are not given and the positions where bromination is effective are indicated in bold

Compound	Method	C2	C3	C4	C5	C6
1R	MOPAC		**−0.3232**	−0.1816		−0.1688
	DFT		**−0.2515**	−0.1008		−0.0916
2R	MOPAC	−0.2966			**−0.3328**	−0.2458
	DFT	−0.3106			**−0.2639**	−0.0949
3R	MOPAC	−0.3340			**−0.3166**	−0.2458
	DFT	0.4677			**−0.0683**	0.1742
4R	MOPAC	−0.0786	**−0.3019**		**−0.2968**	−0.2227
	DFT	−0.0941	0.0910		**−0.1974**	1.0827
5R	MOPAC	−0.1748	**−0.2480**		**−0.4324**	0.0003
	DFT	−0.1825	**−0.1337**		**−0.2628**	−0.0487
6R	MOPAC		−0.2154	−0.0657	**−0.3430**	0.4581
	DFT		−0.0144	−0.0124	**−0.0025**	0.3076
7R	MOPAC			−0.2376	**−0.0739**	−0.0739
	DFT			−0.1853	**−0.1111**	−0.2387
8R	MOPAC	−0.4123			**−0.2926**	0.1997
	DFT	0.3540			**0.1635**	0.3910
9R	MOPAC	−0.4780		−0.3142	**−0.1279**	−0.1854
	DFT	−0.2722		−0.2124	**−0.0085**	−0.1443
10R	MOPAC	**−0.4672**				−0.3154
	DFT	**−0.0263**				−0.0413
11R	MOPAC		−0.5064		**−0.3499**	−0.0830
	DFT		1.6291		**0.7946**	0.2220
12R	MOPAC	−0.5259		**−0.4473**		−0.3396
	DFT	0.2086		**0.6608**		0.2214
13R	MOPAC	−0.3480			**−0.2742**	−0.1455
	DFT	−0.1807			**−0.1795**	−0.1958
14R	MOPAC	−0.2382			**−0.2421**	−0.2374
	DFT	−0.2089			**−0.1543**	−0.1871

favour a free radical mediated reaction pathway in the presence of initiators, and notwithstanding such irradiation, the solid state reactions could follow an electrophilic substitution pathway. However, the influence of the crystal packing on the reactivity is not yet very clear. As observed in the earlier study bromination is very exothermic and either in the solid state or in solution the reaction was carried out at lower temperatures to retain high selectivity.[4] For all the solid state reactive aldehydes, the melting points, reaction temperatures and times are given in Table 1.

Reaction free energy

As different products are formed in the solid state and solution reactions, reaction free energies have been calculated in order to identify which product should be formed preferentially and to study the influence of the substituents on the reactivity and selectivity. However, no solvent effects were included in the MOPAC calculations. These energies are given in Table 2. In the case of reactive aldehydes, solid state nuclear monobromination is slightly more favourable than in the solution phase where benzoyl bromide and in some suitable cases benzyl bromides were formed. Although this trend continues further in the unreactive aldehydes, no solid state reactivity, *i.e.* nuclear bromination, was observed. The difference between solid state and solution products is more marked in the case of unreactive aldehydes (-3.25 kcal mol^{-1}) than in the reactive aldehydes (-2.34 kcal mol^{-1}) with the solid state product being relatively more stable. In spite of this, no reaction was observed in the unreactive aldehydes as the reaction free energies need not necessarily determine the reactivity. This indicates that in the case of unreactive aldehydes higher activation energy may be required or the transition state to be less stable.

HOMO–LUMO energies and electrostatic potential charges

In order to gain an insight into the reactivity in terms of its prediction, ESP charges and HOMO and LUMO energies were calculated. As observed in our earlier study, the HOMO is relatively more stabilised in the unreactive benzaldehydes and the HOMO–LUMO difference is less in the case of reactive aldehydes. This could well be used to predict the reactivity, however, this may be valid only in a given class of compounds or simple systems.

ESP charges have been obtained from the MOPAC and DFT calculations and these values for the unsubstituted aromatic ring C-atoms have been given for the reactive aldehydes in Table 3. In general, the bromination was observed in the *meta* positions with respect to the aldehyde group. However, due to the non-availability of such a position in **10R**, it is observed in the *ortho* position, while in **12R**, bromination is effective in the *para* position. Even though the C-atom where bromination is effective does not have the highest electron density, in general such a tendency is reflected. In **4R**, even though the *N*,*N*-dimethyl-amino group is a relatively better electron donating group compared to the hydroxy group of **5R**, dibromination is feasible only in **5R** but not in **4R**. This may be due to the formation of salt by the monobromo product or **4R** with the hydrobromic acid that is released during the course of the reaction. As the HOMO value of such salt is -13.587 eV no further reactivity is possible. A similar situation may also be possible in **6R**. In the same way, **5R** forms a dibromo product, while the other aldehydes such as **2R**, **7R**, **8R**, **11R**, **13R** and **14R** form monobromo products and interestingly, 3,4-dihydroxybenzaldehyde, **3R**, does not react at room temperature, but reacts at higher temperature to yield a monobromo product. Although the calculated partial atomic charges vary with the nature of the method used, at least in some cases, the selectivity does not follow at the most electron-rich C-atom. Based on these observations, it is believed that to a certain extent, selectivity is also controlled by some other parameter such as crystal packing.

Crystal packing studies

The crystal packing patterns and different contributions to the packing energies for some of both the reactive and unreactive benzaldehydes were analysed. It has been shown by different examples, that crystallinity is essential for the product selectivity. In the case of **8R** (with low melting point) reactions with NBS at room temperature produced a very poor yield, however, when it was cooled to near 0 °C a better yield was obtained. Similarly, the discrepancy in the reactivities of the hydroxy- and methoxybenzaldehydes is mentioned above.
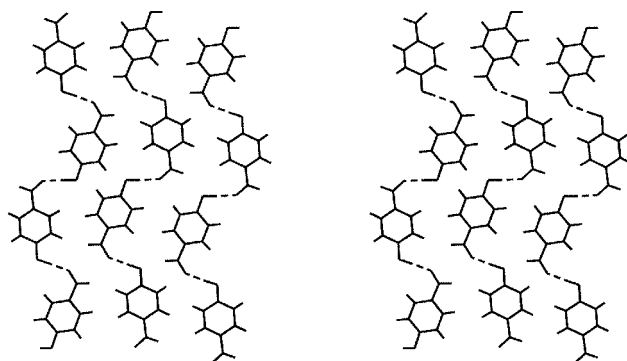
Fig. 1 Crystal packing of *p*-hydroxybenzaldehyde, **5R**, showing the intermolecular O–H⋯O hydrogen bonds with broken lines. The packing is described as a corrugated sheet structure where successive sheets are stacked.
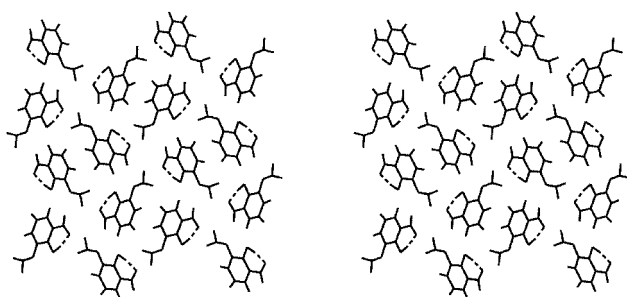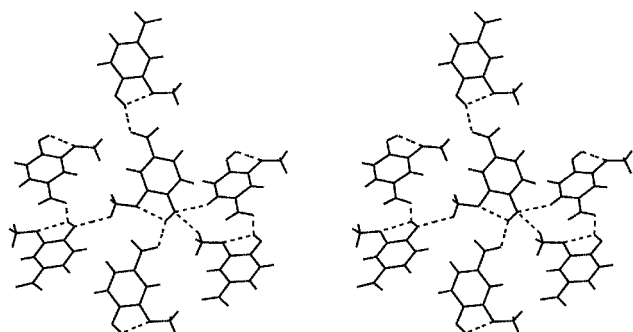

Fig. 2 Crystal packing of *o*-vanillin, **7R**, showing an 'egg-carton' structure. The *o*-hydroxy group is involved in an intramolecular hydrogen bonding with the adjacent carbonyl group. No other strong and specific interactions are observed.

The crystal structure of **5R** is characterised by a series of strong intermolecular O–H⋯O hydrogen bonds between hydroxy and aldehyde groups. It forms corrugated sheets (Fig. 1) wherein the molecules are arranged along with crests and troughs of the sheets.[16] This facilitates the diffusion of molecular bromine on both sides with relative equal ease. In the very early stages of the solid state reaction (long before the product crystallises out), if the product is still reactive then dibromination could be a possibility. Indeed, dibromination was observed in **5R**, as the HOMO and LUMO values of its monobromo product are comparable to that of **5R**. *o*-Vanillin, **7R**, forms a double corrugated sheet (Fig. 2) similar to an 'egg-carton'. The *ortho*-hydroxy is involved in a strong intramolecular hydrogen bond with the carbonyl group and no other specific strong intermolecular contacts are observed. Even though the structure has a very high packing coefficient (Table 4) due to optimal close packing (space group *Fdd*2), bromination is still effective at the *meta* position with respect to the carbonyl group. This may be possible perhaps in the absence of any specific strong intermolecular interactions as evident from a low melting point. Both **2R** and **3R** form linear ribbon structures where in each ribbon the molecules are very strongly held by a set of intermolecular O–H⋯O interactions. However, the successive ribbons along the non-stacking direction are linked by relatively weak C–H⋯O interactions in **2R** (Fig. 3) which are almost replaced by very strong O–H⋯O hydrogen bonds in **3R** (Fig. 4).[16,17] Thus in **3R** the molecules are effectively strongly tied down in all directions, causing less molecular motion. Thus more energy is needed for the molecules either to dissociate from the crystal or for the diffusion of Br$_2$ in the solid. Both these functions could be achieved by heating as the solid state reaction rate of **3R** can be increased with the temperature. If the temperature of the reaction mixture is sufficiently close to the melting point, the long range order may be lost at the reaction cavity thereby losing the selectivity. Thus, the presence of an aldehyde group coupled with strong inter-

Table 4 Crystal structure details and packing energies of some of the reactive and unreactive aromatic compounds. While compounds **2R**, **5R**, **7R** are reactive, **17U**, **24U**, **27U** and **29U** are unreactive. The energies are in kcal mol⁻¹

Compound	Vdw. energy/ kcal mol⁻¹	Coloumb energy/ kcal mol⁻¹	H-bond energy/ kcal mol⁻¹	Total energy/ kcal mol⁻¹	Free volume (%)	Density/ g cm⁻³
2R	−12.31	−8.335	−2.07	−22.71	22.08	1.34
3R	−14.35	−13.49	−5.21	−33.05	21.16	1.50
5R	−11.97	−15.89	−3.71	−31.58	21.74	1.35
7R	−16.37	−25.05	−2.38	−43.80	12.57	1.43
17U[a]	−15.72	−11.49	0.0	−27.41	18.99	1.42
	−15.88	−10.89	0.0	−26.78	20.39	1.45
24U[a]	−14.86	−13.12	0.0	−27.98	19.81	1.47
	−14.85	−15.06	0.0	−29.91	17.61	1.47
27U	−16.27	−11.79	0.0	−28.06	21.28	1.76
29U	−16.15	−18.92	0.0	−35.07	16.41	1.42

[a] Compounds **17U** and **24U** exist in two polymorphic forms.

Fig. 3 Crystal packing of vanillin, **2R**, showing three successive ribbons. In each ribbon the molecules are held by strong O–H⋯O interactions, however, successive layers are held by relatively weak C–H⋯O interactions.
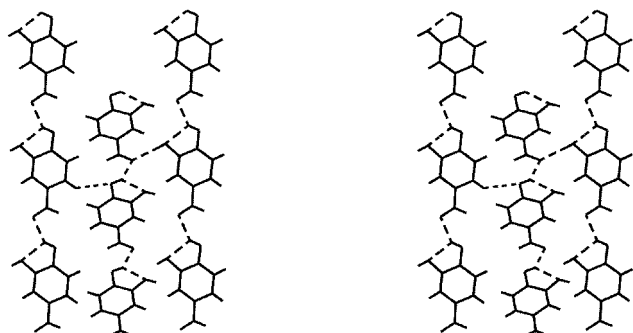
Fig. 4 Crystal packing of 3,4-dihydroxybenzaldehyde, **3R**, can be characterised as a linear ribbon structure similar to **2R**. However, strong O–H⋯O interactions are optimised along the ribbons and on one side between the successive ribbons while on the other side weak C–H⋯O interactions are optimised.

molecular hydrogen bonding makes **3R** a unique example when compared to the other 1,4-quinols.[3]

Experimental

Solid state reactions of aromatic aldehydes and freshly recrystallised NBS (1:1.1 molar equivalents) were ground in a mortar for 2–5 min. Thereafter ethyl acetate was added and products were separated by column chromatography (silica gel/ hexane–ethyl acetate 9:1). The reaction of aldehyde **5R** is comparatively sluggish: work up after 20 min gives rise to ~40% of product along with 50% of starting material. All other details are similar to those discussed in the previous article and some of the necessary experimental conditions are given in Table 1.

Conclusions

Substituted benzaldehydes demonstrate effectively the difference in the reactivities of solid state *versus* solution phase bromination reactions with NBS. It is hoped that the present study will initiate further elaboration of the Wöhl–Ziegler reaction of other aromatic substrates in the solid state, which would culminate in highly efficient and eco-friendly industrial processes.

Acknowledgements

References

1 G. R. Desiraju, *Organic Solid State Chemistry*, Elsevier, Amsterdam, 1987.
2 D. Seebach, *Angew Chem., Int. Ed. Engl.*, 1990, **29**, 1320.
3 B. Satish Goud and G. R. Desiraju, *J. Chem. Res. (S)*, 1995, 244.
4 J. A. R. P. Sarma and A. Nagaraju, *J. Chem. Soc., Perkin Trans. 2*, 2000, preceding paper (DOI: 10.1039/a905466i).
5 L. Hornor and E. H. Winklemann, *Newer methods of preparative organic chemistry*, Academic Press Inc., New York, 1964, vol. 3, p. 151.
6 R. Harvelli, Jr and S. F. Reed, *J. Org. Chem.*, 1968, **33**, 3976.
7 Y.-F. Cheung, *Tetrahedron Lett.*, 1979, **40**, 3809.
8 A. J. Pearson and T. Ray, *Tetrahedron Lett.*, 1986, **27**, 111.
9 W. Dai and J. A. Katzenellenbogen, *J. Org. Chem.*, 1991, **56**, 6893.
10 H. Schmid, *Helv. Chim. Acta*, 1946, **29**, 1144.
11 F. L. Lambert, W. D. Ellis and R. J. Parry, *J. Org. Chem.*, 1965, **30**, 304.
12 V. Paul, A. Sudalai, T. Daniel and K. V. Srinivasan, *Tetrahedron Lett.*, 1994, **35**, 7055.
13 M. C. Carreno and J. L. G. Ruano, *J. Org. Chem.*, 1995, **60**, 5328.
14 I. E. Marko and A. Mekhalfia, *Tetrahedron Lett.*, 1990, **31**, 7237.
15 The Hammett constants, σ^- values are from C. Hansch and A. Leo, *Substituent Constants for Correlation Analysis in Chemistry and Biology*, John Wiley & Sons, New York, 1979.
16 J. A. R. P. Sarma and G. R. Desiraju, *Acc. Chem. Res.*, 1986, **19**, 222.
17 G. R. Desiraju and T. Steiner, *The weak hydrogen bond: Applications to structural chemistry and biology*, Oxford University Press, New York, 1999.