# NMR study of stacking interactions between adenine and xanthine rings

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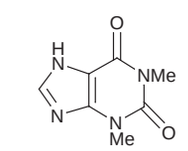
**A relationship between the chemical shifts of adenine and xanthine ring protons of 7-[ω-(6-aminopurin-9-yl)alkyl]-1,3-dimethylxanthines (1) and the number of carbons ($n$ = 2–10) in their polymethylene chains has been compared with that of 1-[ω-(6-aminopurin-9-yl)alkyl]-3,7-dimethylxanthines (2) in the buffer solutions at pD 7.0, 1.0 and 13.0 and in organic solvents. The relationship of 1 is clearly distinct from that of 2. The concentration dependence and the effects of temperature on the chemical shifts of 1 and 2 have also been investigated. While the upfield shifts of the ring protons of 1 and 2 in the buffer solutions at pD 7.0 and 13.0 are explained in terms of stacking interactions between adenine and xanthine rings, the results in the buffer solution at pD 1.0 may be due to cation–π interactions. On the basis of these data, it can be assumed that the stacking interactions do not only consist of interactions between adenine and xanthine rings.**

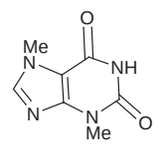
Recently, increasing interest is being shown in non-covalent intermolecular interactions. Stacking interactions are one of these non-covalent interactions between aromatic π-systems (π–π interactions) and have been of interest in connection with the structures of nucleic acids.[1] Sarai *et al.*[2] reported that the origin of the DNA helical structure was attributed largely to the stacking interactions of the base pairs. The interactions also seem to have a fundamental significance as intermolecular interactions in biological systems, *e.g.* the photosynthetic reaction center,[3] the recognition of cofactors by enzymes such as flavoenzymes,[4] and the connection between nucleic acid bases and aromatic amino acids.[5] Furthermore, it is noteworthy that the interactions are widely applicable to the molecular recognition of host–guest molecules.[6] However, the mechanism of stacking interactions is still obscure. For example, do stacking interactions consist of only non-covalent interactions between aromatic π-systems? One of the main purposes of this paper is to elucidate the question.

Much attention has been paid to the stacking interactions of the adenine ring, and the preparation of the adenine host molecules[7] has been extensively investigated. On the other hand, the UV and $^1$H NMR spectra of compounds linked between two adenine rings[8] and between adenine and aromatic molecules such as the other nucleic acid bases,[8a] indole,[9] flavin,[10] DNA intercalating molecules,[11,12] and naphthalene[13] with polymethylene chains[8–11] or other linkers[12,13] have been studied as model compounds for the stacking interactions. When the $^1$H NMR spectra of these compounds are measured in low concentrations close to those used in UV measurements on the studies of hypochromism,[8a–c] it is almost only the interactions between two aromatic rings of the compounds which are observed.[8d] The NMR data represent a population-weighted average of contributions from stacked and unstacked conformations, and random conformational motions of the compounds are presumed to become progressively greater with the length of linkers. Because changes of chemical shifts of the aromatic ring protons are expected to correspond to an increase in the population of stacked conformers compared with the random motions,[8d] it is of interest to investigate relationships between the chemical shifts and the length of the linkers in connection with the mechanism of stacking interactions.

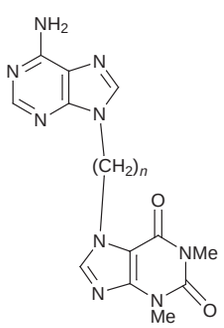
Since theophylline (1,3-dimethylxanthine) and theobromine (3,7-dimethylxanthine) are isomeric with each other, the present investigation was undertaken to determine the difference in



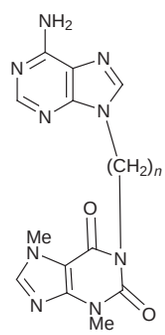
Theophylline
(1,3-Dimethylxanthine)



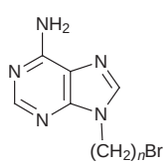
Theobromine
(3,7-Dimethylxanthine)



**1**



**2**



**3**

| | $n$ |
|---|---|
| **a** | 2 |
| **b** | 3 |
| **c** | 4 |
| **d** | 5 |
| **e** | 6 |
| **f** | 7 |
| **g** | 8 |
| **h** | 9 |
| **i** | 10 |

stacking interactions between 7-[ω-(6-aminopurin-9-yl)alkyl]-1,3-dimethylxanthines (**1**) and 1-[ω-(6-aminopurin-9-yl)alkyl]-3,7-dimethylxanthines (**2**), which are linked between adenine and theophylline and between adenine and theobromine by polymethylene chains, respectively.

## Results and discussion

The preparation of **1** and **2** was performed by treatment of 9-(ω-bromoalkyl)adenine (**3**) with theophylline or theobromine. The $^1$H NMR measurements of **1** and **2** were performed in the buffer solutions at pD 7.0, 1.0 and 13.0[14] containing sodium

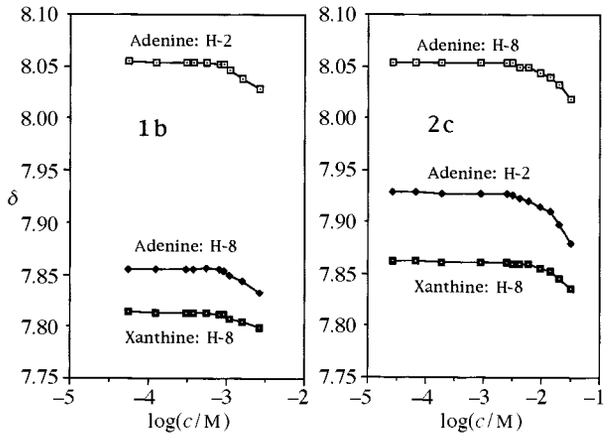



**Fig. 1** Relationship between the chemical shifts of the aromatic protons of **1b** and **2c** and the concentrations in the buffer solution at pD 7.0 at 27 °C

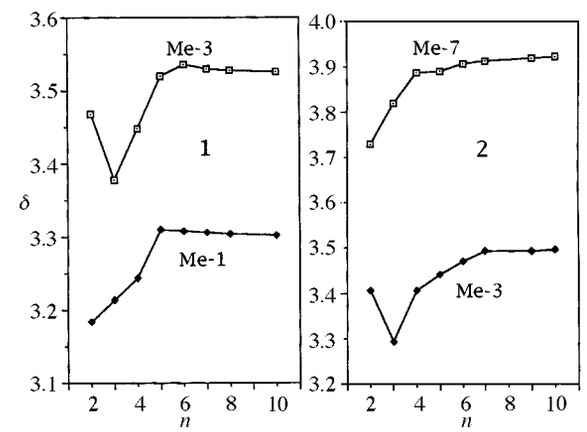



**Fig. 2** Relationship between the chemical shifts of the methyl group of the xanthine ring of **1** and **2** and the carbon numbers of the polymethylene chains in the buffer solution at pD 7.0 at 27 °C

3-(trimethylsilyl)[2,2,3,3-$^2H_4$]propionate and in organic solvents such as $CD_3OD$, $CDCl_3$ and $CD_3COCD_3$ containing tetramethylsilane as the references.

In order to establish appropriate concentrations of **1** and **2** for the $^1H$ NMR spectroscopy, a search was made for concentration dependence of the chemical shifts of the aromatic ring protons of **1b** and **2c** in the buffer solution at pD 7.0. Fig. 1 shows that aggregation of **1b** and **2c** in the buffer solution at pD 7.0 occurred gradually above 1.0 and 3.0 mM, respectively. From a consideration of the concentration dependence, aggregation of **1** and **2** is expected to be practically negligible at concentrations of less than 1–3 mmol $dm^{-3}$.

The hydrogen atoms of the adenine ring at the 2- and 8-positions and of the xanthine ring at the 8-position of **1a–i** ($n$ = 2–10) and **2a–i** ($n$ = 2–10) were assigned on the basis of the $^1H$ NMR spectra of the compounds containing an 8-deuterioadenine moiety as well as the comparison of the $^1H$ NMR spectra with those of 9,9′-(alkane-α,ω-diyl)diadenines.[8d] The compounds containing an 8-deuterioadenine moiety were obtained by the heating of **1** or **2** in $D_2O$ under reflux, although the xanthine moieties of **1** and **2** also somewhat underwent the deuterium exchange at their 8-positions.

The relationship between the chemical shifts of the adenine and xanthine ring protons of low concentrations (less than 1.0 mmol $dm^{-3}$) of **1** and the number of carbon atoms in the polymethylene chains was compared with that of **2**. The two methyl groups of the xanthine ring of **1** and **2** were assigned on the basis of the comparison of $^1H$ NMR spectra of **1** with those of **2**. The results are summarized in Tables 1 and 2. It can be seen from Tables 1 and 2 that the upfield shifts of the chemical

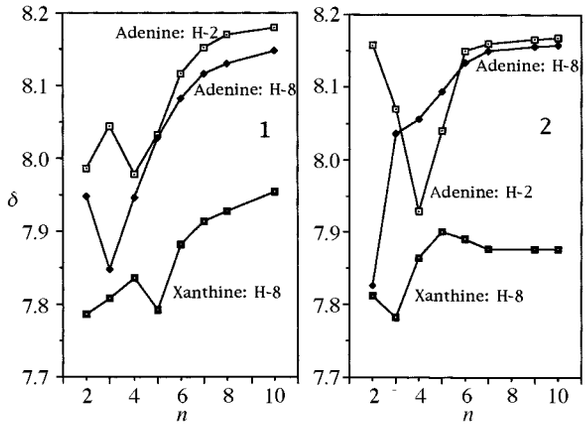



**Fig. 3** Relationship between the chemical shifts of the aromatic protons of **1** ($n$ = 2–10) and **2** ($n$ = 2–10) and the carbon numbers of the polymethylene chains in the buffer solution at pD 7.0 at 27 °C. The values of the chemical shifts of the protons are shown in Table 1 and Table 2.

shifts of two methyl groups of the xanthine ring of **1** and **2** in the buffer solutions used were pronounced when there were 2, 3 and 4 carbon atoms in the chain. Among the chemical shifts of the methyl groups at the 3-position of both **1** and **2**, the chemical shifts of **1b** and **2b** ($n$ = 3) were interestingly shifted to high field in the buffer solutions (Fig. 2).

The lines in Fig. 3 shows how the chemical shifts of the ring protons of **1** and **2** in the buffer solution at pD 7.0 varied with the number of carbons in the polymethylene chains at 27 °C. The upfield shifts of the ring protons of **1** and **2** are expected to result from the stacking interactions between the adenine and xanthine rings. Among the chemical shifts of adenine ring protons of **1**, the chemical shifts of H-2 of **1c** ($n$ = 4) and of H-8 of **1b** ($n$ = 3) were both shifted to high field. In Fig. 3, the two lines of the H-2 and H-8 protons of the adenine ring of **1** did not intersect each other, while the two lines of **2** intersected each other. The relationship of **1** is similar to that of 9,9′-(alkane-α,ω-diyl)diadenines reported previously.[8d] On the other hand, the relationship of **2** was peculiar. It is particularly noteworthy that the upfield shifts of H-2 of **2c** ($n$ = 4) and H-8 of the adenine ring of **2a** ($n$ = 2) were prominent among the chemical shifts of adenine ring protons of **2**.

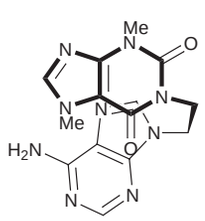
The temperature dependence of the chemical shifts of **1a–d** and **2a–d** ($n$ = 2–5) was studied in the range of 24 to 80 °C. The results are shown in Tables 3 and 4. The temperature dependence of the H-2 protons of the adenine ring was larger than that of the H-8 protons except for **2a**. The notable upfield shifts of the H-2 of **2c** and the H-8 of **2a**, which are shown in Fig. 3, were confirmed by their temperature dependence. The H-2 proton of the adenine ring of **2c** has pronounced temperature dependence, *i.e.* the differences between the chemical shifts of the H-2 proton of **2c** at 24 °C and those at 80 °C were 0.124 ppm (in the case of the concentration of 0.75 mmol $dm^{-3}$) and 0.165 ppm (at a concentration of 9.12 mmol $dm^{-3}$). The difference of the H-8 proton of the adenine ring of **2a** was 0.086 ppm. The temperature dependence of the chemical shifts of the methyl groups of the xanthine ring of **1** and **2** was not prominent, but the differences of the methyl group at the 3-position of **2b** and **2c** and of the methyl group at the 7-position of **2a** were somewhat larger, compared with those of the other methyl group.

The NMR studies may offer significant information about stacked conformations. In view of the above data, stacked conformations of **2a** seem to be different from those of **2c**. That is to say, the stacked conformations may vary with the change of the carbon numbers of the polymethylene chains of **2a** and **2c**, although the stacked conformations of **2a** may result in the shorter polymethylene chain. The stacked conformations of **2a** and **2c** may be tentatively presumed to be the structures shown below.

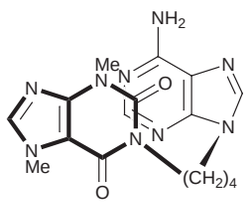
**Table 1** Chemical shifts of adenine and xanthine ring protons of **1a**–**i**[a]

| Solvent, Temp. | | **1a** ($n$ = 2) | **1b** ($n$ = 3) | **1c** ($n$ = 4) | **1d** ($n$ = 5) | **1e** ($n$ = 6) | **1f** ($n$ = 7) | **1g** ($n$ = 8) | **1i** ($n$ = 10) |
|---|---|---|---|---|---|---|---|---|---|
| pD 7.0,[b] 27 °C | Ade: H-2 | 7.985 | 8.043 | 7.978 | 8.033 | 8.117 | 8.152 | 8.170 | 8.180 |
| | Ade: H-8 | 7.948 | 7.848 | 7.945 | 8.029 | 8.082 | 8.117 | 8.130 | 8.148 |
| | Xan: H-8 | 7.786 | 7.808 | 7.835 | 7.792 | 7.882 | 7.913 | 7.927 | 7.954 |
| | Xan: Me-3 | 3.468 | 3.377 | 3.447 | 3.520 | 3.535 | 3.530 | 3.527 | 3.525 |
| | Xan: Me-1 | 3.184 | 3.214 | 3.244 | 3.310 | 3.307 | 3.306 | 3.304 | 3.302 |
| pD 7.0, 50 °C | Ade: H-2 | 8.012 | 8.066 | 8.007 | 8.068 | 8.150 | 8.179 | 8.205 | 8.215 |
| | Ade: H-8 | 7.938 | 7.865 | 7.943 | 8.022 | 8.080 | 8.114 | 8.123 | 8.139 |
| | Xan: H-8 | 7.755 | 7.798 | 7.824 | 7.786 | 7.875 | 7.907 | 7.921 | 7.940 |
| | Xan: Me-3 | 3.470 | 3.388 | 3.466 | 3.519 | 3.535 | 3.538 | 3.538 | 3.540 |
| | Xan: Me-1 | 3.200 | 3.224 | 3.249 | 3.310 | 3.314 | 3.317 | 3.318 | 3.318 |
| pD 1.0,[c] 27 °C | Ade: H-2 | 8.290 | 8.381 | 8.354 | 8.396 | 8.412 | 8.414 | 8.421 | 8.420 |
| | Ade: H-8 | 8.102 | 8.189 | 8.232 | 8.290 | 8.330 | 8.346 | 8.352 | 8.360 |
| | Xan: H-8 | 7.800 | 7.941 | 7.974 | 7.984 | 8.053 | 8.082 | 8.094 | 8.098 |
| | Xan: Me-3 | 3.496 | 3.436 | 3.496 | 3.525 | 3.534 | 3.532 | 3.531 | 3.530 |
| | Xan: Me-1 | 3.234 | 3.263 | 3.273 | 3.325 | 3.326 | 3.326 | 3.327 | 3.327 |
| pD 1.0, 50 °C | Ade: H-2 | 8.290 | 8.381 | 8.358 | 8.399 | 8.417 | 8.420 | 8.426 | 8.427 |
| | Ade: H-8 | 8.117 | 8.201 | 8.236 | 8.289 | 8.328 | 8.342 | 8.349 | 8.357 |
| | Xan: H-8 | 7.803 | 7.932 | 7.949 | 7.961 | 8.032 | 8.057 | 8.068 | 8.072 |
| | Xan: Me-3 | 3.492 | 3.444 | 3.501 | 3.524 | 3.533 | 3.530 | 3.529 | 3.529 |
| | Xan: Me-1 | 3.236 | 3.266 | 3.276 | 3.323 | 3.324 | 3.326 | 3.326 | 3.327 |
| pD 13.0,[b] 27 °C | Ade: H-2 | 7.998 | 8.053 | 7.976 | 8.029 | 8.128 | 8.160 | 8.175 | 8.183 |
| | Ade: H-8 | 7.952 | 7.854 | 7.944 | 8.029 | 8.082 | 8.123 | 8.137 | 8.144 |
| | Xan: H-8 | 7.787 | 7.812 | 7.834 | 7.790 | 7.881 | 7.918 | 7.934 | 7.951 |
| | Xan: Me-3 | 3.471 | 3.384 | 3.456 | 3.520 | 3.538 | 3.535 | 3.533 | 3.532 |
| | Xan: Me-1 | 3.186 | 3.221 | 3.251 | 3.311 | 3.311 | 3.310 | 3.309 | 3.308 |
| pD 13.0, 50 °C | Ade: H-2 | 8.012 | 8.072 | 8.007 | 8.068 | 8.153 | 8.183 | 8.211 | 8.208 |
| | Ade: H-8 | 7.940 | 7.868 | 7.941 | 8.023 | 8.081 | 8.116 | 8.129 | 8.137 |
| | Xan: H-8 | 7.755 | 7.800 | 7.823 | 7.787 | 7.875 | 7.910 | 7.927 | 7.944 |
| | Xan: Me-3 | 3.469 | 3.390 | 3.466 | 3.520 | 3.539 | 3.534 | 3.533 | 3.533 |
| | Xan: Me-1 | 3.200 | 3.226 | 3.249 | 3.311 | 3.316 | 3.316 | 3.318 | 3.318 |
| $CD_3OD$,[d] 27 °C | Ade: H-2 | 8.081 | 8.142 | 8.115 | 8.160 | 8.182 | 8.185 | 8.188 | 8.190 |
| | Ade: H-8 | 7.852 | 8.040 | 8.048 | 8.091 | 8.104 | 8.106 | 8.108 | 8.111 |
| | Xan: H-8 | 7.524 | 7.895 | 7.875 | 7.873 | 7.902 | 7.907 | 7.911 | 7.914 |
| | Xan: Me-3 | 3.486 | 3.484 | 3.512 | 3.534 | 3.535 | 3.533 | 3.535 | 3.533 |
| | Xan: Me-1 | *e* | *e* | *e* | 3.348 | 3.347 | 3.345 | 3.346 | 3.346 |
| $CDCl_3$,[f] 27 °C | Ade: H-2 | 8.364 | 8.370 | 8.343 | 8.348 | 8.349 | 8.355 | 8.360 | 8.365 |
| | Ade: H-8 | 7.459 | 7.826 | 7.791 | 7.788 | 7.788 | 7.787 | 7.786 | 7.784 |
| | Xan: H-8 | 7.084 | 7.816 | 7.513 | 7.493 | 7.521 | 7.524 | 7.524 | 7.523 |
| | Xan: Me-3 | 3.562 | 3.591 | 3.583 | 3.591 | 3.592 | 3.592 | 3.593 | 3.595 |
| | Xan: Me-1 | 3.458 | 3.415 | 3.409 | 3.408 | 3.404 | 3.405 | 3.405 | 3.407 |
| $CD_3COCD_3$,[f] 27 °C | Ade: H-2 | 8.119 | 8.179 | 8.141 | 8.157 | 8.169 | 8.176 | 8.175 | 8.185 |
| | Ade: H-8 | 7.679 | 8.023 | 7.985 | 7.984 | 7.982 | 7.994 | 7.990 | 7.010 |
| | Xan: H-8 | 7.418 | 7.997 | 7.877 | 7.846 | 7.868 | 7.872 | 7.878 | 7.886 |
| | Xan: Me-3 | 3.439 | 3.473 | 3.470 | 3.480 | 3.480 | 3.480 | 3.482 | 3.482 |
| | Xan: Me-1 | 3.314 | 3.307 | 3.274 | 3.292 | 3.285 | 3.287 | 3.288 | 3.288 |

[a] The $^1$H NMR spectra of **1** were measured at least twice and the chemical shifts were reproduced within ±0.003 ppm. [b] The concentrations of **1** in the buffer solutions at pD 7.0 and 13.0 were 1.0 mmol dm$^{-3}$ except for **1g** (0.5 mmol dm$^{-3}$) and **1i** (0.1 mmol dm$^{-3}$). [c] The concentrations of **1** in the buffer solution at pD 1.0 were 1.5 mmol dm$^{-3}$ except for **1g** (1.0 mmol dm$^{-3}$) and **1i** (0.5 mmol dm$^{-3}$). [d] The concentrations of **1** in $CD_3OD$ was 2.0 mmol dm$^{-3}$. [e] The methyl peaks were overlapped with those of $CD_3OD$. [f] The concentrations of **1** in $CDCl_3$ and in $CD_3COCD_3$ were 2.0 mmol dm$^{-3}$ except for **1a**,**b** (1.0 mmol dm$^{-3}$).




**2a**




**2c**

In an effort to determine the effect of the protonation of the adenine ring on the stacking, the NMR spectra of **1** and **2** in the buffer solution at pD 1.0 were studied.[14] Fig. 4 shows the concentration dependence of **1c** and **2c** in the buffer solution at pD 1.0. The aggregation of **1c** and **2c** occurred gradually above 10 mM. Whereas Fig. 1 shows that the aggregation of **1b** and **2c** in the buffer solution at pD 7.0 produced a shift to a higher field in the adenine proton resonance as compared to the isolated ones, the chemical shifts of adenine ring protons of **1c** and **2c** in the buffer solution at pD 1.0 were shifted to a lower field with the increase of the concentrations. The results are similar to those of the interactions between $N^7$-methylated guanine and indole rings.[15] Ishida and co-workers[15] explained the results in terms of ionic interactions between the electron positive proton of guanine and the π-electron-rich indole ring.

Fig. 5 shows the relationship between the chemical shifts of the concentrations of less than 1.5 mmol dm$^{-3}$ of **1** and **2** and the number of carbons in the linkage chain, in the buffer solution at pD 1.0 at 27 °C. The relationship in the buffer solution at pD 1.0 at 50 °C was similar to that at 27 °C (Tables 1 and 2). Table 4 further shows that the effect of temperature on the H-2 proton of the adenine ring of **2c** in the buffer solution at pD 1.0 was significantly smaller than that in the buffer solution at pD 7.0. The data reported herein indicate that the interactions between adenine and xanthine rings in the buffer solution at pD 1.0 were slightly affected by the temperature. The chemical shifts of H-8 protons of adenine and xanthine rings of **1** were shifted to higher fields with the decrease of the carbon numbers but the shifts of H-2 of the adenine ring of **1** were small as compared with those of the H-8 protons. Furthermore, the chemical shifts of the ring protons of **2** were almost kept constant when more than five carbons were present in the poly-

**Table 2** Chemical shifts of adenine and xanthine ring protons of **2a**–**i**[a]

| Solvent, Temp. | | **2a** ($n = 2$) | **2b** ($n = 3$) | **2c** ($n = 4$) | **2d** ($n = 5$) | **2e** ($n = 6$) | **2f** ($n = 7$) | **2h** ($n = 9$) | **2i** ($n = 10$) |
|---|---|---|---|---|---|---|---|---|---|
| pD 7.0,[b] 27 °C | Ade: H-2 | 8.157 | 8.069 | 7.929 | 8.039 | 8.150 | 8.160 | 8.165 | 8.167 |
| | Ade: H-8 | 7.826 | 8.035 | 8.055 | 8.094 | 8.133 | 8.150 | 8.155 | 8.157 |
| | Xan: H-8 | 7.812 | 7.782 | 7.864 | 7.901 | 7.891 | 7.876 | 7.877 | 7.877 |
| | Xan: Me-7 | 3.728 | 3.820 | 3.888 | 3.890 | 3.908 | 3.914 | 3.920 | 3.924 |
| | Xan: Me-3 | 3.407 | 3.293 | 3.405 | 3.443 | 3.470 | 3.492 | 3.495 | 3.498 |
| pD 7.0, 50 °C | Ade: H-2 | 8.142 | 8.093 | 7.977 | 8.090 | 8.182 | 8.193 | 8.200 | 8.202 |
| | Ade: H-8 | 7.846 | 8.041 | 8.056 | 8.078 | 8.115 | 8.135 | 8.143 | 8.145 |
| | Xan: H-8 | 7.820 | 7.779 | 7.856 | 7.890 | 7.892 | 7.880 | 7.866 | 7.867 |
| | Xan: Me-7 | 3.740 | 3.824 | 3.892 | 3.901 | 3.910 | 3.920 | 3.925 | 3.928 |
| | Xan: Me-3 | 3.407 | 3.317 | 3.422 | 3.450 | 3.479 | 3.493 | 3.500 | 3.503 |
| pD 1.0,[c] 27 °C | Ade: H-2 | 8.321 | 8.381 | 8.355 | 8.398 | 8.411 | 8.419 | 8.420 | 8.420 |
| | Ade: H-8 | 8.233 | 8.358 | 8.348 | 8.354 | 8.363 | 8.369 | 8.368 | 8.368 |
| | Xan: H-8 | 7.945 | 7.933 | 7.995 | 8.015 | 8.021 | 8.022 | 8.021 | 8.022 |
| | Xan: Me-7 | 3.814 | 3.898 | 3.933 | 3.944 | 3.951 | 3.957 | 3.956 | 3.957 |
| | Xan: Me-3 | 3.427 | 3.405 | 3.468 | 3.487 | 3.500 | 3.513 | 3.513 | 3.514 |
| pD 1.0, 50 °C | Ade: H-2 | 8.320 | 8.385 | 8.364 | 8.402 | 8.418 | 8.425 | 8.428 | 8.429 |
| | Ade: H-8 | 8.232 | 8.357 | 8.347 | 8.350 | 8.361 | 8.367 | 8.365 | 8.365 |
| | Xan: H-8 | 7.935 | 7.926 | 7.982 | 8.000 | 8.007 | 8.009 | 8.008 | 8.009 |
| | Xan: Me-7 | 3.817 | 3.898 | 3.932 | 3.943 | 3.951 | 3.957 | 3.956 | 3.957 |
| | Xan: Me-3 | 3.425 | 3.414 | 3.472 | 3.487 | 3.502 | 3.513 | 3.514 | 3.514 |
| pD 13.0,[b] 27 °C | Ade: H-2 | 8.160 | 8.075 | 7.929 | 8.031 | 8.144 | 8.158 | 8.162 | 8.164 |
| | Ade: H-8 | 7.828 | 8.038 | 8.054 | 8.088 | 8.128 | 8.148 | 8.153 | 8.156 |
| | Xan: H-8 | 7.816 | 7.781 | 7.862 | 7.892 | 7.886 | 7.876 | 7.873 | 7.874 |
| | Xan: Me-7 | 3.731 | 3.829 | 3.874 | 3.886 | 3.902 | 3.912 | 3.918 | 3.920 |
| | Xan: Me-3 | 3.410 | 3.306 | 3.404 | 3.438 | 3.466 | 3.493 | 3.499 | 3.502 |
| pD 13.0, 50 °C | Ade: H-2 | 8.146 | 8.094 | 7.976 | 8.086 | 8.171 | 8.189 | 8.199 | 8.200 |
| | Ade: H-8 | 7.848 | 8.042 | 8.058 | 8.075 | 8.109 | 8.135 | 8.143 | 8.145 |
| | Xan: H-8 | 7.824 | 7.777 | 7.855 | 7.884 | 7.878 | 7.872 | 7.865 | 7.864 |
| | Xan: Me-7 | 3.742 | 3.829 | 3.880 | 3.897 | 3.907 | 3.923 | 3.924 | 3.925 |
| | Xan: Me-3 | 3.408 | 3.322 | 3.421 | 3.447 | 3.477 | 3.498 | 3.505 | 3.506 |
| $CD_3OD$,[d] 27 °C | Ade: H-2 | 8.067 | 8.142 | 8.131 | 8.166 | 8.184 | 8.189 | 8.192 | 8.194 |
| | Ade: H-8 | 7.910 | 8.170 | 8.131 | 8.117 | 8.131 | 8.129 | 8.124 | 8.122 |
| | Xan: H-8 | 7.790 | 7.817 | 7.834 | 7.841 | 7.842 | 7.842 | 7.841 | 7.842 |
| | Xan: Me-7 | 3.798 | 3.931 | 3.943 | 3.947 | 3.956 | 3.958 | 3.962 | 3.964 |
| | Xan: Me-3 | 3.414 | 3.475 | 3.495 | 3.501 | 3.509 | 3.513 | 3.516 | 3.518 |
| $CDCl_3$,[e] 27 °C | Ade: H-2 | 8.227 | 8.341 | 8.344 | 8.350 | 8.354 | 8.358 | 8.365 | 8.368 |
| | Ade: H-8 | 7.773 | 7.988 | 7.879 | 7.804 | 7.806 | 7.805 | 7.800 | 7.794 |
| | Xan: H-8 | 7.473 | 7.503 | 7.501 | 7.498 | 7.500 | 7.498 | 7.494 | 7.492 |
| | Xan: Me-7 | 3.872 | 3.972 | 3.975 | 3.975 | 3.980 | 3.982 | 3.982 | 3.983 |
| | Xan: Me-3 | 3.524 | 3.563 | 3.566 | 3.566 | 3.568 | 3.571 | 3.571 | 3.572 |
| $CD_3COCD_3$,[e] 27 °C | Ade: H-2 | 7.951 | 8.157 | 8.148 | 8.160 | 8.169 | 8.172 | 8.179 | 8.180 |
| | Ade: H-8 | 7.951 | 8.105 | 8.039 | 8.008 | 8.021 | 8.023 | 8.014 | 8.007 |
| | Xan: H-8 | 7.767 | 7.810 | 7.806 | 7.801 | 7.803 | 7.803 | 7.805 | 7.807 |
| | Xan: Me-7 | 3.835 | 3.966 | 3.963 | 3.968 | 3.970 | 3.972 | 3.974 | 3.976 |
| | Xan: Me-3 | 3.388 | 3.458 | 3.456 | 3.458 | 3.460 | 3.463 | 3.466 | 3.468 |

[a] The $^1$H NMR spectra of **2** were measured at least twice and the chemical shifts were reproduced within ±0.004 ppm. [b] The concentrations of **2** in the buffer solutions at pD 7.0 and 13.0 were 1.0 mmol dm$^{-3}$ except for **2h** (0.5 mmol dm$^{-3}$) and **2i** (0.1 mmol dm$^{-3}$). [c] The concentrations of **2** in the buffer solution at pD 1.0 was 1.5 mmol dm$^{-3}$ except for **2h** (1.0 mmol dm$^{-3}$) and **2i** (0.2 mmol dm$^{-3}$). [d] The concentrations of **2** in $CD_3OD$ were 2.0 mmol dm$^{-3}$. [e] The concentrations of **2** in $CDCl_3$ and in $CD_3COCD_3$ were 2.0 mmol dm$^{-3}$ except for **2a**,**b** (1.0 mmol dm$^{-3}$).

methylene chains. When the data shown in Figs. 4 and 5 are compared with those in Figs. 1 and 3, interactions of **1** and **2** in the buffer solution at pD 1.0 seem to be different from those in the buffer solution at pD 7.0. The initial stage of the reaction of the adenine ring in aqueous solution at pH 1 instead of pH 7 is the protonation at the 1-position.[1] Therefore, the results in the buffer solution at pD 1.0 may be interpretable in terms of electrostatic interactions between the cation formed by the protonation of the adenine ring and the π-electrons of xanthine ring (cation–π interactions[16]), whereas the interactions in the buffer solution at pD 7.0 are due to stacking interactions.

The relationship between the chemical shifts of the ring protons of low concentrations (less than 1.0 mmol dm$^{-3}$) of **1** and **2** and the number of carbons in the polymethylene chains in the buffer solution at pD 13.0[14] at 27 °C (Tables 1 and 2) resembled that in the buffer solution at pD 7.0. The relationship in the buffer solution at pD 13.0 at 50 °C was also similar to that in the buffer solution at pD 7.0 at 50 °C. Accordingly, stacked conformations of **1** and **2** may not be altered by a change of pH in the pH 7 to 13 region.

The relationship between the chemical shifts of the concentrations of less than 2.0 mmol dm$^{-3}$ of **1** and **2** and the number of carbons was investigated in organic solvents such as $CD_3OD$, $CDCl_3$ and $CD_3COCD_3$ at 27 °C in order to compare with that in aqueous solutions (Tables 1 and 2). The relationship in $CD_3OD$ is somewhat similar to that in the buffer solution at pD 7.0, although the change of the chemical shifts was very small. When the number of carbons in the polymethylene chains was more than 4, the chemical shifts of **1** and **2** in $CDCl_3$ and in $CD_3COCD_3$ were little influenced by the carbon numbers. Furthermore, the prominent upfield shifts of H-2 of **2c** ($n = 4$) in the buffer solution at pD 7.0 were not observed in $CDCl_3$ and in $CD_3COCD_3$. The results confirmed an effect of water as solvent on the aggregation of **1** and **2**.

If stacking interactions depend only on interactions between two aromatic π-systems, the relationships between the chemical shifts and the carbon numbers of **1** in the buffer solutions at pD 7.0 and 13.0 are expected to be similar to those of **2**. However, the relationships of **1** in aqueous solutions were plainly distinct from those of **2**. In view of the results, one might conclude that the stacking interactions did not consist of only interactions between adenine and xanthine rings.

Stacking interactions between aromatic molecules play an important role in the tertiary structures of biomolecules, but

**Table 3** Effect of temperature on the chemical shifts of **1a**–**d**[a]

| | δ | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **1a** (concentration: 2.40 mmol dm$^{-3}$) | | | | | **1b** (2.46 mmol dm$^{-3}$) | | | | |
| *T*/°C | Ade-2 | Ade-8 | Xan-8 | Xan-Me-3 | Xan-Me-1 | Ade-2 | Ade-8 | Xan-8 | Xan-Me-3 | Xan-Me-1 |
| 24 | 7.976 | 7.944 | 7.786 | 3.466 | 3.179 | 8.035 | 7.841 | 7.803 | 3.372 | 3.210 |
| 30 | 7.984 | 7.942 | 7.779 | 3.466 | 3.184 | 8.042 | 7.845 | 7.800 | 3.375 | 3.213 |
| 40 | 7.996 | 7.939 | 7.766 | 3.467 | 3.191 | 8.054 | 7.854 | 7.798 | 3.381 | 3.218 |
| 50 | 8.008 | 7.936 | 7.754 | 3.468 | 3.197 | 8.064 | 7.863 | 7.795 | 3.386 | 3.223 |
| 60 | 8.019 | 7.931 | 7.740 | 3.468 | 3.205 | 8.074 | 7.870 | 7.792 | 3.392 | 3.228 |
| 70 | 8.030 | 7.927 | 7.727 | 3.469 | 3.210 | 8.083 | 7.877 | 7.788 | 3.396 | 3.231 |
| 80 | 8.040 | 7.922 | 7.715 | 3.469 | 3.217 | 8.092 | 7.884 | 7.785 | 3.401 | 3.235 |
| Δδ[b] | +0.064 | −0.022 | −0.071 | +0.003 | +0.038 | +0.057 | +0.043 | −0.018 | +0.029 | +0.025 |
| | **1c** (1.70 mmol dm$^{-3}$) | | | | | **1d** (1.78 mmol dm$^{-3}$) | | | | |
| *T*/°C | Ade-2 | Ade-8 | Xan-8 | Xan-Me-3 | Xan-Me-1 | Ade-2 | Ade-8 | Xan-8 | Xan-Me-3 | Xan-Me-1 |
| 24 | 7.960 | 7.934 | 7.827 | 3.446 | 3.244 | 8.007 | 8.019 | 7.786 | 3.511 | 3.302 |
| 30 | 7.968 | 7.934 | 8.825 | 3.449 | 3.244 | 8.024 | 8.019 | 7.785 | 3.512 | 3.303 |
| 40 | 7.985 | 7.935 | 7.822 | 3.456 | 3.245 | 8.044 | 8.019 | 7.784 | 3.513 | 3.305 |
| 50 | 8.000 | 7.936 | 7.819 | 3.461 | 3.245 | 8.061 | 8.018 | 7.784 | 3.515 | 3.307 |
| 60 | 8.016 | 7.938 | 7.816 | 3.467 | 3.246 | 8.078 | 8.018 | 7.783 | 3.516 | 3.308 |
| 70 | 8.030 | 7.940 | 7.812 | 3.471 | 3.247 | 8.094 | 8.017 | 7.783 | 3.517 | 3.310 |
| 80 | 8.046 | 7.942 | 7.809 | 3.476 | 3.248 | 8.109 | 8.015 | 7.783 | 3.518 | 3.310 |
| Δδ[b] | +0.086 | +0.008 | −0.018 | +0.030 | +0.004 | +0.102 | −0.004 | −0.003 | +0.007 | +0.008 |

[a] Chemical shifts in the buffer solution at pD 7.0. [b] $\Delta\delta = \delta(80\ °C) - \delta(24\ °C)$.

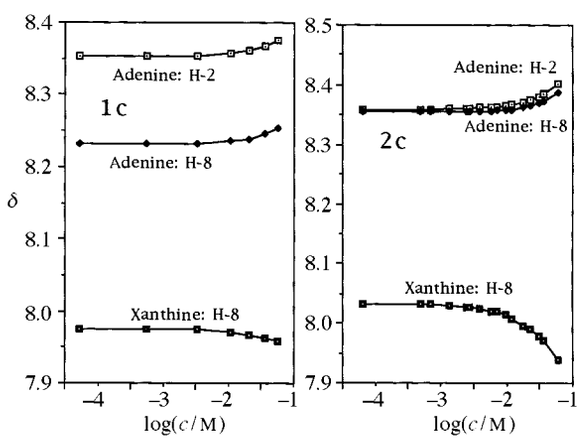



**Fig. 4** Relationship between the chemical shifts of the aromatic protons of **1c** and **2c** and the concentrations in the buffer solution at pD 1.0 at 27 °C

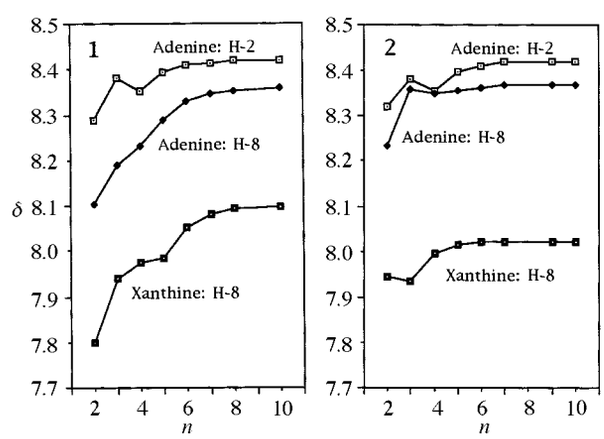



**Fig. 5** Relationship between the chemical shifts of the aromatic protons of **1** and **2** and the carbon numbers of the polymethylene chains in the buffer solution at pD 1.0 at 27 °C. The values of the chemical shifts of the protons are shown in Tables 1 and 2.

the relation between the stacking interactions and backbone of biomolecules, such as in the case of DNA helical structures,[1,2] is not sufficiently clear. The reason why the stacking of **1** is different from that of **2** is of interest in connection with this relation. The difference may be attributable to hydrophobic effects of the polymethylene chains on the interactions between adenine and xanthine rings. Although the literature contains several references to the contribution of hydrophobic (solvophobic) effects to stacking interactions,[7f,17] this investigation suggests that the hydrophobic effects of the polymethylene chains as the linkers between two aromatic rings may influence the interactions.

## Experimental

The melting points were determined on a Yanagimoto micro melting-point apparatus and are uncorrected. The elemental analyses were performed by the Analytical Center of Kyoto University.

### NMR spectroscopy

The $^1$H NMR spectra (400 MHz) and $^{13}$C NMR spectra (100 MHz) were obtained with a JEOL GSX400 spectrometer. The chemical shifts (δ values) were measured in parts per million (ppm) downfield from sodium 3-(trimethylsilyl)[2,2,3,3-$^2H_4$]propionate in the buffer solutions and from tetramethylsilane in organic solvents as internal references. The concentrations of 3-(trimethylsilyl)[2,2,3,3-$^2H_4$]propionate were 0.6 mmol dm$^{-3}$ in the sodium phosphate buffer solution at pD 7.0 and 0.8 mmol dm$^{-3}$ in the HCl–KCl buffer solution at pD 1.0 and the NaOH–NaCl buffer solution at pD 13.0. The $^1$H NMR spectra were obtained from accumulation of 40–3000 free induction decays after each 45° pulse (5.7 μs) repeated every 5.73 s and were observed over a spectral width of 6002.4 Hz, corresponding to 32 768 data points for an acquisition time of 2.73 s. The $^1$H NMR spectra of **1** and **2** were measured at least twice and the chemical shifts of **1** and **2** were reproduced within ±0.003 and ±0.004 ppm, respectively. *J* Values are given in Hz.

**9-(ω-Bromoalkyl)adenine (3).** Into a solution of adenine (10 mmol) in DMF (150 ml), potassium carbonate (10 mmol) and α,ω-dibromoalkane (12 mmol) were added. The mixture was stirred at room temperature for 15–24 h. The resulting mixture was evaporated to give a residue which was extracted with chloroform. The extract was evaporated and chromatographed over silica gel. By elution with a mixture of ethyl acetate and methanol, **3** was obtained. The preparation of **3a**,[8d] **3b**,[8a] **3e**,[8d] **3f**[8d] and **3i**[8d] has already been reported.

**Table 4** Effect of temperature on the chemical shifts of **2a**–**d**[a]

| | $\delta$ | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **2a** (concentration: 2.50 mmol dm$^{-3}$) | | | | | **2b** (2.71 mmol dm$^{-3}$) | | | | |
| *T*/°C | Ade-2 | Ade-8 | Xan-8 | Xan-Me-7 | Xan-Me-3 | Ade-2 | Ade-8 | Xan-8 | Xan-Me-7 | Xan-Me-3 |
| 24 | 8.152 | 7.799 | 7.824 | 3.722 | 3.402 | 8.047 | 8.019 | 7.770 | 3.815 | 3.286 |
| 30 | 8.149 | 7.811 | 7.823 | 3.726 | 3.403 | 8.058 | 8.024 | 7.771 | 3.817 | 3.294 |
| 40 | 8.145 | 7.826 | 7.822 | 3.732 | 3.403 | 8.073 | 8.030 | 7.772 | 3.820 | 3.305 |
| 50 | 8.139 | 7.842 | 7.820 | 3.738 | 3.403 | 8.085 | 8.034 | 7.772 | 3.823 | 3.316 |
| 60 | 8.133 | 7.856 | 7.816 | 3.743 | 3.403 | 8.095 | 8.038 | 7.772 | 3.825 | 3.324 |
| 70 | 8.127 | 7.871 | 7.814 | 3.748 | 3.404 | 8.105 | 8.040 | 7.771 | 3.828 | 3.333 |
| 80 | 8.118 | 7.885 | 7.809 | 3.753 | 3.404 | 8.116 | 8.043 | 7.771 | 3.831 | 3.342 |
| $\Delta\delta$[c] | +0.034 | −0.086 | −0.015 | +0.031 | +0.002 | +0.069 | +0.024 | −0.001 | +0.016 | +0.056 |
| | **2c** (0.75 mmol dm$^{-3}$) | | | | | **2c** (9.12 mmol dm$^{-3}$) | | | | |
| *T*/°C | Ade-2 | Ade-8 | Xan-8 | Xan-Me-7 | Xan-Me-3 | Ade-2 | Ade-8 | Xan-8 | Xan-Me-7 | Xan-Me-3 |
| 24 | 7.920 | 8.055 | 7.864 | 3.888 | 3.405 | 7.869 | 8.018 | 7.840 | 3.843 | 3.363 |
| 30 | 7.937 | 8.056 | 7.862 | 3.890 | 3.408 | 7.892 | 8.023 | 7.841 | 3.849 | 3.372 |
| 40 | 7.957 | 8.057 | 7.860 | 3.892 | 3.415 | 7.926 | 8.033 | 7.842 | 3.858 | 3.387 |
| 50 | 7.978 | 8.059 | 7.857 | 3.894 | 3.422 | 7.954 | 8.040 | 7.842 | 3.864 | 3.397 |
| 60 | 8.000 | 8.060 | 7.854 | 3.895 | 3.428 | 7.982 | 8.045 | 7.842 | 3.872 | 3.409 |
| 70 | 8.022 | 8.060 | 7.852 | 3.897 | 3.435 | 8.009 | 8.051 | 7.842 | 3.876 | 3.416 |
| 80 | 8.044 | 8.062 | 7.850 | 3.899 | 3.441 | 8.034 | 8.056 | 7.842 | 3.882 | 3.425 |
| $\Delta\delta$[c] | +0.124 | +0.007 | −0.014 | +0.011 | +0.036 | +0.165 | −0.038 | +0.002 | +0.039 | +0.062 |
| | **2c**[b] (61.28 mmol dm$^{-3}$ in pD 1.0) | | | | | **2d** (1.74 mmol dm$^{-3}$) | | | | |
| *T*/°C | Ade-2 | Ade-8 | Xan-8 | Xan-Me-7 | Xan-Me-3 | Ade-2 | Ade-8 | Xan-8 | Xan-Me-7 | Xan-Me-3 |
| 24 | 8.401 | 8.388 | 7.939 | 3.924 | 3.436 | 8.016 | 8.082 | 7.887 | 3.874 | 3.430 |
| 30 | 8.403 | 8.388 | 7.938 | 3.926 | 3.441 | 8.031 | 8.082 | 7.886 | 3.877 | 3.434 |
| 40 | 8.409 | 8.389 | 7.936 | 3.931 | 3.452 | 8.052 | 8.083 | 7.883 | 3.881 | 3.440 |
| 50 | 8.413 | 8.389 | 7.934 | 3.936 | 3.460 | 8.072 | 8.083 | 7.880 | 3.885 | 3.445 |
| 60 | 8.416 | 8.388 | 7.930 | 3.940 | 3.467 | 8.089 | 8.081 | 7.875 | 3.888 | 3.449 |
| 70 | 8.419 | 8.387 | 7.925 | 3.943 | 3.472 | 8.105 | 8.080 | 7.872 | 3.892 | 3.453 |
| 80 | 8.421 | 8.386 | 7.920 | 3.946 | 3.476 | 8.119 | 8.079 | 7.867 | 3.895 | 3.457 |
| $\Delta\delta$[c] | +0.020 | −0.002 | −0.019 | +0.022 | +0.040 | +0.103 | −0.003 | −0.020 | +0.021 | +0.027 |

[a] Chemical shifts in the buffer solution at pD 7.0 except for **2c**. [b] Chemical shifts in the buffer solution at pD 1.0. [c] $\Delta\delta = \delta(80\ °C) - \delta(24\ °C)$.

**9-(4-Bromobutyl)adenine (3c).** Yield 22%, mp >300 °C; $\delta_H(CDCl_3)$ 8.37 (s, 1H), 7.81 (s, 1H), 5.67 (s, 2H, $NH_2$), 4.25 (t, 2H, *J* 7.2), 3.44 (t, 2H, *J* 6.8), 2.10 (quint, 2H, *J* 7), 1.90 (quint, 2H, *J* 7); $\delta_C(CDCl_3)$ 155.43, 153.10, 150.21, 140.27, 119.70, 42.98, 32.45, 29.55, 28.78. Found: C, 40.12; H, 4.47; N, 26.23. Calc. for $C_9H_{12}N_5Br$: C, 40.02; H, 4.48; N, 25.93%.

**9-(5-Bromopentyl)adenine (3d).** Yield 34%, mp 148–149 °C; $\delta_H(CDCl_3)$ 8.37 (s, 1H), 7.80 (s, 1H), 5.66 (s, 2H, $NH_2$), 4.22 (t, 2H, *J* 7.2), 3.39 (t, 2H, *J* 7.2), 1.95 (quint, 2H, *J* 7.2), 1.91 (quint, 2H, *J* 7.2), 1.51 (quint, 2H, *J* 7.2); $\delta_C(CDCl_3)$ 155.65, 153.02, 150.11, 140.31, 119.70, 43.71, 33.15, 31.99, 29.26, 25.21. Found: C, 42.14; H, 4.91; N, 24.64. Calc. for $C_{10}H_{14}N_5Br$: C, 42.27; H, 4.97; N, 24.65%.

**9-(8-Bromooctyl)adenine (3g).** Yield 30%, mp 140–141 °C; $\delta_H(CDCl_3)$ 8.37 (s, 1H), 7.79 (s, 1H), 5.57 (s, 2H, $NH_2$), 4.19 (t, 2H, *J* 7.2), 3.39 (t, 2H, *J* 6.8), 1.90 (quint, 2H, *J* 7), 1.83 (quint, 2H, *J* 7), 1.41 (quint, 2H, *J* 7), 1.37–1.25 (m, 6H); $\delta_C(CDCl_3)$ 155.53, 152.98, 150.15, 140.41, 119.71, 43.92, 33.86, 32.66, 30.05, 28.85, 28.53, 27.98, 26.54. Found: C, 48.05; H, 6.03; N, 21.51. Calc. for $C_{13}H_{20}N_5Br$: C, 47.86; H, 6.18; N, 21.47%.

**9-(9-Bromononyl)adenine (3h).** Yield 32%, mp 120.5–121.5 °C; $\delta_H(CDCl_3)$ 8.37 (s, 1H), 7.79 (s, 1H), 5.89 (s, 2H, $NH_2$), 4.19 (t, 2H, *J* 7.2), 3.39 (t, 2H, *J* 6.8), 1.90 (quint, 2H, *J* 7), 1.84 (quint, 2H, *J* 7), 1.41 (quint, 2H, *J* 7), 1.36–1.25 (m, 8H); $\delta_C(CDCl_3)$ 155.53, 152.97, 150.16, 140.42, 119.72, 43.95, 33.94, 32.74, 30.07, 29.19, 28.92, 28.59, 28.06, 26.60. Found: C, 49.43; H, 6.55; N, 20.78. Calc. for $C_{14}H_{22}N_9Br$: C, 49.42; H, 6.52; N, 20.58%.

**7-[ω-(6-Aminopurin-9-yl)alkyl]-1,3-dimethylxanthine (1) and 1-[ω-(6-aminopurin-9-yl)alkyl]-3,7-dimethylxanthine (2).** Into a solution of theophylline (1,3-dimethylxanthine) or theobromine (3,7-dimethylxanthine) (1.2 mmol) in DMF (50 ml), potassium carbonate (1 mmol) and 9-(ω-bromoalkyl)adenine (**3**) (1 mmol) were added. The mixture was stirred at room temperature for 40 h. The resulting mixture was evaporated to give a residue which was submitted to chromatography over silica gel. Elution of a mixture of ethyl acetate and methanol gave **1** or **2**.

7-[2-(6-*Aminopurin*-9-*yl*)*ethyl*]-1,3-*dimethylxanthine* (**1a**).—Yield 43%, mp 290–293 °C; $\delta_H(CDCl_3)$ 8.36 (s, 1H), 7.46 (s, 1H), 7.08 (s, 1H), 5.52 (s, 2H, $NH_2$), 4.81 (t, 2H, *J* 6.5), 4.73 (t, 2H, *J* 6.5), 3.56 (s, 3H), 3.46 (s, 3H); $\delta_H([^2H_6]DMSO, 27\ °C)$ 8.04 (s, 1H), 7.78 (s, 1H), 7.56 (s, 1H), 7.16 (s, 2H, $NH_2$), 4.66–4.59 (m, 4H), 3.38 (s, 3H), 3.21 (s, 2H); $\delta_H([^2H_6]DMSO, 50\ °C)$ 8.04 (s, 1H), 7.79 (s, 1H), 7.56 (s, 1H), 7.02 (s, 2H, $NH_2$), 4.67 (t, 2H, *J* 6.5), 4.60 (t, 2H, *J* 6.5), 3.38 (s, 3H), 3.24 (s, 3H); $\delta_C([^2H_6]$-DMSO) 155.78, 154.42, 152.29, 150.98, 149.40, 148.45, 142.33, 140.53, 118.43, 106.05, 46.07, 43.04, 29.32, 27.50. Found: C, 49.02; H, 4.43; N, 37.05. Calc. for $C_{14}H_{15}N_9O_2$: C, 49.26; H, 4.43; N, 36.93%.

7-[3-(6-*Aminopurin*-9-*yl*)*propyl*]-1,3-*dimethylxanthine* (**1b**).—Yield 38%, mp 298–302 °C; $\delta_H(CDCl_3)$ 8.37 (s, 1H), 7.83 (s, 1H), 7.82 (s, 1H), 5.55 (s, 2H, $NH_2$), 4.35 (t, 2H, *J* 6.5), 4.27 (t, 2H, *J* 6.5), 3.59 (s, 3H), 3.42 (s, 3H), 2.56 (quint, 2H, *J* 6.5); $\delta_H([^2H_6]DMSO, 27\ °C)$ 8.11 (s, 1H), 8.10 (s, 1H), 8.09 (s, 1H), 7.17 (s, 2H, $NH_2$), 4.30 (t, 2H, *J* 7.2), 4.16 (t, 2H, *J* 7.2), 3.41 (s, 3H), 3.21 (s, 3H), 2.40 (quint, 2H, *J* 7.2); $\delta_C([^2H_6]DMSO)$ 155.83, 154.24, 152.17, 150.89, 149.42, 148.31, 142.38, 140.57, 118.64, 105.91, 43.88, 40.14, 30.17, 29.30, 27.45. Found: C, 50.73; H, 4.81; N, 35.64. Calc. for $C_{15}H_{17}N_9O_2$: C, 50.70; H, 4.82; N, 35.47%.

7-[4-(6-*Aminopurin*-9-*yl*)*butyl*]-1,3-*dimethylxanthine* (**1c**).—Yield 38%, mp 225–227 °C; $\delta_H(CDCl_3)$ 8.34 (s, 1H), 7.79 (s, 1H),

7.51 (s, 1H), 5.50 (s, 2H, $NH_2$), 4.33 (br t, 2H, *J* 6.5), 4.25 (br t, 2H, *J* 6.5), 3.58 (s, 3H), 3.41 (s, 3H), 2.0–1.9 (m, 4H); $\delta_H$([$^2H_6$]DMSO) 8.10 (s, 1H), 8.09 (s, 1H), 8.06 (s, 1H), 7.17 (s, 2H, $NH_2$), 4.26 (br, 2H), 4.14 (br, 2H), 3.42 (s, 3H), 3.21 (s, 3H), 1.75 (br, 4H); $\delta_C$([$^2H_6$]DMSO) 155.82, 154.26, 152.20, 150.97, 149.42, 148.43, 142.43, 140.87, 118.71, 105.89, 45.62, 42.38, 29.40, 27.55, 27.20, 26.00. Found: C, 51.75; H, 5.39; N, 33.90. Calc. for $C_{16}H_{19}N_9O_2$: C, 52.03; H, 5.18; N, 34.13%.

7-[5-(6-*Aminopurine*-9-*yl*)*pentyl*]-1,3-*dimethylxanthine* (**1d**).—Yield 40%, mp 204–206 °C; $\delta_H$($CDCl_3$) 8.35 (s, 1H), 7.79 (s, 1H), 7.49 (s, 1H), 5.65 (s, 2H, $NH_2$), 4.26 (t, 2H, *J* 7.2), 4.20 (t, 2H, *J* 7.2), 3.59 (s, 3H), 3.41 (s, 3H), 1.97 (quint, 2H, *J* 7.2), 1.95 (quint, 2H, *J* 7.2), 1.37 (quint, 2H, *J* 7.2); $\delta_C$($CDCl_3$) 155.45, 155.15, 153.04, 151.68, 150.15, 149.03, 140.79, 140.40, 119.69, 106.94, 46.86, 43.47, 30.31, 29.80, 29.40, 28.03, 23.34. Found: C, 53.53; H, 5.52; N, 33.14. Calc. for $C_{17}H_{21}N_9O_2$: C, 53.26; H, 5.52; N, 32.88%.

7-[6-(6-*Aminopurin*-9-*yl*)*hexyl*]-1,3-*dimethylxanthine* (**1e**).—Yield 44%, mp 185–186 °C; $\delta_H$($CDCl_3$) 8.35 (s, 1H), 7.79 (s, 1H), 7.52 (s, 1H), 5.88 (s, 2H, $NH_2$), 4.26 (t, 2H, *J* 7.2), 4.20 (t, 2H, *J* 7.2), 3.59 (s, 3H), 3.40 (s, 3H), 1.91 (quint, 2H, *J* 7.2), 1.87 (quint, 2H, *J* 7.2), 1.39 (br quint, 4H, *J* 7.2); $\delta_C$($CDCl_3$) 155.52, 155.14, 152.83, 151.71, 149.96, 148.97, 140.82, 140.35, 119.37, 106.98, 47.06, 43.83, 30.69, 29.85, 29.81, 28.03, 26.03, 25.79. Found: C, 51.44; H, 5.98; N, 29.88. Calc. for $C_{18}H_{23}N_9O_2\cdot H_2O$: C, 52.04; H, 6.07; N, 30.34%.

7-[7-(6-*Aminopurin*-9-*yl*)*heptyl*]-1,3-*dimethylxanthine* (**1f**).—Yield 43%, mp 175–176 °C; $\delta_H$($CDCl_3$) 8.36 (s, 1H), 7.79 (s, 1H), 7.52 (s, 1H), 5.94 (s, 2H, $NH_2$), 4.26 (t, 2H, *J* 7.2), 4.19 (t, 2H, *J* 7.2), 3.59 (s, 3H), 3.41 (s, 3H), 1.89 (quint, 2H, *J* 7.2), 1.85 (quint, 2H, *J* 7.2), 1.40–1.20 (m, 6H); $\delta_C$($CDCl_3$) 155.51, 155.13, 152.91, 151.72, 150.13, 148.97, 140.79, 140.38, 119.67, 106.98, 47.16, 43.82, 30.77, 29.93, 29.78, 28.44, 28.01, 26.42, 26.16. Found: C, 53.29; H, 6.25; N, 29.38. Calc. for $C_{19}H_{25}N_9O_2\cdot H_2O$: C, 53.14; H, 6.34; N, 29.35%.

7-[8-(6-*Aminopurin*-9-*yl*)*octyl*]-1,3-*dimethylxanthine* (**1g**).—Yield 37%, mp 140–141 °C; $\delta_H$($CDCl_3$) 8.36 (s, 1H), 7.79 (s, 1H), 7.52 (s, 1H), 5.52 (s, 2H, $NH_2$), 4.26 (t, 2H, *J* 7.2), 4.18 (t, 2H, *J* 7.2), 3.59 (s, 3H), 3.41 (s, 3H), 1.87 (quint, 4H, *J* 7.2), 1.35–1.25 (m, 8H); $\delta_C$($CDCl_3$) 155.78, 155.11, 152.94, 151.72, 150.06, 148.94, 140.82, 140.30, 119.65, 106.97, 47.20, 43.83, 30.81, 29.97, 29.78, 28.78, 28.77, 28.00, 26.45, 26.19. Found: C, 56.60; H, 6.49; N, 29.51. Calc. for $C_{20}H_{27}N_9O_2$: C, 56.46; H, 6.40; N, 29.63%.

7-[10-(6-*Aminopurin*-9-*yl*)*decyl*]-1,3-*dimethylxanthine* (**1i**).—Yield 38%, mp 161–162 °C; $\delta_H$($CDCl_3$) 8.37 (s, 1H), 7.78 (s, 1H), 7.52 (s, 1H), 5.83 (s, 2H, $NH_2$), 4.27 (t, 2H, *J* 7.2), 4.19 (t, 2H, *J* 7.2), 3.60 (s, 3H), 3.41 (s, 3H), 1.87 (quint, 4H, *J* 7.2), 1.35–1.20 (m, 12H); $\delta_C$($CDCl_3$) 155.59, 155.13, 152.84, 151.74, 150.09, 148.94, 140.82, 140.39, 119.63, 107.00, 47.31, 43.96, 30.87, 30.03, 29.79, 29.23, 29.22, 28.93, 28.92, 28.01, 26.56, 26.34. Found: C, 58.51; H, 6.76; N, 27.80. Calc. for $C_{22}H_{31}N_9O_2$: C, 58.26; H, 6.89; N, 27.79%.

1-[2-(6-*Aminopurin*-9-*yl*)*ethyl*]-3,7-*dimethylxanthine* (**2a**).—Yield 30%, mp 289–292 °C; $\delta_H$($CDCl_3$) 8.23 (s, 1H), 7.77 (s, 1H), 7.47 (s, 1H), 5.48 (s, 2H, $NH_2$), 4.54 (t, 2H, *J* 6.0), 4.48 (t, 2H, *J* 6.0), 3.87 (s, 3H), 3.52 (s, 3H); $\delta_H$([$^2H_6$]DMSO) 8.05 (s, 1H), 7.96 (s, 1H), 7.89 (s, 1H), 7.10 (s, 2H, $NH_2$), 4.41 (t, 2H, *J* 5.2), 4.26 (t, 2H, *J* 5.2), 3.75 (s, 3H), 3.32 (s, 2H); $\delta_C$([$^2H_6$]DMSO) 155.69, 154.12, 151.91, 150.78, 149.88, 148.29, 142.77, 140.84, 118.49, 106.38, 41.01, 40.37, 32.92, 29.19. Found: C, 49.24; H, 4.50; N, 36.78. Calc. for $C_{14}H_{15}N_9O_2$: C, 49.26; H, 4.43; N, 36.93%.

1-[3-(6-*Aminopurin*-9-*yl*)*propyl*]-3,7-*dimethylxanthine* (**2b**).—Yield 23%, mp 269–272 °C; $\delta_H$($CDCl_3$) 8.34 (s, 1H), 7.99 (s, 1H), 7.50 (s, 1H), 5.49 (s, 2H, $NH_2$), 4.29 (t, 2H, *J* 7.2), 4.13 (t, 2H, *J* 7.2), 3.97 (s, 3H), 3.56 (s, 3H), 2.35 (quint, 2H, *J* 7.2); $\delta_H$([$^2H_6$]DMSO) 8.15 (s, 1H), 8.11 (s, 1H), 7.97 (s, 1H), 7.08 (s, 2H, $NH_2$), 4.19 (t, 2H, *J* 7.2), 3.92 (t, 2H, *J* 7.2), 3.86 (s, 3H), 3.39 (s, 3H), 2.14 (quint, 2H, *J* 7.2); $\delta_C$([$^2H_6$]DMSO) 156.09, 154.64, 152.44, 151.10, 149.77, 148.51, 143.16, 141.16, 119.02, 106.92, 41.36, 38.42, 33.39, 29.62, 28.17. Found: C, 49.63; H, 4.80; N, 34.81. Calc. for $C_{15}H_{17}N_9O_2\cdot 0.5H_2O$: C, 49.45; H, 4.98; N, 34.60%.

1-[4-(6-*Aminopurin*-9-*yl*)*butyl*]-3,7-*dimethylxanthine* (**2c**).—Yield 28%, mp 230–233 °C; $\delta_H$($CDCl_3$) 8.34 (s, 1H), 7.88 (s, 1H), 7.50 (s, 1H), 5.83 (s, 2H, $NH_2$), 4.28 (t, 2H, *J* 7.2), 4.08 (t, 2H, *J* 7.2), 3.98 (s, 3H), 3.57 (s, 3H), 1.96 (quint, 2H, *J* 7.2), 1.73 (quint, 2H, *J* 7.2); $\delta_C$($CDCl_3$) 155.45, 155.27, 152.94, 151.50, 150.10, 148.89, 141.58, 140.77, 119.67, 107.63, 43.35, 40.25, 33.60, 29.75, 27.27, 24.99. Found: C, 49.69; H, 5.21; N, 32.89. Calc. for $C_{16}H_{19}N_9O_2\cdot H_2O$: C, 49.60; H, 5.46; N, 32.54%.

1-[5-(6-*Aminopurine*-9-*yl*)*pentyl*]-3,7-*dimethylxanthine* (**2d**).—Yield 35%, mp 216–218 °C; $\delta_H$($CDCl_3$) 8.35 (s, 1H), 7.80 (s, 1H), 7.50 (s, 1H), 5.48 (s, 2H, $NH_2$), 4.21 (t, 2H, *J* 7.2), 4.00 (t, 2H, *J* 7.2), 3.98 (s, 3H), 3.57 (s, 3H), 1.97 (quint, 2H, *J* 7.2); 1.73 (quint, 2H, *J* 7.2), 1.42 (quint, 2H, *J* 7.2); $\delta_H$([$^2H_6$]DMSO) 8.13 (s, 1H), 8.13 (s, 1H), 7.99 (s, 1H), 7.19 (s, 2H, $NH_2$), 4.14 (t, 2H, *J* 7.2), 3.88 (s, 3H), 3.83 (t, 2H, *J* 7.2), 3.40 (s, 3H), 1.84 (quint, 2H, *J* 7.2), 1.58 (quint, 2H, *J* 7.2), 1.26 (quint 2H, *J* 7.2); $\delta_C$([$^2H_6$]DMSO) 156.31, 154.74, 152.70, 151.17, 149.93, 148.56, 143.25, 141.16, 119.11, 107.00, 43.11, 40.51, 33.51, 29.71, 29.51, 27.37, 23.78. Found: C, 53.22; H, 5.50; N, 32.89. Calc. for $C_{17}H_{21}N_9O_2$: C, 53.26; H, 5.52; N, 32.88%.

1-[6-(6-*Aminopurin*-9-*yl*)*hexyl*]-3,7-*dimethylxanthine* (**2e**).—Yield 38%, mp 202–204 °C; $\delta_H$($CDCl_3$) 8.35 (s, 1H), 7.81 (s, 1H), 7.50 (s, 1H), 5.50 (s, 2H, $NH_2$), 4.19 (t, 2H, *J* 7.2), 3.98 (t, 2H, *J* 7.2), 3.98 (s, 3H), 3.57 (s, 3H), 1.92 (quint, 2H, *J* 7.2), 1.66 (quint, 2H, *J* 7.2), 1.45–1.38 (m, 4H); $\delta_C$($CDCl_3$) 155.55, 155.31, 152.94, 151.51, 150.10, 148.78, 141.46, 140.41, 119.61, 107.68, 43.90, 41.12, 33.58, 29.90, 29.70, 27.76, 26.32, 26.29. Found: C, 53.83; H, 5.75; N, 31.35. Calc. for $C_{18}H_{23}N_9O_2$: C, 54.40; H, 5.83; N, 31.72%.

1-[7-(6-*Aminopurin*-9-*yl*)*heptyl*]-3,7-*dimethylxanthine* (**2f**).—Yield 37%, mp 203–205 °C; $\delta_H$($CDCl_3$) 8.36 (s, 1H), 7.81 (s, 1H), 7.50 (s, 1H), 5.53 (s, 2H, $NH_2$), 4.19 (t, 2H, *J* 7.2), 3.98 (t, 2H, *J* 7.2), 3.98 (s, 3H), 3.57 (s, 3H), 1.90 (quint, 2H, *J* 7.2), 1.64 (quint, 2H, *J* 7.2), 1.45–1.30 (m, 6H); $\delta_C$($CDCl_3$) 155.45, 155.34, 152.77, 151.51, 150.13, 148.78, 141.41, 140.54, 119.70, 107.71, 43.92, 41.25, 33.58, 29.97, 29.69, 28.68, 27.87, 26.70, 26.52. Found: C, 55.18; H, 6.10; N, 30.59. Calc. for $C_{19}H_{25}N_9O_2$: C, 55.46; H, 6.12; N, 30.64%.

1-[9-(6-*Aminopurin*-9-*yl*)*nonyl*]-3,7-*dimethylxanthine* (**2h**).—Yield 32%, mp 170–171 °C; $\delta_H$($CDCl_3$) 8.37 (s, 1H), 7.80 (s, 1H), 7.49 (s, 1H), 5.63 (s, 2H, $NH_2$), 4.19 (t, 2H, *J* 7.2), 3.98 (t, 2H, *J* 7.2), 3.98 (s, 3H), 3.57 (s, 3H), 1.89 (quint, 2H, *J* 7.2), 1.63 (quint, 2H, *J* 7.2), 1.40–1.25 (m, 10H); $\delta_C$($CDCl_3$) 155.62, 155.32, 152.83, 151.51, 150.02, 148.73, 141.42, 140.43, 119.46, 107.71, 44.00, 41.42, 33.58, 30.02, 29.69, 29.21, 29.10, 28.91, 27.97, 26.85, 26.59. Found: C, 55.89; H, 6.61; N, 28.01. Calc. for $C_{21}H_{29}N_9O_2\cdot 0.5H_2O$: C, 56.01; H, 6.74; N, 28.11%.

1-[10-(6-*Aminopurin*-9-*yl*)*decyl*]-3,7-*dimethylxanthine* (**2i**).—Yield 30%, mp 125–126 °C; $\delta_H$($CDCl_3$) 8.37 (s, 1H), 7.79 (s, 1H), 7.49 (s, 1H), 5.78 (s, 2H, $NH_2$), 4.19 (t, 2H, *J* 7.2), 3.98 (t, 2H, *J* 7.2), 3.98 (s, 3H), 3.57 (s, 3H), 1.89 (quint, 2H, *J* 7.2), 1.64 (quint, 2H, *J* 7.2), 1.38–1.23 (m, 12H); $\delta_C$($CDCl_3$) 155.66, 155.32, 152.89, 151.50, 150.10, 148.73, 141.38, 140.42, 119.63, 107.70, 43.98, 41.46, 33.56, 30.04, 29.67, 29.31, 29.28, 29.20, 28.96, 28.02, 26.93, 26.61. Found: C, 56.60; H, 6.93; N, 26.81. Calc. for $C_{22}H_{31}N_9O_2\cdot H_2O$: C, 56.04; H, 7.05; N, 26.73%.

**Deuterium exchange of the C-8 hydrogen of the adenine ring of 1 and 2**

The solution of **1a**–**f** or **2a**–**f** (50 mg) in $D_2O$ (20–50 ml) was heated at reflux temperature for 12–14 h. The compounds **1i**, **2h** and **2i** (50 mg) were not sufficiently soluble in $D_2O$ (50 ml) but the solutions containing the insoluble materials were heated at reflux temperature for 48 h. The reaction mixtures were evaporated to give the corresponding compounds containing the 8-deuterioadenine moiety.

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