Structural Analysis of the Purine Repressor, an *Escherichia coli* DNA-binding Protein*

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The purine repressor protein, PurR, is a member of the *lac* repressor, LacI, family. The periplasmic binding proteins, has been noted (Muller-Hill, 1983; Vartak et al., 1991), and fructose repressor protein (Stokes and Hall, 1985), the *B. subtilis* amylase repressor protein (Henkin et al., 1991), and fructose repressor (Jahreis et al., 1991; Vartak et al., 1991). Proteins of this family contain two separate functional domains, a smaller N-terminal helix-turn-helix DNA binding domain (Brennan and Matthews, 1989) and a larger C-terminal effector binding/oligomerization domain. LacI is unique in this family in that it exists as a tetramer (Riggs and Bourgeois, 1968; Barkley et al., 1975; Whitson and Matthews, 1986; Brenowitz et al., 1991; Chen and Matthews, 1992), whereas the other members appear to exist only as dimers. Specific proteolytic cleavage of PurR after Arg adds a further step in the cleavage of the periplasmic binding proteins to high resolution by x-ray crystallography, showing them to have a highly conserved β/α type structure (Quiocho, 1991; Mowbray and Cole, 1992). The homology between the periplasmic binding proteins and the LacI superfamily is found within the effector binding domains of the LacI members and the metabolite binding domains of the periplasmic proteins. Because the structures of several of the

In *Escherichia coli*, the genes encoding enzymes required for purine biosynthesis are scattered throughout the chromosome in the form of polycistronic and monocistronic operons. Ten of these genes are regulated by a 38-kDa DNA-binding protein, the purine repressor, PurR. In addition, PurR participates in the regulation of five other genes involved in pyrimidine biosynthesis, pyrimidine salvage, and the generation of one-carbon units (Zalkin and Dixon, 1992) and is autoregulated (Rolfes and Zalkin, 1990a). PurR is activated to bind its cognate DNA by binding the purine corepressors, hypoxanthine or guanine, thereby leading to repression of the Pur region (Rolfes and Zalkin, 1990b).

PurR is a member of the LacI family, which includes CytR (Valentin-Hansen et al., 1986), galactose repressor protein (von Wicken-Bergmann and Müller-Hill, 1982), ribose repressor protein (Mauzy and Hermodson, 1992a), maltose repressor protein (Reid et al., 1989), raffinose repressor protein (Aslanidis and Schmitt, 1990), evolved β-galactosidase repressor protein (Stokes and Hall, 1985), the *B. subtilis* amylase repressor protein (Henkin et al., 1991), and fructose repressor (Jahreis et al., 1991; Vartak et al., 1991). Proteins of this family contain two separate functional domains, a smaller N-terminal helix-turn-helix DNA binding domain (Brennan and Matthews, 1989) and a larger C-terminal effector binding/oligomerization domain. LacI is unique in this family in that it exists as a tetramer (Riggs and Bourgeois, 1968; Barkley et al., 1975; Whitson and Matthews, 1986; Brenowitz et al., 1991; Chen and Matthews, 1992), whereas the other members appear to exist only as dimers. Specific proteolytic cleavage of PurR after Arg provides support for this two-domain organization within PurR. This cleavage produces an N-terminal DNA binding domain (residues 1–52) and a corepressor binding domain (CBD, residues 53–341) (Choi and Zalkin, 1992).

Homology between this family of DNA-binding proteins and another group of *E. coli* binding proteins, the periplasmic binding proteins, has been noted (Muller-Hill, 1983; Vartak et al., 1991; Mauzy and Hermodson, 1992b; Weickert and Adhya, 1992). This homology exists despite lack of significant sequence identity. Of particular interest to this work is the recent study by Bowie et al. that suggested a striking structural homology between PurR and RBP (Bowie et al., 1991). The periplasmic binding proteins, including RBP, consist of a small N-terminal signal sequence, which targets these proteins to the bacterial inner membrane and is subsequently cleaved, and a larger C-terminal metabolite binding domain. The metabolite binding domain itself is further divided into two domains. Importantly, the structures of several of these proteins have been solved to high resolution by x-ray crystallography, showing them to have a highly conserved β/α type structure (Quiocho, 1991; Mowbray and Cole, 1992). The homology between the periplasmic proteins and the LacI superfamily is found within the effector binding domains of the LacI members and the metabolite binding domains of the periplasmic proteins. Because the structures of several of the

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periplasmic proteins are known, they can potentially be used as scaffolds upon which to model the structures of the effector binding domains of LacI members. To further our understanding of PurR and its structural relationship to RBP, we have compiled a comprehensive sequence homology studies and secondary structure analyses and CD spectroscopic studies on PurR, its corepressor binding domain, and RBP. A complete secondary structure topology of PurR is presented and its functional ramifications discussed.

**EXPERIMENTAL PROCEDURES**

**Sequence Homology**—A sequence identity comparison program (Ohlendorf et al., 1983; Brennan et al., 1986) was used to analyze the primary structures of GBP-E, RBP, PurR, LacI, and CytR. The secondary structure prediction of PurR was carried out using the method of Wilmot and Thornton (1988). Sequence alignments were made based on the algorithm of Feng and Doolittle (1990).

The final, “knowledge-based” alignment of PurR was carried out in five steps. First, as a control, the secondary structures of GBP-E and RBP were predicted by using the above described methods and compared with their x-ray-determined secondary structures. The secondary structure of PurR was simultaneously predicted by this method. The three sequences were subsequently aligned employing the algorithm of progressive alignments of Feng and Doolittle. The final alignment of PurR was refined and confirmed by calculating the significance of the alignment via direct amino acid comparisons (DAAC) and minimum base change per codon (MBC/C) comparisons between eight variable-length stretches of RBP and CBD (Ohlendorf et al., 1983; Brennan et al., 1986) and by using the recent sequence alignment of RBP against the *E. coli* and *Salmonella typhimurium* GBP (Mowbray, 1992). To complete the topological analysis, the NMR-determined secondary structure of the LacI headpiece region (Kaptein et al., 1985) was used to model the secondary structure of the N-terminal region of PurR.

**CD Spectroscopy**—CD spectra of CBD, PurR, and RBP were taken on a JASCO J-500A spectrophotometer. Measurements were made using a 0.1-mm path length cell (Helma) thermostatted cell at room temperature. The instrument was calibrated by using (+)-10-camphorsulfonic acid (Δε = +3.37 m−1 cm−1) at 290.5 nm and −4.95 at 192.5 nm. Data were collected on an IBM/PC-XT using the IF-500 interface and software provided by JASCO. Spectra and buffer base lines were the average of four to eight scans each recorded at 0.1-nm intervals, using a scanning rate of 5 nm/min and a 4-s time constant taken at room temperature. The buffer used for the spectral measurements of CBD and RBP was 10 mM potassium phosphate, pH 7.5, and because of decreased solubility at low ionic strength, 100 mM potassium phosphate, pH 7.5, for PurR. All proteins were purified as described previously (Choi and Zalkin, 1992; Mowbray and Cole, 1992). The protein concentrations were determined by amino acid analysis and by absorbance at 280 nm. Before spectral deconvolution for secondary structure analysis, the buffer base line was subtracted, and the resulting spectrum was smoothed using the smoothing program provided by JASCO. The CD spectra for each protein were deconvoluted for secondary structure content using the singular-value and variable selection methods described in detail elsewhere (Compton et al., 1987). For this analysis combinations of 12 of the 22 basis spectra are used to find those that result in the best fit using the criteria described elsewhere (Compton et al., 1987). All secondary structure values resulting from each combination which met these criteria were averaged to give the final secondary structure values for each experimental spectra.

**RESULTS AND DISCUSSION**

**Corepressor Binding Domain**—The analysis of PurR was undertaken to establish the extent of this protein’s homology to the PBP and to determine which PBP family it most closely resembles. The periplasmic binding proteins contain several hallmark features that are highly conserved among its members (Spurlino et al., 1991). All mature PBP, i.e., after signal sequence cleavage, are divided into two structural domains, an N terminus-containing domain and a C terminus-containing domain. Especially striking is the finding that in all periplasmic binding proteins, the x-ray structures of which have been determined, the first six secondary structural elements, which comprise approximately 100 residues, have the identical topological arrangement, βα′βα′βα′β (Quiocio, 1991; Mowbray and Cole, 1992). The N- and C-terminal domains are connected by two or three peptide crossovers, which although not sequentially close, are structurally close. These peptide crossovers have been used to delineate members of the periplasmic proteins into two families and indicate the secondary structures being connected. The first family, the ABP family, includes RBP, ABP, GBP-S, and GBP-E and exhibits β→α crossovers for the first two crossovers and a β→α crossover for the third. The second family, the GBP family, includes GBP and maltose-binding protein and exhibits β→β crossovers for the first two crossovers and an α→α crossover as the last.

The structural analysis of PurR commenced by initially focusing on the corepressor binding domain. Primary and secondary structure analyses and comparisons were carried out against selected PBP, the high resolution x-ray structures of which are known, and followed by DAAC and MBC/C significance analyses (Fig. 1 and Table I). Interestingly, the secondary structure predicted for CBD is that of the repeating β/α structure, with similarly located and sized helices and β-sheets as seen in the periplasmic binding proteins (Fig. 1). On the basis of all independent and corroborating methods used, it became evident that the first six secondary structural elements of CBD follow the βα′βα′βα′βα′β topology of the PBP. These elements begin with residue 61 of PurR and end at residue 167. Thus, they are contained within 100 residues as observed in the periplasmic proteins. Secondary structural analysis reveals a second similar C-terminal motif which spans βα′βα′βα′βα′βα′β. The search for β/α motifs in the CBD well as. Interestingly, self-alignment of CBD sequence reveals 44.8% of the PG-L and CBD sequence 184-318 reveals little sequence identity (12%). This is consistent with similar internal comparisons made between domains within the periplasmic binding proteins in which sequence identities are only ~14%. Indeed, sequence identity was shown to be greater than the corresponding domains of RBP and GBP-E (~24%) (Mowbray, 1992) and RBP and CBD (~24%) (this study).

To determine which family of periplasmic proteins PurR most closely resembles, the potential crossover regions need to be identified. This presented a problem as the secondary structure prediction data were ambiguous in the regions in which the crossovers were likely to occur. This problem was first addressed by studying the alignment data. Here it was noticed that, whereas the sequence of PurR aligns well with GBP family members within the N-terminal subdomain (data not shown), it aligns well with ABP family members, especially GBP-E and RBP, throughout its entire sequence, including the crossover regions (Fig. 1). For example, the helix in the first β→α crossover in RBP and GBP-E contains several highly conserved residues. In particular, residues Gly108, Gly112, and Ile116 of GBP correspond directly to Gly110, Gly114, and Ile118 of GBP-E. PurR has the corresponding glycines at positions 166 and 170 and a conservative change at position 173, a leucine for isoleucine (Fig. 1). Further comparison of PurR with GBP reveals even more striking identity within this region in that Gly108, Ala112, and Tyr115 of GBP correspond directly to Gly108, Ala112, and Tyr115 of GBP-E. Additionally, several other conservative substitutions within the GBP, RBP, and PurR sequences are found within this region (Fig. 1). Together, these identities strongly implicate this region as being the first crossover helix in PurR. Further corroborating this assignment is the secondary structure analysis which strongly predicts residues 162-176 of PurR to
PurR, therefore, a second crossover should be located near the third crossover region of PurR and the CBD. The predicted secondary structure of PurR against RBP and GBP-E is shown below the sequence alignment.

**TABLE I**

Identity scores of contiguous segments of RBP and the CBD of PurR

Results of a search carried out the entire sequence of PurR with various stretches of RBP. Significance scores were calculated by the method of Ohlendorf et al. 1983.

| Amino acid segment | Disagreement score (DAAC)a | Significance score (DAAC) | Disagreement score (MBC/C)b | Significance score (MBC/C) |
|-------------------|---------------------------|--------------------------|----------------------------|---------------------------|
| RBP               |                           |                          |                            |                           |
| PurR              |                           |                          |                            |                           |
| 2-41              | 60-100                    | 0.77                     | 4.21                       | 0.98                      | 4.72                      |
| 41-62             | 99-120                    | 0.73                     | 4.10                       | 1.00                      | 3.62                      |
| 83-126            | 140-183                   | 0.77                     | 4.95                       | 1.11                      | 3.78                      |
| 126-159           | 183-216                   | 0.76                     | 3.96                       | 1.00                      | 4.21                      |
| 169-190           | 217-247                   | 0.71                     | 5.07                       | 1.16                      | 3.00                      |
| 191-230           | 248-287                   | 0.73                     | 5.23                       | 1.20                      | 2.66                      |
| 231-247           | 288-304                   | 0.71                     | 3.86                       | 0.88                      | 3.39                      |
| 251-258           | 310-317                   | 0.63                     | 3.99                       | 0.88                      | 2.88                      |

*a The DAAC disagreement score for two random sequences is 0.94.

*b The MBC/C disagreement score for two random sequences is 1.44.

be helical (Fig. 1). On the basis of this assignment, PurR belongs to, or is closely related to, members of the ABP family. Therefore, a second $\beta\rightarrow\alpha$ crossover should be located near residue 292 in PurR after $\beta$-strand J (Fig. 1). In accordance with this supposition CBD residues 300–311 are predicted to be helical.

The analysis of PurR's third crossover was aided greatly by the recent x-ray structure of RBP (Mowbray and Cole, 1992). In that structure the third crossover is $\beta\rightarrow\beta$ from $\beta$-strand K (residues 260–263) to $\beta$-strand L (residues 266–268) (Fig. 1). Corresponding PurR residues 318–321 and 324–326 are predicted to be $\beta$-strands by alignment and sequence identity data (Fig. 1). Additional evidence implicating PurR residues 318–326 as the third crossover region is the near identity between the sequences of residues 289–291 and 324–325 of PurR and 232–234 and 266–268 of RBP, respectively. In RBP, residues 232–234 are Thr-Ile-Ala and residues 266–268 are Lys-Leu-Val, whereas in PurR the corresponding residues are Thr-Ile-His and Arg-Leu-Ile. The finding that PurR exhibits such similarity to RBP in these two distant regions, which form the only antiparallel $\beta$-sheet in RBP, suggests strongly that it contains the same secondary structure.

Further support for CBD's striking similarity to RBP and other ABP family members comes from the recent structural comparison of the high resolution structures of RBP, GBP-S, and GBP-E (Mowbray, 1992). This study identified several conserved residues as being key structural elements, whereby the regions of highest sequence identity are those involved in forming the hydrophobic cores of these proteins. Remarkably, these same regions are also the most conserved between RBP and PurR (Fig. 1). For example, PurR residues Ile6', Leu124', Leu125', Met126', and Leu153 correspond directly to RBP residues Ile4, Leu4, Leu6, Met172, and Leu177, respectively. Importantly, these identities span both the N- and C-terminal domains. Conserved residues in RBP and GBP-E were also noted as forming unusual and highly specific interactions within these proteins. For example, Asp191 in RBP and Asp212 in GBP-E, located within helices adjacent to a ligand binding site residues, are buried within the protein. Critical to the stabilization of this buried aspartate are hydrogen bonds to main chain amide nitrogens from a nearby loop and to the side chain of Thr235 in RBP and Thr236 in GBP-E. The presence of this interaction in PurR is strongly implicated by the presence of the corresponding pair Asp248 and Thr280. Furthermore, Asp248 is predicted to be in a helix (Fig. 1).

Other striking amino acid conservations include several glycines that in RBP and GBP-E are C-CAP residues (Richardson and Richardson, 1988). In PurR two of these glycines are Gly59 and Gly262 and are predicted to be near the C-terminal end of helices (Fig. 1). An unusual interaction in RBP is a $\alpha$-helix hydrogen bonding interaction involving residues 88–90, which contains a central aspartate residue, Asp99, that
is also involved in sugar binding. The equivalent position in PurR is Asp14', pointing out again the extraordinary conservation between PurR and RBP in residues known to be structurally important in RBP, despite the lack of significant global sequence identity between these two proteins. The main differences between RBP and GBP-E have been noted as occurring in regions in which GBP-E binds Ca2+ (Mowbray et al., 1990; Vyas et al., 1991). Since RBP does not bind Ca2+, the corresponding sequences in RBP contain deletions within the alignment (Mowbray and Cole, 1992). Gaps also occur in these regions for PurR, indicating, as expected, that there are no Ca2+ binding sites within PurR (Fig. 1).

To provide statistical verification for the remarkable similarity between RBP and CBD, DAAC and MBC/C analyses were carried out by comparing various stretches of RBP against the entire sequence of CBD (Ohlendorf et al., 1983; Brennan et al., 1986). The results of DAAC and MBC/C comparisons between eight variable length segments of RBP and the entire CBD are shown in Table I and reveal overall 27.3% amino acid sequence identity. These segments were chosen around the few gaps and insertions that were necessary to align the two sequences optimally. In both DAAC and MBC/C analyses, the better scores are those obtained from comparisons between the N-terminal regions, with the lower scores corresponding to the C-terminal region. The significance scores (Table I, fourth column) for the DAAC analysis for the eight aligned pairs of sequences of RBP versus CBD are 4.21, 4.10, 4.56, 3.96, 5.07, 5.23, 3.86, and 3.99 and underscore the very strong homologies between these segments. Remarkably, the best scores were found in regions in which the predicted secondary structure of PurR matches exactly the known secondary structure of RBP. The values of the given MBC/C also support this homology with significance values of 4.72, 3.62, 3.78, 4.21, 3.00, 2.66, 3.39, and 2.88 (Table I, sixth column). However, in the MBC/C analyses, two segments of RBP (residues 191–230 and 251–258) score lower scores corresponding to the C-terminal region. The significances of locating probable loop locations, the site of PBP-ligand interaction, and PurR residues can be implicated in ligand binding.

Specific examples include the three polar and planar groups that have been shown to be critical in protein-ligand hydrogen bonding interactions on GBP-E and RBP (Vyas, 1991; Mowbray and Cole, 1992). In RBP these are Asp15', Arg14', and Asn18', and in GBP-E (Table II). The corresponding PurR residues are Asp14', Arg15', and Asp275. In RBP and GBP-E these amino acids make extensive cooperative and bidentate H-bonds with other protein residues as well as the ligand. Stacking interactions have also been shown to be important in RBP and GBP-E, acting to

**Fig. 2. Alignment of PurR against E. coli DNA-binding proteins, LacI and CytR.** The region of the helix-turn-helix-loop-helix (H-T-H-L-H) in LacI, as determined by NMR, and the corresponding regions in PurR and CytR are approximately designated. Also designated is a fourth, predicted helix.
asparagines, and function in H-bonding and van der Waals interactions. It is possible that in family and unlike members of the periplasmic proteins, exists domains particularly well conserved (Weickert and Adhya, 1992). Sequence alignment of PurR with LacI reveals almost 50% identity within this region (residues 1–60) (Fig. 2). The corresponding residues in PurR and CytR, Tyr282 and Cys281, have also been implicated as important in subunit interaction. Substitution of Cys281 with virtually any amino acid does not affect dimerization, but does influence inducer affinity and cooperativity (Chakerian and Matthews, 1991). It is interesting to speculate that the corresponding residues in PurR and CytR, Tyr282 and Cys281, respectively, play analogous roles in ligand binding and subunit cooperativity and that their aromatic nature reflects their aromatic ligands.

CD Analysis—The above described primary and secondary structure analyses strongly suggest that the corepressor binding domain of PurR has a β/α type structure and fold very similar to that of RBP. When combined with NMR studies on the LacI DNA binding domain, these analyses also clearly indicate that PurR’s N-terminal DNA binding domain has a closely related helix-turn-helix-loop-helix structure. However, they provide no direct physical evidence. Perhaps one of the best physical methods available for the examination of protein structure, exclusive of X-ray crystallography and NMR, is circular dichroism spectroscopy. By measuring primarily the absorbance at 220 nm, two wavelengths that are particularly sensitive to a protein’s helix content. Therefore, CD spectroscopy is exquisitely sensitive to a protein’s secondary structure (Johnson, 1990). If, indeed, the CBD and RBP have similar secondary structures, their CD spectra should reveal this. Additionally, the intact form of PurR should also produce a similar spectrum, albeit with a greater helical content than the CBD and a slightly lower helical content than RBP. This difference will be reflected by a more positive absorbance at 192 nm and a more negative absorbance at 220 nm, two wavelengths that are particularly sensitive to a protein’s helix content. Therefore, CD spectroscopic studies were undertaken on RBP and both the intact form and the CBD of PurR.

The CD spectra of RBP, CBD, and PurR are shown in Fig. 3. The known or calculated percentages of the various secondary structural elements present in all three proteins, taken from either the X-ray crystallographically determined structure (RBP) or the optimum alignment (CBD and PurR) are presented in Table III as are those values for each protein calculated after deconvolution of its CD spectrum. These
results correlate extremely well with the predicted values for CBD given that the correlation coefficients for proteins of CD versus x-ray are 0.97 for α-helix, 0.76 for β-sheet, 0.49 for β-turn, and 0.86 for other (Johnson, 1990). The close match between the amount of known secondary structure of RBP as determined from the x-ray structure and that calculated by the algorithm employed in this study, which only examines the linear sequence of the chain.

**TABLE III**

| Protein and method | H    | B    | T    | O    | Total |
|--------------------|------|------|------|------|-------|
| PurR               | 0.40 | 0.27 | 0.16 | 0.20 | 1.03  |
| CD                 | 0.39 | 0.15 | 0.19 | 0.27 |       |
| CBD                | 0.33 | 0.16 | 0.21 | 0.32 | 1.02  |
| Predicted          | 0.33 | 0.17 | 0.21 | 0.29 |       |
| RBP                | 0.46 | 0.19 | 0.11 | 0.23 | 0.99  |
| CD                 | 0.48 | 0.20 | 0.11 | 0.21 |       |

**CONCLUSIONS**

A diagram describing the purine repressor protein’s deduced secondary structure topology is presented in Fig. 4. Both predictive and physical methods indicate that the structure of PurR’s corepressor binding domain is very similar to the β/α structure observed for the metabolite binding domains of the PBP, especially RBP, and that PurR’s DNA binding domain assumes the structure of the helix-turn-helix-loop-helix DNA binding domain of LacI. A similarly conserved topology is anticipated for all members of the LacI family. Significantly, although the intact LacI protein (Pace et al., 1990) and the LacI core domain (Steitz et al., 1980) have been crystallized, no inducer binding domain of the LacI superfamily has been solved. The high resolution x-ray structure determination of the corepressor binding domain of PurR (in progress) could serve as a potential model for other inducer binding sites of proteins within the LacI family (Schumacher et al., 1992). Furthermore, this structure will allow the comparison of the predicted secondary structure of PurR’s corepressor binding domain from sequence analyses and the CD analysis with that found in CBD’s crystal structure. It is anticipated that CBD will have a structure very similar to GBP-E and RBP. However, certain regions, in particular the purported dimerization domain, will likely be different but conserved among the LacI family members. Knowledge of those subunit interactions that affect dimerization are essential to understanding not only how and where dimerization occurs, but should shed considerable light on the biochemistry and dynamics of cooperativity in ligand binding by PurR.

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